SOCIETY OF ACTUARIES

Article from:

The Actuary

December 1989 – Volume 23, No. 11

The viral advantage

A crowded world ensures prosperous futures for disease-causing viruses

(Ed. note: This article is reprinted with permission from Science News, the weekly newsmagazine of science, copyright 1989 by Science Service, Inc.)

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.

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 microbiologist 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 globe-trotting 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 over-

Continued on page 5 column 1

Viral advantage cont'd

whelming, 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.

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 outbreaks 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

Continued on page 6 column 1

Viral advantage cont'd

of predictability, a modest effort toward surveillance and rapid response capability seems both feasible 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."

1989 Halmstad Prize and AERF Practitioners' Award announced

The Actuarial Education and Research Fund selected two papers to share the annual Halmstad Prize for the best English-language paper on actuarial research published in 1987. The first paper, "Assessing the Solvency and Financial Strength of a General Insurance Company," was written by the Working Party on Solvency of the General Insurance Study Group of the Institute of Actuaries. The article appeared in Volume 114 of the *Journal of the Institute of Actuaries.*

The second paper to share in the Halmstad Prize was "Classical Risk Theory in an Economic Environment" by F. Delbaen and J. Haezendonck. The article appeared in the publication *Insurance: Mathematics and Economics.* The exact reference for this and other papers nominated for the Halmstad appear at the end of this article.

The winner of the 1989 AERF Practitioners' Award is Alfred O. Weller, FCAS, for his paper on "Generalized Bondy Development." The purpose of this award is to acknowledge the considerable research done by actuaries in a nonacademic setting and to encourage the publication of research performed in the working environment. Weller's paper will be printed in the first 1989 edition of the *Actuarial Research Clearing House (ARCH).*

The following seven papers were selected as finalists for the Halmstad Prize. The two winners are included:

- Daykin, C.D., et al, "Assessing the Solvency and Financial Strength of a Great Insurance Company," *Journal of the Institute of Actuaries*, V. 114, Part 2, 1987.
- Daykin, C. D., et al, "The Solvency of a General Insurance Company in Terms of Emerging Costs," *ASTIN Bulletin*, V. 17, #1, 1987.
- Delbaen, F. and J. Haezendonck, "Classical Risk Theory in an Economic Environment," *Insurance & Mathematics*, V. 6, #2, 1987.
- Klugman, Stuart, "Credibility for Classification Ratemaking via the Hierarchal Normal Linear Model," *Proceedings of the Casualty Actuarial Society*, V. 74, 1987.
- Promislow, S. David, "Measurement of Equity," *Transactions of the Society of Actuaries*, V. 39, 1987.
- Wilkie, A. D., "An Option Pricing Approach to Bonus Policy," *Journal of the Institute of Actuaries*, V. 114, Part 1, 1987.
- Wilmot, G. E., and H. H. Panjer, "Difference Equation Approaches in Evaluation of Compound Distributions," *Insurance: Mathematics & Economics*, V. 6, #1, 1987.

In memoriam

James A. Attwood F.S.A. 1952
Henry E. Blagden F.S.A. 1930
Clarence R. Goodrich F.S.A. 1926
J. Rae Jamieson F.S.A. 1955
Sham S. Kataria *A.S.A. 1976
Loren G. Logan F.S.A. 1951
Julian M. Miller F.S.A. 1932
Stuart D. Nevermann A.S.A. 1988
Thomas E. Reinhardt A.S.A. 1964
R. Arthur Saunders F.S.A. 1937