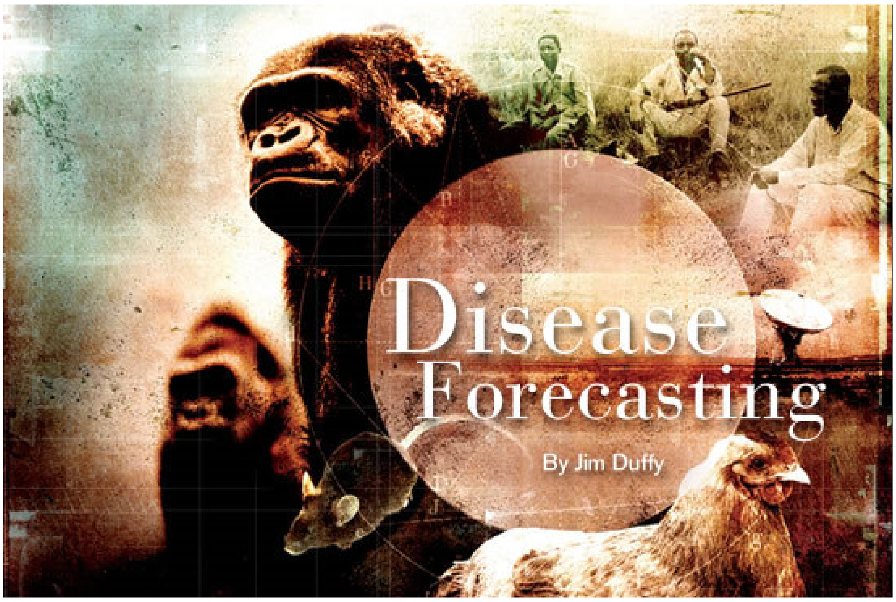
JOHNS HOPKINS PUBLIC HEALTH
The MAGAZINE of the Johns Hopkins Bloomberg School of Public Health
FALL 2005 ONLINE EDITION



Relying on satellites, computers, African hunters and even the humble chicken, researchers are building disease warning systems to catch viruses on the verge of sparking epidemics.

Nathan Wolfe has spent his share of time in Central Africa. As an assistant professor of Epidemiology, he's also done his share of thinking about the AIDS pandemic that emerged from the African jungle to take 20 million—and counting—lives around the world.

Is this the way things had to turn out?

"Think about what an earlier warning of just five years or 10 years on that pandemic could have meant," says Wolfe, DSc. "It would have been monumental in terms of the lives and the billions of dollars it would have saved."

The emergence of new threats—whether AIDS or Ebola in recent years or cholera or smallpox in the past—is nothing new to public health. AIDS has been deadlier than most scourges, to be sure, but public health developed over the centuries in response to an ever-changing cast of diseases. It is always scrambling to learn the workings of a strange new foe in time to stem a rising tide of disease.

In this sense at least, the fieldwork is reactive. The question Wolfe and a number of fellow researchers are now asking is this: What if public health fieldwork could be proactive as well? What if it could anticipate emerging diseases before they gain a foothold? What if it saw where the next pandemic-ready killer would likely come from? What if it knew how the next one would likely behave and evolve?

Such a future may not be so far out of reach. Don Burke, a professor of International Health, has been a pioneer in forecasting emerging diseases, advocating for the importance of prediction and prevention, and assembling a cadre of like-minded faculty (including Wolfe), postdocs and graduate students. The scientific world glimpsed the power of scientific prediction in 1997, when Burke examined the relative levels of future threats posed by various viruses. His stock lecture around that time featured a memorable laugh line.

"If I were king," he said time and again, "I'd be investing in coronaviruses."

Previously, coronaviruses (gene-swapping viruses common in animal populations) had been known only to cause sporadic minor illnesses in humans, like colds—never a major epidemic. That changed in 2003, when the SARS epidemic caught everyone by surprise, or at least everyone who hadn't heard one of Burke's lectures.

This work of forecasting emerging disease threats remains a rather novel undertaking. But it's one that Burke, Wolfe and other Bloomberg School researchers and alumni are pursuing in places as far-flung as Cameroon, Thailand and Chile. The projects described in this story all have the potential to boost human health in the here and now. But all also aim to spur the development of public health toward a future in which it gains powerful new predictive tools.

The work is full of unknowns. Science knows surprisingly little about zoonosis, the emergence of human disease from other animals. It knows little about the reservoir of diseases in animals or how those diseases move among species. Much remains mysterious, too, about how viruses fit into the broader ecological environment.

"But all these things are knowable, to some degree," says Burke, MD. "It could very well be that we're entering a phase—especially in microbiology— where we can seriously start tracking individual virus strains and how they interact with each other, where we can finally start to measure the right things and ask the right questions."

Tracking Hunters

Nathan Wolfe expected that he'd prove his point eventually, but he didn't expect to do it so quickly. His initial batch of blood samples covered only 1,000 hunters in Central Africa, and that's a small window to peer through while looking at the population-level risk of contracting chronic retroviruses from nonhuman primates. (Retro-viruses like HIV insinuate themselves in a host cell's DNA and then replicate, making it difficult for the immune system to destroy them.)

Wolfe had long harbored doubts about the conventional but unproven wisdom that such viruses cross into humans only rarely. In 1998, while a doctoral student at Harvard, he mused in the journal *Emerging Infectious Diseases* about the surprises that might turn up if scientists looked closely at hunters working in a biodiversity hotspot.

"Shortly after that came out—I was in Borneo at the time—I got this strange email from my mother," Wolfe recalls. "Some general from the U.S. military was calling for me, and my mother wanted to know what sort of trouble I was in."

That "general" turned out to be Colonel Don Burke, then a public health officer with the U.S. Army's Walter Reed Hospital. When Wolfe got in touch, Burke dangled before him the prospect of postdoctoral fieldwork in Cameroon. The jungles there boast all the biodiversity—and hence, viral diversity—Wolfe could ask for. And as primate hunting makes for a lot of bloody mixing among the species, why shouldn't viruses jump from one to another?

"These are basic biological phenomena we're talking about," Wolfe says. "All sorts of things have the potential to move back and forth."

Initially, Wolfe set out to develop a cross-sectional picture of hunters' exposures to primate retroviruses. Hunters have drawn scant scientific interest over the years, in part because they are seen by many as a threat to endangered animals.

> Primate hunting in the biologically diverse jungles of Central Africa makes for a lot of bloody mixing among the species. Why shouldn't viruses jump from one to another?

"When we go in these villages, what we find is that no one has ever showed any interest in their health or in their work," Wolfe says. "Nobody has even come in to talk with them."

Wolfe learned early on that the ways his hunters interact with their ecosystem have changed recently, increasing their exposures to other primates. Greater access to firearms has made hunters more efficient. New logging roads have opened the way into previously inaccessible hunting grounds and simultaneously connected hunters with new urban bushmeat markets.

When Wolfe gathered blood from hunters, he divided each sample proactively into plasma and lymphocyte collections to facilitate tracking the genetic lineage of any viruses that popped up. Last year, in *The Lancet*, Wolfe reported that 10, or 1 percent, of his 1,000 samples had antibodies to simian foamy viruses (SFV), one of the three classes of retroviruses found in African primates. Among the 10 were SFVs from three different primates: the mandrill, the gorilla and the DeBrazza's guenon.

Such transmissions had never before been documented in the wild.

Next, Wolfe turned to the deltaretroviruses. Unlike SFVs, these have been known to cause human illness. Only two deltas—HTLV-1 and HTLV-2—had been detected in humans until earlier this year when Wolfe, Burke and others announced in the *Proceedings of the National Academy of Sciences* that they had doubled that total by discovering two more.

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Wolfe and University of Yaoundé doctoral student Cyrille Djoko are now combing the samples for the lentiviruses that include the simian immunodeficiency viruses (SIV), the source in humans of HIV-1 and HIV-2. Wolfe sees no reason to expect anything different in this class, so look for him to report soon that some of his hunters are carrying SIVs.

"And all of these discoveries have come out of those first 1,000 samples," Wolfe says. "We've only looked at 20 or 30 percent of our existing collection."

Wolfe is now aiming to develop a longitudinal portrait of the workings of zoonosis in the Central African jungle. In addition to donating their own blood, hunters are gathering filter-paper samples from animals they kill.

One of Wolfe and Burke's doctoral students, David Sintasath, is analyzing these for prevalence data on retro-viruses among nonhuman primates. (Another, Amy Peterson, is screening for similar numbers on primate malarias.)

Wolfe is well-positioned, then, to boost basic knowledge about primate viruses and their movement into humans. He's hopeful that his work will shed light on lingering mysteries surrounding the precise origins of the AIDS epidemic. And he has a chance, too, at an exciting scientific first: capturing the "actual moment" of a virus transmission via samples from both hunted and hunter.

"That's not going to be easy," he says, "but it's something we have the potential to do."

Smallpox's Lethal Cousin

But Wolfe is not waiting until all this basic science is sorted out before pursuing a future in which science can see the next AIDS coming in enough time to make a monumental difference. It's the driving force behind a just-off-the-ground collaboration with Anne Rimoin, an assistant professor of Epidemiology at the UCLA School of Public Health and adjunct assistant professor in International Health at the Bloomberg School.

Rimoin, too, studies African hunters. Her hunters are even more isolated than Wolfe's, as she spends half of each year in a stretch of the Democratic Republic of Congo (DRC, formerly Zaire) accessible only by cargo plane.

"Basically, I'm the only person crazy enough to go out there," says Rimoin, PhD '03. Her research centers on monkeypox. The relative of smallpox was discovered in 1958 in laboratory monkeys, though its real animal reservoir remains unknown. It was first observed in humans in 1970, at the tail end of the smallpox eradication campaign. While rarely fatal in the developed world, according to the Centers for Disease Control (CDC), monkeypox can kill as many as 10 percent of its victims in less developed countries.

Most experts who looked at monkeypox early on in places like DRC weren't overly concerned. They saw a rural disease in countries that were urbanizing. They saw a hunter's disease in countries increasingly using domesticated livestock.

But neither trend survived the onset in the late 1990s of the Second Congo War, which claimed millions of lives and is considered the world's deadliest conflict since World War II. The military forces that occupied the area where Rimoin now works slaughtered livestock, burned fields and brutalized the local populace, driving them into the rainforest. "People are now exclusively reliant on bushmeat," reports Rimoin.

> Big picture, eye-in-the-sky technology now chases epidemiological mysteries: Satellite imagery of the southwestern U.S. uncovered a chain of natural events that culminated in a 1993 hantavirus outbreak.

When reports of monkeypox cases began filtering out of the jungle, Rimoin got in touch with DRC's public health officials and volunteered to investigate. The disease had always been regarded as one that appeared only in brief, sporadic outbreaks, but what Rimoin found was something else: endemic monkeypox.

Her research is an attempt to sort through the biological, ecological, epidemiological and sociological factors behind this surprise. How much of the monkeypox that she is finding can be attributed to increased exposures? Is its resurgence related to the disappearance of smallpox, an ecological competitor? Why does the disease predominantly strike young adolescents?

"There are lots of reasons why this is a very, very interesting disease," Rimoin says.

In her collaboration with Wolfe, Rimoin will gather information on Wolfe's retroviruses from her hunters, while Wolfe will bring Rimoin's acute disease surveillance techniques to Cameroon.

But their goal is bigger than this simple swap of information and techniques. They're out to create a pair of pilot "hunter networks" to serve as sentinel stations that could warn of the emergence of new viral disease.

Key to the project will be building a strong relationship with hunting communities. "In the past, they've been considered the enemy of conservation," Rimoin says. "But we're looking at them as an untapped resource. We're not just going to engage them as study participants. We'll also work with them as active collaborators."

Hunters will monitor the jungle for animal die-offs, often a precursor to human disease. They will alert researchers to new and virulent human disease events. In addition, researchers and hunters will look together at hunting behaviors such as butchering, with an eye toward developing techniques that protect hunters' health.

These networks are prototypes for the sort of sentinel disease surveillance stations that may someday operate in disease hotspots around the world, sounding alerts to the appearance of new pathogens. To Wolfe, this is a critical next step for public health.

"In a hundred years," he says, "I [don't want] people to look back at the way we do things today and say, 'They went chasing after diseases too late. They didn't pay attention until the diseases were global.' That's not doing it the right way."

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