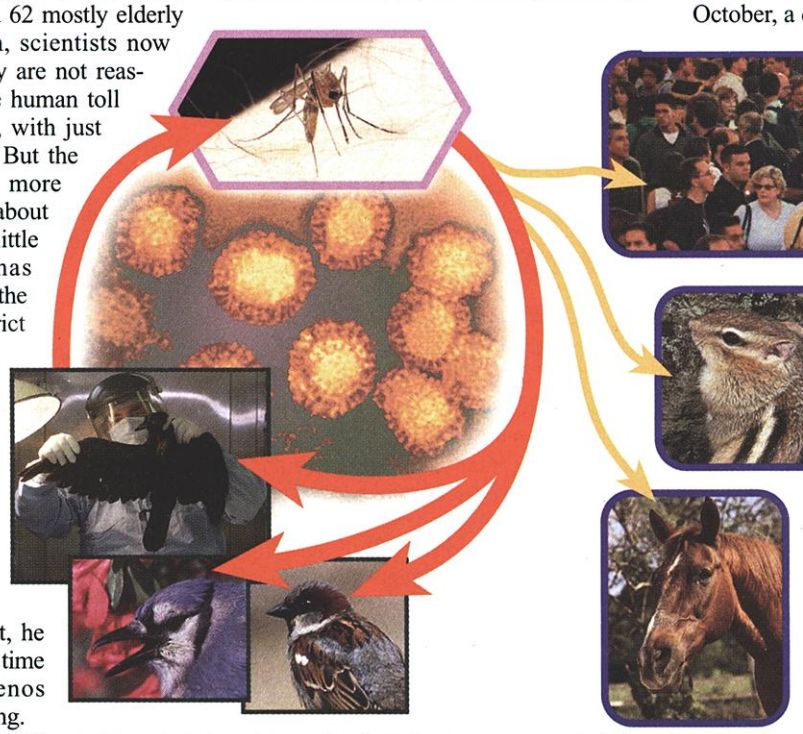
A year after it invaded New York City, there's still much that scientists don't know about the West Nile virus. But they're sure it will keep spreading.

The Enigma of West Nile

When the West Nile virus gained a foothold in New York City last summer, it found a land of endless opportunities. It had its pick of dozens of bird species that had never been in contact with the virus before; who knew how many might be hosts in which the virus could live? There are more than 100 mosquito species in the United States—how many could transmit the virus from one bird to another? How fast would the newcomer colonize the entire continent?

Fifteen months after the 1999 West Nile outbreak, which sickened 62 mostly elderly people and killed seven, scientists now have some answers. They are not reassuring. This summer, the human toll has been relatively mild, with just 18 cases and one death. But the virus has been found in more than 60 bird species and about a dozen mammals; in a little more than a year, it has spread to 11 states along the East Coast and the District of Columbia. "There's a good chance it will reach the West Coast within 5 years," predicts vertebrate ecologist Nicholas Komar of the Centers for Disease Control and Prevention (CDC) in Fort Collins, Colorado. And with no natural barriers to stop it, he adds, it's just a matter of time before citizens of Buenos Aires should start worrying.



Accidental victims. Mammals—including humans—can be infected too, but they are "dead-end" hosts. The West Nile virus (center) primarily replicates in birds.

Yet researchers are still hard pressed to predict how abundant the virus will eventually become or how serious a public health threat it will pose. Like St. Louis encephalitis, which occasionally flares up in the southern United States, West Nile virus is primarily a bird virus that is spread by mosquitoes. Humans, as well as horses and several other mammals, are "dead-end hosts." They become infected when a mosquito bites an infected bird and then a human. But the disease stops there; unlike malaria, say, mosquitoes don't transmit the West Nile virus from person to person. That puts a natural limit on the human epidemic; but the complex dynamics of birds, mosquitoes, and humans also cause erratic outbreak patterns. "People have studied St. Louis encephalitis for 50 years, and outbreaks are still unpredictable," says Lyle Petersen, a CDC physician who studies the West Nile virus. "They just sort of happen."

North or south?

After its surprise debut last year, some researchers said there was a 50–50 chance that West Nile would never make it in its new home. Except for one infected crow found in Baltimore, the virus seemed confined to an 80-kilometer radius around New York City, and as temperatures dropped and mosquito populations dwindled, they said, it might well die out. Alternately, some researchers predicted that migrating birds would carry the virus south as they escaped the New York winter; it would likely show up in Florida or the Caribbean in spring. Neither scenario proved right. This winter, after searching for mosquitoes in underground sewers and abandoned buildings in New York, CDC researchers discovered a few overwintering mosquitoes, and one sample was infected with the virus, dashing any hopes that the virus would simply disappear. Nor did the southward migration occur—at least not initially. The virus has mostly traveled north this past summer. From July on, increasing numbers of infected birds were found in upstate New York, Connecticut, Rhode Island, Massachusetts, Vermont, and New Hampshire. "That took most people by surprise," says Linda Glaser, a researcher with the U.S. Geological Survey's National Wildlife Health Center in Madison, Wisconsin. Only late this summer did the virus head south. In early October, a dead crow in Virginia tested positive; so did one from Chatham County in North Carolina a few weeks later. Chatham, some 800 kilometers from New York City, is now the southernmost point where the virus has been found.

Ideal hosts

As some researchers tracked the virus in the field, others have been studying its behavior in the lab, trying to determine how it spreads so rapidly. Crows are the virus's most conspicuous hosts because they have been dying en masse. But that doesn't mean they're the most helpful to the virus, says Komar. An ideal host would let the virus replicate for a long time but stay healthy enough to be fed on by mosquitoes. When the host dies quickly, as do crows, the virus goes with it.

Dozens of other bird species tested positive last year for West Nile antibodies, and Komar has studied how well the virus replicates in seven of them. Blue jays were "off the charts," says Komar; they had over a trillion viral particles per milliliter of blood when the infection peaked—similar to what has been found in crows. The humble house sparrow also came in high, although its viral load was a 1000 times lower than the blue jay's. But because house sparrows are so ubiquitous, they may be the virus's prime replication machine, suspects Komar.

Meanwhile, a team led by Michael Turell

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West Nile Drugs, Vaccine Still Years Away

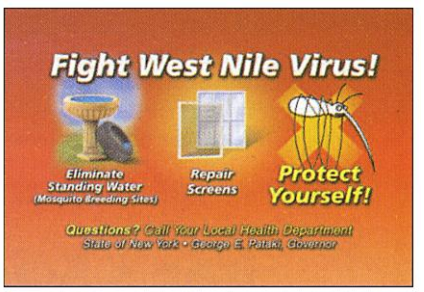
Most people infected with the West Nile virus don't even know it, or they experience only mild, flu-like symptoms. But for 1% or 2% it can be a terrifying, life-threatening experience. For these patients, there are no effective drugs; all doctors can do is treat symptoms as best as they can, while patients fight the brain infection themselves. Many of these patients end up with lingering neurological damage, as often occurs with encephalitic infections, says Marcelle Layton, assistant commissioner for health in New York City. Layton is following 42 survivors of the 1999 outbreak around New York, which killed seven people. Those over 65—a majority of all patients—are especially vulnerable: 3 months after the outbreak, 70% still reported muscle weakness, 75% suffered from memory loss, and 60% from confusion. Although most were previously healthy and active, more than half can no longer live at home. "They've lost their independence," says Layton.

With support from the National Institutes of Health (NIH), several research groups are taking the first steps toward developing drugs to fight the acute phase of the disease. Last month, for instance, a team led by Ian Lipkin from the University of California, Irvine, published a paper in the *Journal of Infectious Diseases* showing that the drug ribavirin—already in use to treat hepatitis C and several other viral diseases—could halt replication of the West Nile virus in cell culture. Lipkin's team now wants to test the compound in infected mice. But other researchers have their doubts; they point out that Lipkin's team used high doses that could prove toxic and, perhaps more important, ribavirin doesn't cross the blood-brain barrier well, so it wouldn't get to where it's most needed.

Ribavirin was tested in 35 West Nile patients in Israel this summer, says Silvio Pitlik of the Rabin Medical Center in Petach Tikvah. Although the results are difficult to interpret because there was no control group, "ribavirin didn't seem to affect the outcome," says Pitlik.

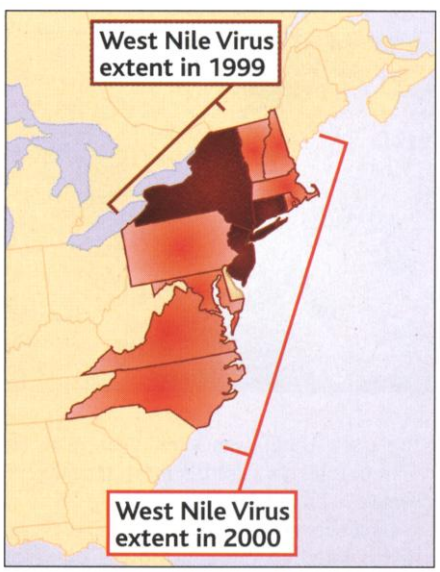
Other candidates are in the wings. At Utah State University in Logan, a group led by virologist Robert Sidwell is screening potential West Nile drugs sent in by a variety of research institutes and companies. Out of 41 compounds tested so far, five have shown strong antiviral activity and didn't seem toxic in cell culture, says team member John Morrey. Like ribavirin, several are already on the market for other diseases, which means they could win approval for use in West Nile patients a little faster than a new compound could. But with so few patients worldwide, West Nile drugs won't exactly be blockbusters, giving companies little incentive to develop them. "I would severely question whether any company would put the money in," says Lyle Petersen, a physician at the Centers for Disease Control and Prevention in Fort Collins, Colorado.

Meanwhile, NIH is also supporting the fast-track development of a West Nile vaccine by OraVax, a biotech company in Cambridge, Massachusetts (owned by Peptide Therapeutics in the United Kingdom). OraVax has a patented strategy for developing vaccines against flaviviruses, the family to which the West Nile virus belongs. The technique, developed by Thomas Chambers of St. Louis University, uses as the vaccine's backbone a weakened yellow fever strain called 17D, which has been used widely as a yellow fever vaccine since the 1930s. OraVax replaces the gene that encodes the yellow fever virus's coat, or envelope, protein with the corresponding gene from the West Nile virus. OraVax's Thomas Monath predicts that the company could start human trials with the West Nile vaccine in just 2 years.



Spreading the news. A public education campaign in New York may have prevented more cases.

NIH has pledged $3 million to carry the vaccine through phase I clinical trials; after that, the company will have to go it alone if, indeed, the vaccine looks promising and the company decides there is a market. It wouldn't make sense to vaccinate the entire population for such a rare disease; rather, elderly people in high-risk areas would be the most obvious candidates. With West Nile now striking the well-educated, relatively affluent urban centers of the East Coast, there may be just enough public demand to make the vaccine viable, says Monath, "but much will depend on how the disease evolves over the next two summers." **–M.E.**



On the move. In 2000, the virus showed up in eight new states.

CREDITS: (TOP) NEW YORK STATE DEPARTMENT OF HEALTH

of the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID) in Fort Detrick, Maryland, has been trying to identify the virus's insect accomplices. The team collected two dozen species of mosquitoes in New York City, Massachusetts, and Virginia and then turned them loose on infected chickens. Two weeks later, they tested whether the mosquitoes themselves had become infected and whether they could transmit the infection to other chickens. Three *Aedes* species turned out to be highly susceptible to West Nile infection, and several others —including *Culex pipiens*, which was first implicated in the outbreak—were moderately efficient vectors.

But lab tests aren't the final word, says USAMRIID's Monica O'Guinn. Each species' role in spreading disease also depends on such factors as population density and feeding habits, about which relatively little is known; these in turn may depend on geography or weather. Some mosquito species are most likely to fuel the virus's avian life cycle, as they primarily feed on birds; others bite both birds and humans and might serve as the "bridge species" that makes people sick.

No early warning

With so many variables in play, the dynamics of the outbreak have been difficult to understand, let alone predict. It's "somewhat of an enigma," for instance, why the virus made such impressive strides across the U.S. map this summer yet sickened only 18 people, Petersen says. He speculates that certain conditions might have favored an explosion in bird transmission but not human transmission. Some attribute at least part of the low case rate to intense spraying of insecticides. Increased public awareness may also have played a role. In

New York City, for instance, the public was bombarded with the message that elderly people, especially, should protect themselves from mosquito bites, says assistant commissioner Marcelle Layton of the city's department of health.

Another riddle of the 2000 outbreak is why an early warning system for viral activity was such a fiasco. In several states, researchers bled so-called sentinel chickens weekly and tested them for West Nile antibodies. For other insect-borne viral diseases, such as St. Louis encephalitis, chickens become infected before people do and are a time-proven indicator. But very few chickens became seropositive for West Nile virus this summer, and not one did so before the first human cases.

Dead birds, on the other hand, are too sensitive an indicator; they have been found in many states where there has not been a single human case, and spraying insecticides would have been premature. CDC researchers are now focusing their efforts on developing surveillance indicators that are a better predictor of human cases, says CDC's Petersen, so that public health authorities can take precautions once the risk becomes substantial. For instance, researchers are now combing through the data gathered this year in Staten Island, the New York borough where there was a cluster of cases. The hope, says Petersen, is that these will reveal a pattern that could have foreboded the epidemic. Researchers found high numbers of infected *Culex salinarius* mosquitoes in the area; they may prove to be significant. "But in all likelihood, it may be a couple of years before we can adequately predict the risk," he says.

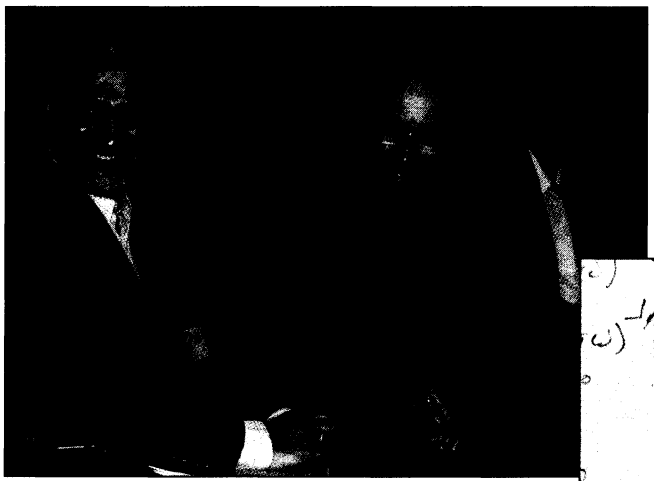
For that reason alone, Petersen won't speculate where the disease will next crop up—but he knows it will. And, because no drugs or a vaccine exists (see sidebar on p. 1483), West Nile is bound to claim new human victims. "We know it's going to be more than just a couple, and we know it's not going to be hundreds of thousands," says Peterson. "But we can't say much more with any certainty." **–MARTIN ENSERINK**

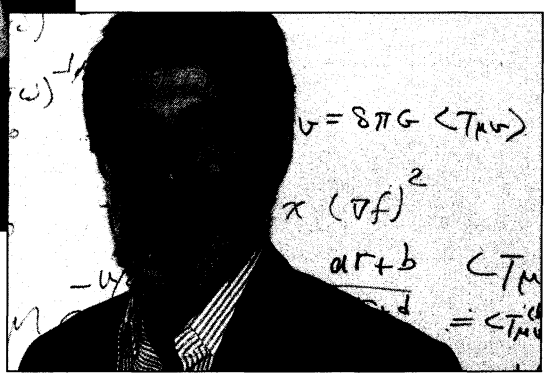
IRANIAN SCIENCE

Iran's Scientists Cautiously Reach Out to the World

Two decades after Iran's Islamic revolution, a reformist president wants researchers to expand collaborations with colleagues abroad

TEHRAN—When Reza Mansouri left a cushy university post in Vienna to return to his native Iran in 1980, the young theoretical physicist found himself caught up in a whirlwind. In the wake of the revolution that overthrew the Shah the year before, the new "Supreme Leader"—the Ayatollah Ruhollah Khomeini—was reinventing Iran as an Islamic republic, and talented researchers were fleeing in droves to safer and more lucrative posts abroad. Mansouri was going against the flow—an opponent of the Shah, he says he wanted "to do something for my country. Everything was in turmoil then, and science was low on the list of priorities." Along with his colleagues, Mansouri endured Iraqi rocket attacks against Sharif University of Technology, where he is a physics professor, during Iran's bloody 8-year war with Iraq in the 1980s. "Back then, people talked about 'Islamic physics' and 'Islamic science.' It took a long time for them to understand that physics is physics and science is science. But I think we're on the right track now."





Restoring an Islamic tradition? Science Minister Moin and President Khatami intend to pour more resources into research. Reza Mansouri (*inset*), who returned to his homeland 20 years ago, thinks that Iran's science is finally back on track.

Today, after what one Iranian chemist describes as "20 years of frustrating trial and error," science in this politically isolated but oil-rich nation may be on the verge of resurgence. The nation's reform-minded president, Mohammad Khatami, and his allies are promising more money for R&D and are reorganizing universities to beef up graduate education and research. They are also cracking open the door to closer cooperation with scientists abroad—including those in the United States, the country Khomeini branded "the Great Satan" in 1979 when revolutionaries occupied the U.S. Embassy here, holding 52 diplomats hostage for more than a year.

Such reforms may seem basic, but Iran's government is walking a tightrope. It's pressured by hard-liners on the right who oppose reforms and by liberal university students—many of whom now glimpse the outside world via the Internet and satellite TV receivers—eager for change. Indeed, even as the hard-liners celebrated the anniversary of the embassy takeover on 3 November with their annual anti-American, flag-burning festival in the streets of Tehran, moderates were quietly working to bridge a gulf of mistrust and heal old wounds. In the first high-level visit in more than 2 decades, a U.S. delegation led by National Academy of Sciences (NAS) president, Bruce Alberts, visited Iran in September, issuing a joint statement with Iran's academy afterward, pledging to initiate six joint workshops over the next 2 years. Although that NAS visit was carefully kept out of the Iranian news media and was not sponsored by either government, Sharif University Professor Abolhassan Vafai—one of the Iranian organizers—told *Science* that it represented "a breakthrough."

But serious obstacles must be overcome if this budding relationship is to blossom. These range from logistical hurdles—such as the lack of diplomatic relations between

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