Emerging Viruses, Emerging Threat

Scientists argue that society has become complacent about the threat of serious infectious diseases brought on by the emergence of previously remote viruses into the human population at large

"THERE IS NO REASON that a great plague could not happen again," Rockefeller University president Joshua Lederberg declares. "Certainly, another influenza pandemic is in the cards. Look at the ravaging epidemic of AIDS. People still do not understand that it is a natural, almost predictable phenomenon."

The emergence of the AIDS virus and other potentially lethal organisms during the 1980s has heightened concern among virologists and infectious disease experts about our vulnerability to unknown viruses. Whether that concern can be harnessed in ways to protect the population is now the issue.

"Some people think I am being hysterical, but there are catastrophes ahead. We live in evolutionary competition with microbes—bacteria and viruses. There is no guarantee that we will be the survivors," Lederberg said ominously during a recent interview with *Science*.

For much of his scientific career, Lederberg has been concerned about man's relation to microbes. "I first got interested in science because I read *The Microbe Hunters*," he recalls. "Then, the hunt was for bacteria. Now there are the virus hunters too."

Lederberg, who won the Nobel Prize in 1958 at age 33 for his work on sexual reproduction in bacteria, ardently believes that society worldwide is in peril because of insufficient understanding of and respect for the viruses with which we coexist.

The AIDS epidemic says it all. An unknown virus gets an opportunity to infect previously unexposed human beings and takes it. Lederberg's Rockefeller colleague Stephen S. Morse echoes an idea that is familiar to virologists when he says, "Biologically, the AIDS virus isn't 'new' even though we talk as if it were. The virus was there all along. Human behavior and travel provided the means for it to spread."

The emergence of AIDS should be sufficient warning to mount an effort to track other "emerging" viruses worldwide, according to Lederberg and Morse, who belong to a small band of scientists who worry about what they regard as "complacency" about infectious diseases.

"We still don't know very much about what makes it possible for a virus to spread from animals to humans or from humans to humans," Morse observes. "We need to know that. What we do know, or think we know, is that there is a vast reservoir of viruses in nature that are a potential threat. We're worried about viruses that are already here."

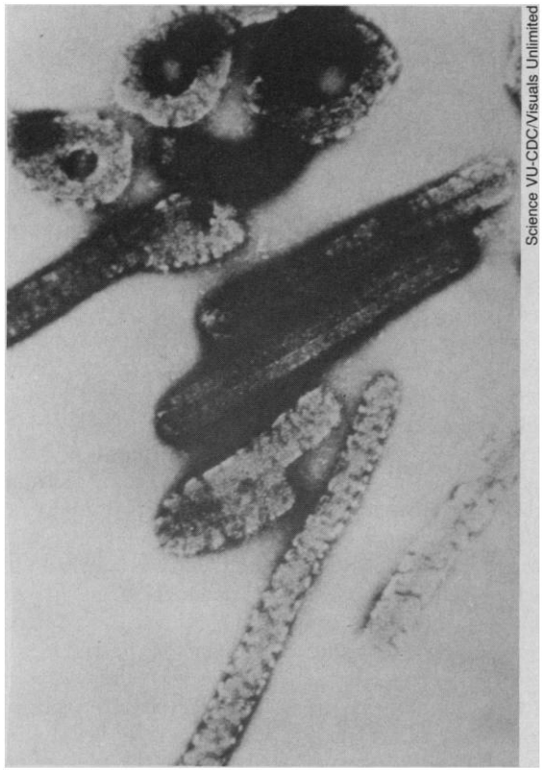
According to a forthcoming account of a conference held last spring on emerging viruses,* most of the so-called new or emerging viruses are zoonotic; that is, their natural hosts are animals, often rodents, birds, or pigs. These zoonotic viruses seem to adhere to the philosophy that says, "I won't bother you if you don't bother me."

Most of these "threatening" viruses have an African or Asian heritage, quite likely because they evolved along with humans, Morse suggests. Many have existed undetected and, apparently relatively harmlessly, in remote areas.

But then as people began hopping planes, moving from the country to the city, pushing back forests, or engaging in agricultural practices that are ecologically congenial to viruses, the viruses could make their way into the human population and multiply and spread. Sometimes they make their way genetically unchanged. At other times, it is believed, they undergo subtle mutations that may affect their capacity to spread or cause disease.

But in general, Morse argues, except for the influenza virus whose potency is known to be related to mutation (see box on p. 280), mutation is not the issue. "We're not dealing with the Andromeda strain, with some brand-new virus popping up out of nowhere," he contends.

The deadly Ebola virus is a recent case in point. Late last year, the virus was detected in monkeys shipped by air to Virginia from the Philippines. It had never shown up in the United States before and no one knows exactly how it got here now, largely because the military unrest in the Philippines made it impossible to trace the histories of the diseased monkeys. None of the people who handled the five now dead monkeys has gotten sick from the virus, but no one is sure how to explain that bit of good fortune.



Science VU-CDC/Visuals Unlimited

Ebola. *An emerging virus that has shown up in the United States forms filamentous particles.*

Another unwelcome immigrant is Seoul virus, a cousin of Asian Hantaan virus, which causes hemorrhagic fever. Victims suffer an often lethal combination of internal bleeding and kidney destruction. Seoul virus, which is rodent borne, recently appeared in rats around the harbor in Baltimore.

James Le Duc, of the U.S. Army Medical Research Institute of Infectious Diseases at Fort Detrick, reported at the emerging virus conference that no one in Baltimore has gotten disease from the virus, but 15 people in a sample of 1148 local residents carried antibodies to it, indicating that they had been exposed. Sixty-four percent of Baltimore's rats also carry the antibodies, he reported. There is speculation that Seoul virus may be a previously

unknown cause of kidney disease.

Changes in agricultural practices are held responsible for the emergence of Junin virus, which causes Argentine hemorrhagic fever. Few people had ever heard of this virus until farmers began clearing the pampas to plant maize, thereby providing a bonanza for a little mouse called *Calomys musculinus*. Junin virus thrives in the mouse, and the mouse thrives on corn. So planting corn equals more mice equals more virus.

The list of worrisome viruses is already quite long. So is the list of questions virologists need to answer.

What, molecularly, accounts for the efficiency with which a virus spreads?

What makes some so much more virulent than others?

Take the AIDS virus—HIV or human immunodeficiency virus—as an example. For reasons that are not well understood, HIV is not easy to transmit, but it is lethal because it seeks out and infects T lymphocytes, which are critical for making immune responses. HIV gets into T lymphocytes by attaching itself to a protein on the cell surface, the CD4 receptor as it's called. The virus goes on to kill the cells, thereby depleting the AIDS victim's immune system.

But HIV is not the only "new" virus that enters cells bearing CD4 receptors. Human herpes virus 6 (HHV-6) infects such lymphocytes growing in laboratory cultures. The virus, which was identified only a few years ago by Robert Gallo's laboratory at the National Cancer Institute, appears to cause roseola, a common rash in children. However, it does not appear to cause serious disease and may be quite common.

The details of the relationship between HIV and HHV-6 have yet to be worked out, but the data so far point to an obvious question: Why is one virus lethal while another apparently is not?

People in the field have little trouble defining the questions they would like to ask in the coming decade. But policy and, as always, money—not science—will determine which ones will be pursued.

Donald Henderson of the Johns Hopkins School of Hygiene and Public Health has called for systematic surveillance of viruses worldwide. With technology such as the polymerase chain reaction or PCR technique that can identify organisms on the basis of the smallest pieces of DNA, such surveillance would be technically possible and epidemiologically invaluable. But it would also be tremendously expensive.

The challenge of emerging viruses is just beginning to make itself felt in Washington policy circles. Staff members at the congressional Office of Technology Assessment are following the issue, although no study is planned. However, the Institute of Medicine has developed a proposal to evaluate the problem and should know soon whether it will go ahead with it.

Meanwhile, Lederberg says he will continue to champion the cause, leaving it to history to determine whether he is a seer or an alarmist. "Never send to know for whom the bell tolls; it tolls for thee," he warns.

■ **BARBARA J. CULLITON**

*"Emerging Viruses: The Evolution of Viruses and Viral Diseases" was held in May 1989, sponsored by the Rockefeller University, the National Institute of Allergy and Infectious Diseases, and NIH's Fogarty International Center. Stephen Morse is currently preparing a review for publication.

Culver Pictures

Masked policemen. *Face masks, not vaccines, were the only protection against the deadly influenza virus that caused the 1918 flu pandemic.*

Influenza Mutants Deadly

It is easy to forget that influenza can kill. But in a typical year, the influenza A virus, which is now sweeping rapidly across the United States, causes 20,000 deaths in this country among the elderly and other particularly vulnerable people.

And some years are much, much worse. Every couple of decades, a strain of influenza A appears that is "new," genetically speaking, and capable of causing a great worldwide pandemic such as the one that killed 20 to 30 million people in 1918.

Flu viruses are well known for their ability to change in subtle ways from year to year. Virologists say that influenza A undergoes "genetic drift"—this year's virus is a minor variant of last year's as the result of an accumulation of a few random mutations. But in the major "genetic shifts" that occur every 20 years or so, the virus emerges with a brand-new form of a surface protein called hemagglutinin. This is caused by a reshuffling of the viral genes. The hemagglutinin protein is the major viral antigen that sets off an immune response in infected people. And since the gene reshuffling produces a form of the virus to which people have never been exposed, they have no natural immunity to it and a worldwide pandemic can ensue.

Recent observations of the life cycle of influenza A suggest that human beings inadvertently do a lot to permit a genetic shift to occur through a cycle that goes from birds to pigs to man.

Influenza A is an avian virus, resident in birds and waterfowl—particularly ducks. In China, from which the virus comes, farming practices create an ideal environment for the genetic rearrangements that cause genetic shifts. Ducks live in close proximity to pigs; so do farmers. Birds cannot transmit the influenza virus to people. But they can transmit it to pigs; and so can people. Thus the pig appears to be a "mixing vessel" in which genes from avian and human virus strains can be exchanged, creating a virus with a new antigen on its surface. A farmer picks up the new virus from the pigs and passage through the human population is begun.

In China and elsewhere in Asia where integrated or multianimal farming is encouraged on ecological grounds, virus-laden excrement from one animal is used as fertilizer for food for another. As these agricultural practices increase, so does the likelihood that new, potentially lethal influenza viruses will increase at the same time.

■ **B.J.C.**