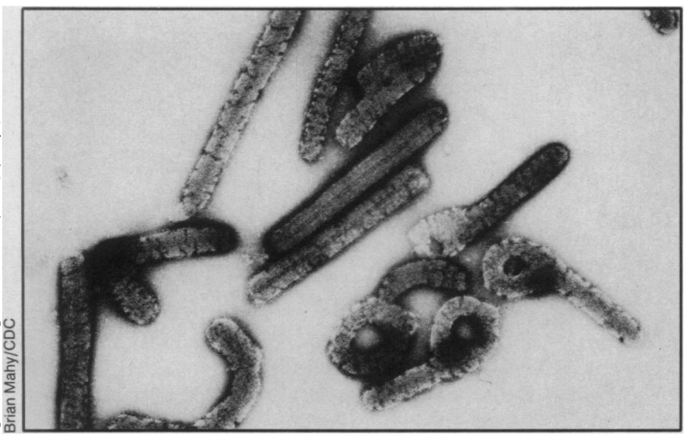
The VIRAL Advantage

A crowded world ensures prosperous futures for disease-causing viruses

By RICK WEISS

In 1983, a poultry virus hit the jackpot in Pennsylvania.

While making a copy of its genetic material, the virus made a tiny error. Because of that error, it began producing a slightly altered protein, which allowed the normally benign organism to spread beyond its usual residence in chicken lungs and intestines. Soon it was burrowing into other parts of the birds' bodies — including the nervous system, where it multiplied rapidly and began to cause disease.



Brian Mahy/CDC

Polio vaccine researchers in West Germany didn't know what hit them when they became infected with this previously unknown virus, now called Marburg, which had hitched a ride from Africa in monkey cells.

With its newly acquired virulence, this otherwise mild-mannered avian influenza virus went wild. And before the epidemic ended six months later, more than 17 million chickens were dead — all because of a minuscule molecular mutation.

"The [1983] chicken population in Pennsylvania is like the world as it is in this moment," says Robert G. Webster, a virologist and molecular biologist at St. Jude Children's Research Hospital in Memphis, Tenn. "What would we have done if this virus had occurred in humans? There are millions of us 'chickens' just waiting to be infected."

Such apprehension is not new to virologists. Indeed, the human influenza virus periodically undergoes mutations similar to the one that popped up in Pennsylvania. In 1918, for example, a particularly virulent mutant strain of human influenza spread around the globe, killing an estimated 20 million people.

More recently, the emergence in humans of a virus that probably once resided only in African monkeys caught the world off guard again. The AIDS virus has now infected 5 million to 10 million people in 149 countries, according to World Health Organization estimates. But despite all the attention drawn by this most recent plague, much more frightening things await us, many virologists fear.

Scientists know of several viruses lurking in the tropics that — with a little help from nature — could wreak far more loss of life than will likely result from the AIDS epidemic. Some virologists worry that a simple mutation in the AIDS virus itself could leave it armed with an ability to infect people as the flu virus does now — via respiratory droplets spread by coughing or sneezing. If the changed virus retained its current lethality, scientists and public health officials would have little chance to contain the disease before immense numbers of individuals became fatally infected.

Scenarios like these leave epidemiologists wondering whether modern science has made a serious enough commitment — or even has the means — to detect emerging viral threats before they reach their devastating potential. At a meeting in Washington, D.C., this past May, scientists discussed the long and continuing history of viral "end runs" around human defenses and suggested public health surveillance strategies that might provide some early warning before the next big viral outbreak.

Scientists hope that proper planning, including the use of scattered tropical laboratories as sensitive "listening posts" to detect newly emerging viral diseases, will enable them to nip the next Big One in the bud — be it a new strain of flu or a completely novel virus with no known history in humans.

Even with the best preparation, however, the battle against these ever-changing biologic specks will remain a seat-of-the-pants test of wits, virologists say. "There will be a few surprises," predicts Nobel laureate Joshua Lederberg, molecular geneticist and president of Rockefeller University in New York City. "Even our own fertile imagination can't match all the tricks nature can play."

To be sure, new viral diseases occasionally emerge after a natural mutation suddenly broadens a virus' host range or virulence. But more frequently, says Rockefeller University mi-

crobiologist Stephen S. Morse, viral emergences can be traced to *human* nature. "Most 'emerging' viruses are not really new but represent existing diseases that acquire new significance," he says. And often that new significance is of our own making.

For example, new viral epidemics have often followed human intrusion into previously inaccessible, virus-infested areas, and others will surely follow as highways infiltrate Earth's final frontiers. In return, viruses find their way into "virgin" human population centers – via insects, for instance, whose ranges gradually shift as global climate patterns change.

Additionally, says Morse, modern medical technologies such as transfusion and transplantation have provided viruses new means of transport between human hosts. So have a variety of social and behavioral changes, ranging from globetrotting among the rich and famous to needle sharing among drug addicts.

Still, viruses themselves remain responsible for many new viral outbreaks. And in this regard, as in the Pennsylvania chicken epidemic, mutation generally provides the key to their success.

"Their mutation frequency is enormous," says John J. Holland, a microbiologist at the University of California, San Diego. Holland says he and his colleagues were shocked when their latest experiments found that viral mutations occurred in about one of 10,000 replications – a value significantly higher than the already impressive ones other researchers have documented, and a full four orders of magnitude greater than that typically seen in human cells.

In particular, he notes, viruses that have RNA rather than DNA for genetic material make numerous errors during replication and appear to have none of the "proofreading" mechanisms that help DNA viruses eliminate such mistakes. In nature, such reproductive sloppiness amounts to a virtual guarantee that new and virulent infectious agents will appear with some degree of regularity and with little advance warning.

Fortunately for us, only rarely do mutations confer a substantial viral advantage. But one can hardly overestimate the significance of a single genetic blunder that provides, for example, a new viral coat capable of evading human immune cells.

The implications of such genetic unpredictability seem at times overwhelming, virologists say. For example, as AIDS researchers well know, it's very difficult to develop an effective vaccine against a virus that keeps changing its molecular "signature."

But things could get worse. So far, the sexually transmitted AIDS virus, HIV, "is a rather poor country cousin in terms of the slowness of its propagation and the obviousness of behavioral readjustments that would check its spread," says William H. McNeill, a University of Chicago historian and author of *Plagues & People* (1977, Doubleday). What if an error-prone HIV hit the genetic jackpot by suddenly gaining the ability to directly infect human respiratory-tract cells and spread via something as simple as a cough?

That scenario became the focus of a memorable exchange between two Nobel laureates at the Washington, D.C., meeting.

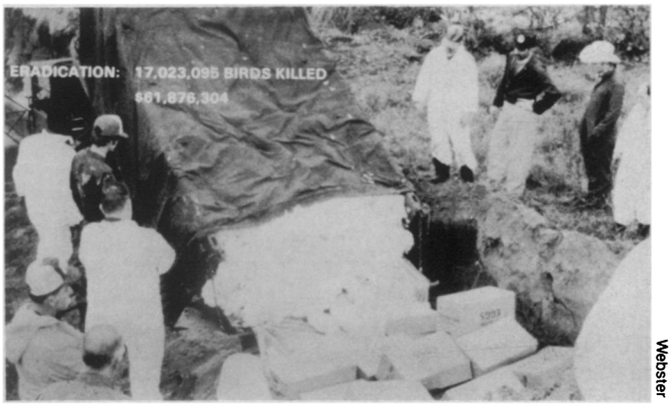
"I think that we can very confidently say that this can't happen," said Howard M. Temin of the University of Wisconsin, Madison. If HIV underwent all the necessary changes allowing it to infect through aerosolized droplets, he asserted, "then we might have a virus that could spread by a respiratory route, but it would no longer cause AIDS. So it would be worse in the sense that it might be more contagious, but it might just be another cold virus."

"I don't share your confidence about what can and cannot happen," Lederberg replied. Blood-borne HIV commonly infects macrophages, a kind of white blood cell often present in the lungs, he noted. Even a minor mutation might enable HIV to infect those cells directly via the respiratory tract.

Temin shook his head. Anything may happen in the future, he conceded, but "you don't have to stay up nights worrying about it."

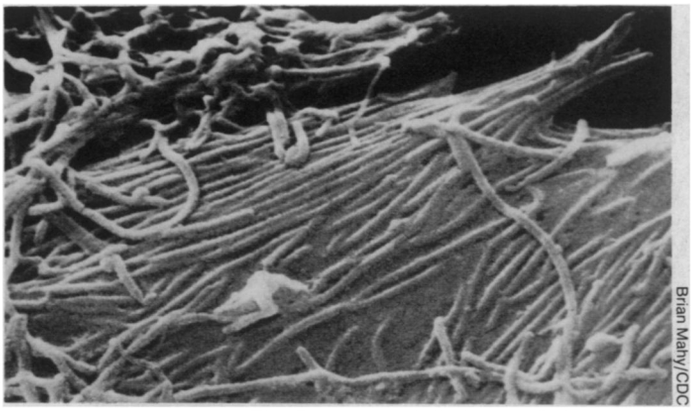
Replied Lederberg, somewhat ominously: "I'm glad I worry enough for both of us, Howard."

While the risk of a radical HIV mutation may appear fanciful to some, there's no denying the significance of existing viral menaces. Even if the world's viral inventory remains stable, researchers say, the tropics already harbor enough viral "fire power" to wipe out large segments of Earth's population. Indeed, despite the lack of U.S. front page coverage, recent history offers vivid examples of viral skirmishes in isolated areas that may foreshadow much broader outbreaks in the future.



Webster

Farmers dump a truckload of dead chickens into a mass grave during the 1983 avian influenza epidemic in Pennsylvania.



Brian Mahy/CDC

The Ebola virus killed many Belgian doctors and nurses treating Zairian and Sudanese patients in a 1976 outbreak.

In the late 1960s, for example, dozens of scientists in West Germany fell seriously ill, and several died, from a mysterious new disease. Victims suffered from a breakdown of liver function and a bizarre combination of bleeding and blood clots, among other symptoms. Investigators traced the outbreak to a batch of fresh monkey cells the scientists had used to grow polio viruses while producing vaccines. The cells, from imported Ugandan monkeys, were infected with a lethal tropical virus never described before – now called the Marburg virus.

In 1977, for reasons nobody fully understands, the virus causing Rift Valley fever moved from its usual hosts – sheep and cattle – into humans in South Africa. The virus, which causes severe weakness, incapacitating headache and damage to the retina, then made its way to Egypt, where millions became infected and thousands died.

Among the most frightening viral out-

breaks in recent years was that of the tropical Ebola virus in Zaire and Sudan in 1976. The Marburg-like disease, which infected more than 1,000 people and left about 500 dead, became concentrated in hospitals, where it killed many of the Belgian doctors and nurses treating infected patients.

"I can tell you we were holding our breaths there for a while," recalls Karl M. Johnson, a public health consultant at National Biosystems Inc. in Rockville, Md., who witnessed the emerging Ebola epidemic. With a mortality rate exceeding 90 percent and no clue to how it passed from person to person, "we thought we were looking at the Andromeda strain," Johnson says, referring to Michael Crichton's 1969 bestseller in which a mutant microorganism nearly destroys all human life on Earth.

Although these epidemics failed to "go global," they provide a humbling vision of humanity's viral vulnerability. Indeed, Johnson asserts, we might expect even bigger outbreaks in the future, since viral epidemics frequently have their roots in the "large and often still accelerating ecological changes brought by a burgeoning *Homo sapiens*."

For example, the 1977 Rift Valley fever epidemic in Egypt appears almost certainly the result of ecological changes associated with construction of the Aswan High Dam – perhaps through increased human contact with domesticated animals once the dam began to provide irrigation.

More recently, health officials linked a Nigerian outbreak of Lassa fever to the discovery of new diamond fields there. The "diamond rush" led to quasi-urban development in previously uninhabited lands that were home to a Lassa-virus-carrying mouse. Often fatal, Lassa fever causes severe muscle pains, body rashes, oral sores, bleeding ulcers and large-scale hair loss.

Other examples abound in which humans sowed the seeds of their own viral fates. When the Argentinian pampas fell to agriculture after World War II, the introduction of herbicides led to a newly dominant species of mouse that happened to carry the Junin virus, which causes Argentinian hemorrhagic fever in humans. Similarly, the 1952 Bolivian revolution led to agricultural changes that triggered a population explosion for a mouse species that harbored a viral hemorrhagic fever never before seen by scientists. Both the Bolivian and Argentinian hemorrhagic diseases resemble Lassa fever but involve additional neurological complications.

Closer to home, U.S. researchers this year revealed new evidence that rats infected with a potentially deadly Korean hemorrhagic virus have become prevalent in Baltimore alleys, where the virus appears to be taking a previously unrecognized toll on the urban poor (SN: 5/13/89, p.292).

History shows that life-threatening viral outbreaks have often followed when humans moved into unexplored terrain or when urban living conditions deteriorated in ways that invited new viral hosts, says Johnson. Unfortunately, he adds, "in each case, medical and scientific energy has been reactive, not proactive."

Could epidemiologists have predicted some of these outbreaks in advance? And if so, could they have prevented them or made them less severe?

"Realistic attempts to predict the probabilities of the timing and the nature of new virus emergences are unlikely in the near future," says Holland. But that doesn't mean we're defenseless, he adds. "In the absence of predictability, a modest effort toward surveillance and rapid response capability seems both feasible

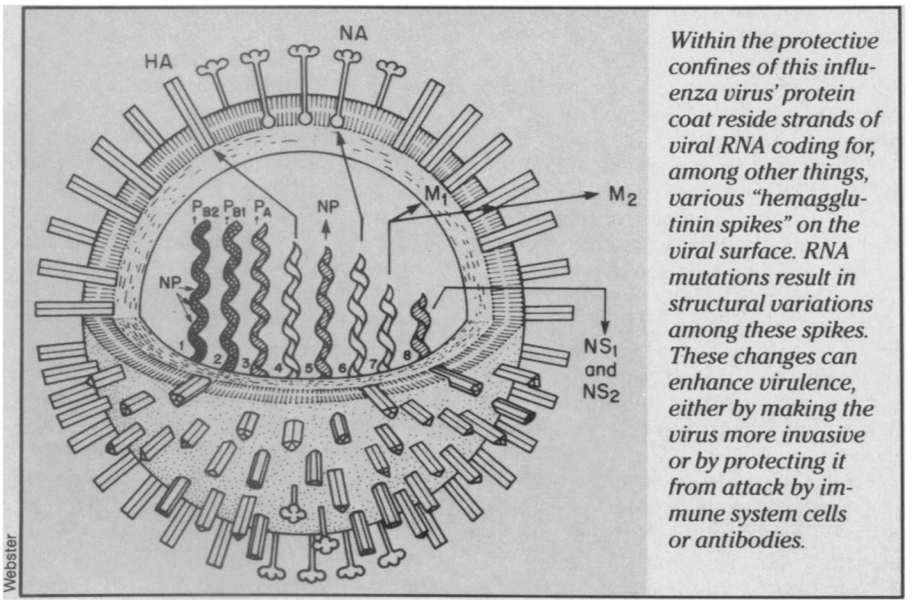
Hitching a ride with imported insects

Not all emerging viral diseases result from human intrusion into viral turf. Viruses, too, have ways of getting around – although even then, humans often provide the free transportation.

Perhaps the best example is one close to home, with its roots in the growing worldwide trade in used tires. In the years since World War II, the United States has imported millions of used tires for retreading. Many of these come from Asia – home of the mosquito *Aedes albopictus*, whose bite can inject the microbes responsible for yellow fever, dengue fever and other tropical diseases. In its native habitat, *A. albopictus* typically matures in rainwater that collects in tree stumps and other hollows. Lately, it has taken a liking to water-filled tires. And as shiploads of these tires have arrived in the United States, so has *A. albopictus*.

The mosquito, which can survive exposure to most commonly used pesticides, has now infiltrated 17 southern U.S. states and several regions of South and Central America. Although no *A. albopictus*-related epidemics have yet occurred in the United States, the immigrant mosquito brings with it the very real threat of a U.S. dengue fever outbreak, say officials from the Centers for Disease Control in Atlanta. This disease, and its more severe form called dengue hemorrhagic fever, already strikes about 100 million people each year through much of Asia and the Southern Hemisphere, where the mosquito is endemic. Mostly affecting children, the hemorrhagic fever can cause internal bleeding, shock and death. To date, all attempts to develop a dengue vaccine have failed.

Elsewhere, human-induced changes in insect ranges have already led to severe viral epidemics. In 1980, for example, Brazil's Amazon valley saw its worst outbreak of a recurring viral disease called Oropouche. While not fatal, the disease debilitates its victims for several days with severe nausea, muscle pains and in 5 to 10 percent of cases progresses to an inflammation of tissues around the brain. Health officials have linked the 1980 outbreak and other Oropouche epidemics to huge piles of cacao husks that have accumulated as the crop's cultivation there has increased. Filled with rainwater, the husks serve as breeding grounds for tiny insects, called midges, that spread the disease. – *R. Weiss*



Within the protective confines of this influenza virus' protein coat reside strands of viral RNA coding for, among other things, various "hemagglutinin spikes" on the viral surface. RNA mutations result in structural variations among these spikes. These changes can enhance virulence, either by making the virus more invasive or by protecting it from attack by immune system cells or antibodies.

and rational."

Unfortunately, new diseases occur most frequently in crowded, poverty-stricken, tropical lands – the areas where people are least prepared to identify and analyze viral trends, says epidemiologist Donald A. Henderson, dean of the Johns Hopkins University School of Hygiene and Public Health in Baltimore.

Moreover, says Robert E. Shope, a viral epidemiologist at the Yale University School of Medicine, tropical-disease programs and specialists are dwindling in number worldwide. In 1973, citing budgetary constraints, the National Institutes of Health closed the last of its laboratories for tropical virology. More recently, an important tropical-virus laboratory in Hawaii shut down. Now, Shope says, the U.S. military plans to close its tropical-disease lab in Kuala Lumpur, Malaysia, even though it has served as an "excellent listening post for new diseases."

Given current social and ecological trends, virologists say, this hardly seems the time to cut back on such programs. Rather, Shope and others recommend constructing sophisticated, on-site laboratories in key tropical areas and creating a global "red alert" reporting system among hospitals in high-risk areas. Shope suggests supplementing local labs with mobile units staffed by microbiologists, epidemiologists and entomologists who could investigate diseases on call.

Such a network could be surprisingly economical, says Henderson. For as little as $150 million a year, he calculates, a global consortium could finance 15 tropical medical centers and 10 U.S. research facilities, leaving $25 million for selected projects in epidemic areas.

There's little time to lose, warns historian McNeill. An expanding human population subject to urban overcrowding now provides an unprecedented opportunity for aspiring viruses. "If you look at the world from the point of view of a vigorous virus, or even a bacterium today, there's a magnificent feeding ground out there, with billions and billions of human bodies where 25 or 27 years ago there was half that."

He recalls what happened in the 1950s when a virus newly introduced to control the rabbit population went out of control in Australia. Ultimately, the rabbits evolved an ability to coexist with the virus, but not before 80 percent of them had fallen to the epidemic. "This seems to me a very exact model of what might happen to human populations exposed to a new and very lethal virus in the world today," McNeill says.

Moreover, "the idea that the medical profession could stand as an effective obstacle to the propagation of such an infection seems to me optimistic, to say the least." If our experience with previous outbreaks is any indication, McNeill says, "the doctors would be the first to go." □

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home. They describe how their children became cheerful, enthusiastic learners. But most of them say it takes a long time to heal completely, and that some scars remain.

This is biased and anecdotal evidence. But it would be very interesting to see some controlled investigations in this direction. That so many children are "growing up sad" is too tragic for us to leave any leaf unturned.

Elizabeth C. Hamill
Director
Northern California Homeschool Association
Berkeley, Calif.

Power conversion 'urgent'

"Where Acids Reign" (SN: 7/22/89, p.56) is the first report I have seen detailing the mechanism by which tree dieback occurs. Nitrogen compounds (interestingly, including ammonia) precipitate the sequence of events that weakens trees and eventually leads to forest loss.

The article indicates that the major U.S. sources of atmospheric nitrogen compounds are motor vehicles, fossil-fueled power plants and industrial furnaces. Thus it becomes particularly urgent that we follow the French example and convert to nuclear power as rapidly as is consistent with safe and prudent construction.

In addition, another look might be taken at the automotive pollution control tradeoff between higher-temperature burning that produces more nitrogen oxide and less carbon monoxide or lower-temperature burning that produces less nitrogen oxide and more carbon monoxide.

Further, a question arises as to whether pH or nitrogen compounds are the key parameter causing forest loss. Perhaps the resources spent to further decrease particulate matter and sulfur dioxide should be diverted to reduce nitrogen oxides and ammonia.

Lloyd McAulay
New York, N.Y.

Unconventional cay

Your report on the discovery of a Maya site on Ambergris Cay suggests there may be other sites on other coral islands of Belize ("Late Maya Culture Gets an Island Lift," SN: 7/8/89, p.20). This suggestion proceeds from a faulty premise. Ambergris Cay is not a typical coral island. It is my understanding that Ambergris is an island only by virtue of Spanish civil engineering: For military purposes during the colonial period, the Spanish excavated the channel that now separates Ambergris from the Yucatán. When the Maya lived on Ambergris, it was the southern tip of the Yucatán, not an island.

Jan Konigsberg
Helena, Mont.

Ambergris is indeed atypical, says Elizabeth Graham of the Royal Ontario Museum in Toronto, because it is connected to Yucatán by a narrow spit of land. Nonetheless, she asserts, modern-day residents of Belize travel to Ambergris in boats rather than by land, and the Maya probably did not use the sandy channel for transportation. Graham knows of no solid evidence that the Spanish created the cay. Furthermore, she says she and her co-workers have now uncovered evidence of Maya occupation on nearby cays. – B. Bower