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Can We Stop the Next Killer Flu?

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By Joel Achenbach

Scientists like Jeffery Taubenberger aren't just going to sit there waiting for a pandemic. They're gearing up for the war between bugs and humans.

ARMED FORCES INSTITUE OF PATHOLOGY

Dr. Jeffery Taubenberger examines DNA from 1918 Spanish flu lung samples.

Jeffery Taubenberger, virus hunter, goes to work in a bland building overlooking I-270 in Rockville. It's the Armed Forces Institute of Pathology, and it is scheduled to be "disestablished" as part of the broader plan to close military bases around the country. Taubenberger doesn't know for sure what he'll be doing in a year or so. For now, he's still walking past the fluttering flags every day, down a flight of steps to a windowless office, where he's trying to save the world from a mysterious germ.

Doom and Gloom Talk Will Be Limited to 30 Minutes Daily, reads a sign on his bookshelf. I ask if that's a reference to the avian flu. No, he says, that's about the base closings.

The office is small and cluttered, with multiple stacks of documents, suggesting a man who is struggling to impose order on an overly busy life. His phone keeps ringing — everyone wants a piece of him. You can't pick up a newspaper without seeing a story about the possible plague of avian flu, also known as bird flu or, to be scientifically correct, influenza A/H5N1. Millions could die, the stories say. Or tens of millions. Or hundreds of millions. Avian flu has reached a cultural and media tipping point, a kind of celebrity as the premier biological menace to civilization.

Avian flu is certainly a frightening virus. It kills birds, can infect human beings and has been lethal in about half of the documented cases so far in Asia and Indonesia. More than 60 people have died already. But so far it hasn't become easily transmissible from one human to another, unlike the common influenza virus that circulates every winter. Avian flu is still just that — a bird flu, not a human flu. Every article about this flu has a boilerplate paragraph, as if mandated by law, stating that scientists fear the virus will mutate, become highly contagious in humans, and create a pandemic that will rival the catastrophe of the Spanish influenza of 1918.

Taubenberger is doing his part to keep that from happening. He wants to understand the various types of flu viruses at the most essential level — tunneling deep into their genetic mysteries. What kind of mutation could turn avian flu into a pandemic pathogen? What genetic improvisations in these little nodules of RNA and protein — these things so small and spare they hardly deserve the grandiose label of "microbe" — can turn an ordinary flu into a cold-blooded killer?

He'll pause at some point to get a flu shot. "I'm susceptible to respiratory infections," he says. Taubenberger is something of an alpha nerd. Modest of stature, rather boyish at 44, quick of speech, he keeps on his desk a prop from his 10th-grade science fair project at Robert E. Lee High School in Springfield, the one that merited the grand prize for Fairfax County. It's a homemade model of the double helix, the structure of the DNA molecule. When discussing the genome of the flu virus, he will touch parts of the double helix and give a quick lecture on how life works: The adenine always binds to the thymine, the guanine to the cytosine . . .

The only flu in the room, as far as anyone can tell, is on a shelf. It's a stuffed, fuzzy influenza virus with plastic eyeballs, a joke flu from a company called Giant Microbes. It's just a blob. That's scientifically accurate, because flu virus has an unremarkable appearance.

CONTINUED ON PAGE 23

CONTINUED FROM PAGE 22

In an electron microscope, you see a knobby little ball.

The effects of flu are more dramatic. Taubenberger keeps autopsy samples of lung tissue from a soldier who died of the 1918 virus. These are thin sections of lung, cut and stained, and preserved in paraffin on a glass slide. He puts a slide under his microscope. First we look at healthy tissue: Clearly visible are the air sacs, ready to breathe, with a scattering of red blood cells. Then we look at diseased tissue. They're filled, completely choked, with little red circles. Blood cells.

"You don't see any open air sacs anywhere. They're all filled with blood. This person drowned in his own blood," Taubenberger says. "This is not good, to use a highly technical medical term."

The 1918 flu killed more people in a short period of time than any other plague in human history. Taubenberger and his scientific collaborators hope that the virus will serve as a Rosetta stone for understanding avian flu. They have literally rebuilt the 1918 virus and brought it back to life. Taubenberger has come to the conclusion that there was something very weird about this germ. It was a bird flu that jumped to humans, but the fine print of its genetic code is noticeably different from that of other bird flus.

As he works on the mystery, one thing is clear: This is a scientific drama that involves not only disease but also evolution, the process by which organisms mutate and adapt to changing conditions. And it's evolution in real time, at a frantic pace, happening as we speak, here at the start of the flu season. There is much debate these days about whether evolution explains life on Earth, but in the real world, on the ground, among living things, evolution is not only real — it's dangerous.

A Long War

Man vs. microbe is an old narrative. The plot's been twisting. A few decades ago, medical science sensed that it had the germs in full retreat. Antibiotics saved lives once lost to the most routine infections. It's hard to remember, but people used to die of strep throat, a small cut, a hacking cough gone bad. Vaccines turned the tide; germs stopped killing babies in their cribs; smallpox disappeared outright.

And then the tide turned back. Drug-resistant bacteria began flourishing. HIV became pandemic. Scientists began talking of "emerging" diseases. They come from the rain forest, from the dark recesses of tropical caves, from foul duck ponds and fetid chicken coops. They take advantage of a world of abundant human and animal meat. It would appear from the unfolding concern over avian flu, and from recent outbreaks of panic over other pathogens — SARS, for example — that civilization is increasingly vulnerable to pandemics, and that the human face of the future will be covered with a mask.

By overcrowding the planet, by ravaging our environment, by jetting promiscuously around the world with all manner of microbes in tow, by overprescribing antibiotics and helping breed superbugs, we've set ourselves up for a plague. That's the basic argument.

But here's another possibility: That we're at a turning point in the war between people and germs. That we've learned, just in the past half-century or so, how to read the code of life. That we've developed techniques, just in the past two decades, to discern the complete genetic code of an organism. That, just in the last few years, we've started to figure out the innermost secrets of microbes and what turns some of them into pathogens.

Jeffrey Gordon, who studies intestinal bacteria at Washington University in St. Louis, says: "We have the tools in the year 2005 to define the genetic evolution of a lot of these pathogens, particularly in the case of viruses like flu. It's a race between our society, our politics, our societal will and the viruses."

No one knows how the race will turn out, but the advantage at the moment is not necessarily on the side of the microbes. We're on to their game. Or, to use a more appropriate metaphor, we're not a bunch of sitting ducks.

The Secret of Life

Taubenberger became inspired in 1995 by a story of human eyeballs floating in a jar. They belonged to John Dalton, the pioneering chemist. Dalton died in 1844, but his eyeballs stuck around. He was colorblind, and he saw his defective vision as an experiment waiting to happen.

He hypothesized that a fluid in the eye (the vitreous humor) would, upon close examination, prove to be blue, filtering out the normal hues. He instructed his assistant to pluck out his eyes upon his death. After the great man died, the assistant examined one of the eyes and saw no blue fluid. He nicked the other one in the rear and looked through it — literally looked at the world through John Dalton's eye. The world appeared normal. The colorblindness was thus neurological, a problem rooted in Dalton's brain.

In 1995, researchers reported that they had taken the Dalton case a step further. Genetic testing — a relatively new analytical tool unthinkable in the day of Dalton — showed that he had an inherited colorblindness gene.

Taubenberger loved that. How very cool, he thought, to solve an old mystery through some aging tissue sitting in someone's lab. "Everything about life is interesting, when you start to get into the details of how things work," he says. Taubenberger, the head of the molecular pathology department at his institute, wondered: What could I do that would

CONTINUED ON PAGE 24

be really nifty, but also of significance to the world? A mentor once told him, "Work on an important problem."

He considered studying the yellow fever that killed so many people in the 1800s. But then he seized upon the Spanish influenza of 1918. It was wildly infectious, and virtually everyone on the planet was exposed. About 2.5 percent of those who became sick died, which seems like a modest level of lethality until you realize that it added up to more than 600,000 American deaths in just a matter of months and something like 40 million deaths worldwide. Taubenberger knew that the institute had millions of autopsy specimens from soldiers dating to the Civil War. If he could retrieve even a few genetic scraps of that virus, perhaps he could figure out why it was so contagious and virulent.

Ten years later, his project is still going, centered in the rather ordinary laboratory directly next to his office (he has collaborators in labs around the country). Taubenberger doesn't do a lot of bench work these days, what with giving interviews, taking meetings, trying to get things published, but he has assistants busily at work, filling tiny vials with fluids containing DNA, sequencing genes, tapping on computers, accessing databanks and doing all the highly detailed work of decoding the 1918 influenza virus. Taubenberger also has a new project in collaboration with the National Institutes of Health and a nearby genomics institute, to find the genetic codes of many thousands of different strains of viruses harvested from people and wild birds.

The overarching goal for both projects is to learn how these viruses evolve and which mutations might make them more or less likely to become adapted to humans and develop into potential killers. By removing from influenza some of its element of surprise, we might be able to forecast likely outbreaks, in the same way that we can forecast which tropical depression is going to turn into a hurricane. It's a sweeping plan, using all the hardware Taubenberger can round up.

If you take a left out of his lab, go through another lab (more vials, bottles, jars, tubes, refrigerators) and cross another hallway, you'll reach the room with the automated sequencers. There's a big one from Applied Biosystems, the 3132 Genetic Analyzer. Somehow, this thing can read the language of a genome, letter by letter.

Life on Earth operates on a genetic system that, at its core, is remarkably simple, considering that it gives rise to creatures as diverse as sea urchins, praying mantises and humans. The genome is written out on a very, very long molecule called deoxyribonucleic acid — DNA.

Molecular biology is to some extent the study of architecture. It's all about structure. Proteins — which do most of the heavy lifting in the body, such as building cells and tissues — have many ways of folding themselves in three dimensions. Their structure determines their function. They roam the body in search of a correctly shaped receptor. They just want to fit in somewhere.

When Francis Crick and James Watson rocked the scientific world in 1953, it wasn't by discovering DNA. Rather, they found the structure of the molecule, and proved that it was the source of genetic information. "We've found the secret of life," Crick exulted that winter day to friends at the Eagle pub in Cambridge, England, and the secret, it turned out, wasn't some special juice, some exotic energy source, but just a well-framed, two-stranded, ladderlike molecule with rungs in all the right places and a nifty ability to make copies of itself.

A gene is historically defined as a segment of DNA with instructions for making a single protein, though the one-gene, one-protein rule is pretty loose. Humans have upwards of 30,000 genes. The flu virus has just 11.

The code of a gene is written in the form of tiny chemicals called nucleotides, more commonly referred to as the "bases" or "letters" of the genome. Life uses a very short alphabet. There are only four bases used by living things: adenine, cytosine, guanine and thymine, or A, C, G and T.

DNA sequencing, the process of finding the order of the letters, isn't terribly new. As far back as 1977, Fred Sanger and colleagues managed to piece together all 5,386 letters of a tiny organism called phi-X174. In the mid-1980s, Kary Mullis developed a technique still used in Taubenberger's lab, called polymerase chain reaction, which amplifies pieces of DNA and makes them easier to study.

Automated sequencing machines came online only in the past decade or so. They're like reverse vending machines. You open a door, place a tray of DNA samples in a slot, watch it recede into the interior of the machine, and wait. Inside the machine, needles descend into the DNA vials and pull the fluid through a tiny glass tube, known as a fiber-optic capillary. The machine examines the thin stream of fluid with laser light; the nucleotides, the bases, go slipping through the laser beam one by one, guanines glowing differently from cytosines, and so on. Soon, the results flash on an adjacent computer screen: the letters. The code. The process is hardly push-button simple — the machines can examine only short segments of genes at one time, and scientists are often working with scraps to begin with. But it's definitely a scientific marvel.

"There's this kind of voodoo part," Taubenberger says. "Nothing you do can be seen. It's all invisible. It's all magic." But, he adds, in homage to the requirements of the scientific method, "it's reproducible magic."

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