THE NEXT GLOBAL PLAGUE

The possibiliity of an anthrax attack is frightening,
but that's not what keeps public health officials awake at night.

BY WILLIAM HOLDER '75

The death in September 2004 of an 11-year-old Thai girl never would have made international news if her mother and her aunt had not become ill, too. Only when the older women were diagnosed with the feared avian flu did Thai public health officials realize that the young girl, whose body had been quietly cremated, could have been the first case of a global pandemic—the sort that killed tens of millions of healthy people in 1918.

Dr. Scott Dowell '85, an expert on influenza at the U.S. Centers for Disease Control and Prevention, was ready. He and his team in Bangkok had been worried that avian flu, which already had a toehold in Southeast Asia, would start spreading from person to person. Until then, every documented case had arisen from individuals handling infected chickens.

On hearing the news that two women close to the young girl had also been infected, Dowell and the Thai public health team drove four hours to the hospital where the young girl had died. They ordered a full quarantine for the aunt, with whom the girl had been living, and protective equipment for hospital workers. The aunt received oseltamivir, an antiviral known to help infected individuals. She recovered. The girl's mother, who had stayed by her daughter's bedside, wasn't so lucky. She died while the aunt was being treated.

The bad news was that the mother, who had been living in Bangkok and had no contact with chickens, almost certainly had contracted avian flu directly from her daughter. But the good news, as Dowell and Thai public health officials soon discovered, was that their illness was genetically pure avian flu. The virus had not acquired strands of human flu DNA, which scientists believe is a prerequisite for the start of a pandemic.

Public health officials destroyed all the chickens in the village where the girl lived, and no further cases of human-to-human transmission have emerged. Dowell knows, however, that another case of human transmission could come at any time.

Southeast Asia is a breeding ground for emerging infectious diseases. It's now abundantly clear that illnesses such as avian flu or SARS can spring up, seemingly overnight, and assault defenseless populations. In this respect, emerging diseases can be viewed as the flip side of bioterrorism. The besieged human immune system doesn't know the difference between an attack from a naturally emerging infectious disease and one developed in a laboratory.

So far, nature has proved herself to be much more adept at genetically engineering new pathogens than humans. Could that change? A CIA report titled "The Darker Bioweapons Future" notes that biologists have already synthesized a key smallpox viral protein and shown its effectiveness in blocking the human immune response. Another team of biologists, sponsored by the Defense Department, recently created a polio virus from scratch, based on genetic sequencing information.

"Growing understanding of the complex biochemical pathways that underlie life processes," says the CIA report, "has the potential to enable a class of new, more virulent biological agents engineered to attack distinct biochemical pathways and elicit specific effects. The same science that may cure some of our worst diseases could be used to create the world's most frightening weapons."

International agreements such as the 1972 Biological Weapons and Toxins Convention have done little to deter foreign biological warfare programs, according to experts with the Defense Intelligence Agency. Writing in Biosecurity and Bioterrorism: Biodefense Strategy, Practice and Science, James Petro and his coauthors observe that in the former Soviet Union, research reached "new heights of sophistication" following ratification of the agreement (which has no provision for compliance checks). Soviet efforts included a massive program to make weaponized anthrax, which came to light when Russian authorities finally admitted that a cluster of deaths around Sverdlovsk in 1979 resulted from the accidental release into the atmosphere of anthrax.

Petro and his colleagues envision a future in which fields of transgenic plants indistinguishable from ordinary crops have been engineered to produce biotoxins, in which mosquitoes have been altered to produce toxins in their saliva,

and in which nanoparticles are designed to encapsulate biologically active organisms to enhance their capacity for storage and survival.

"The ultimate expression of this technology," they write, "would be development of a vector that encapsulates, protects, penetrates, and releases DNA-based biological weapons agents into target cells but is not recognized by the immune system. Such a 'stealth' agent would significantly challenge current medical countermeasure strategies."

The possibility that someone, somewhere will be able to modify microorganisms in terrifying new ways has moved a little closer into the realm of the conceivable because the technology behind genetic engineering has advanced so rapidly. Tasks that required highly skilled Ph.D.s only a few years ago can now be done by just about anyone with a few weeks of training at a community college. Experts wonder if humans might catch up with nature in the 21st century. In the wake of 9/11, the unthinkable has become thinkable.

Yet, for all the alarming prognostications, so far only nature has the proven ability to kill millions of people with microorganisms. Many experts believe that the greatest microbiological danger to human welfare comes not from bioterrorism, but from emerging diseases.

William Firshein is skeptical about

the threat of designer superbugs. Recently retired as professor of molecular biology and biochemistry at Wesleyan, he has been familiar with nature's more potent microbes ever since the Korean War when he studied anthrax at Fort Dietrick (then Camp Dietrick), the army's premier research facility for pathogenic organisms.

With characteristic assertiveness, Firshein says the difficulty of genetically engineering a bacteria or virus remains formidable, though not impossible. (Researchers in Australia caused a stir not long ago when they inadvertently modified a mousepox virus in way that made it much more deadly.) But why bother, he suggests, when nature has already done the work.

Take anthrax, for example, the first bacterium to be observed under a microscope. Scientists believe that anthrax was once a harmless soil organism. During the course of evolution, it acquired genes contained in plasmids—chunks of genetic material that microorganisms exchange as freely as party favors. This particular gift contained genes for manufacturing toxins, thereby transforming anthrax into a killer microbe.

Other microbes have acquired virulence in much the same way. Cholera, a marine organism, acquired genes for the cholera toxin through exchange of plasmids. E. coli: O157, made infamous by contaminated hamburgers, picked up toxin genes from another bacterium, shigella, which causes dysentery.

The ability to sequence genes rapidly has enabled scientists to trace the lineage of bacteria, according to Firshein. Altogether, more than 140 bacteria have been fully sequenced. In combination with bioinformatics, a powerful technique for examining thousands of genes at once to see which are active, scientists are making rapid progress in decoding the genetic mysteries of pathogenic organisms.

For all its lethality, anthrax has one shortcoming in the world of terror weapons: it's not contagious. "Anthrax is a good fear weapon, a weapon of mass hysteria, but it's not a good weapon for producing widespread casualties," says Firshein. "It's not as dangerous as smallpox, plague, or Ebola."

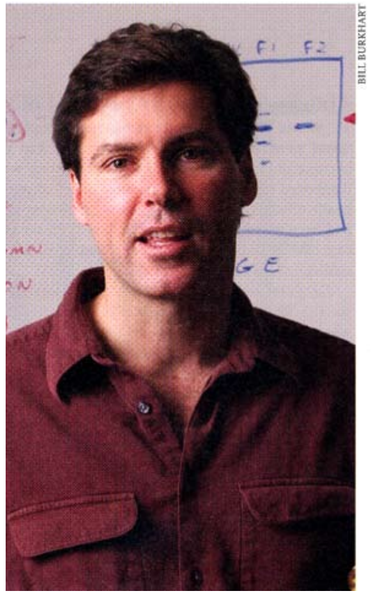
Firshein doubts that terrorists have the technical sophistication to work with the genes of dangerous pathogens, particularly viruses, which are far more difficult to grow and manipulate in laboratory settings than bacteria.

If rogue scientists ever do outstrip nature's ability to engineer pathogens, they will owe their success to the attribute of science most responsible for progress: the free exchange of information. The genes of many organisms, including bacteria and viruses, are available as digital files to anyone over the Internet.

Nonetheless, knowledge that could render harm has already conferred great benefit. Hepatitis B and C are pathogens that resisted development of conventional vaccines. Once researchers sequenced their genomes, they identified genes that led to the development of vaccines created through the tools of molecular biology. The vaccine for hepatitis B is used for the universal immunization of children, and clinical testing is proceeding on a vaccine for hepatitis C. The technique is known as reverse vaccinology and is being used to develop vaccines for streptococci, Chlamydiae, staphylococci, and potential bioterrorism agents such as Yersinia pestis (plague).

Politics and money influence

research into emerging diseases and bioterrorism, as Irwin Gelman '80 knows well. Introduced to pathogenicity as an honors thesis student with Firshein, Gelman is a researcher at Roswell Park Cancer Institute. It is a sprawling complex of buildings in a rundown section of Buffalo, where he recently moved from a faculty position at Mount Sinai School of Medicine. After pursuing research into hantaviruses, the cause of a mysterious and lethal outbreak of pulmonary infection in the Four Corners area of New Mexico during the 1980s, he turned his attention to HIV.


BILL BURKHART

Wesleyan molecular biologist Michael McAlear says that nature is much more skilled than scientists at creating new and sometimes deadly variants of bacteria and viruses.

Because the HIV virus mutates so readily, scientists became concerned that tests for HIV that rely on identification of specific DNA sequences might fail to detect new variations of the virus. Using techniques they had developed with hantaviruses, Gelman and his colleagues developed a test that would identify every member of the HIV family, including animal variants, regardless of mutations. Successful, they published and patented their work. Then they sent out letters to clinicians around the country, seeking patients who exhibited AIDS syndrome but did not test positive for HIV.

"In the late '80s, we were stepping on a land mine," he relates. "Whether HIV was the cause of AIDS was still highly provocative given arguments that it was a lifestyle disease. We weren't trying to dismiss HIV as the cause. We were trying to say that HIV was a more diverse group of viruses than had been recognized."

The result of their work was a scientific success and a public relations disaster. They published a paper in The Lancet claiming to have discovered a variant of HIV1, the principal cause of AIDS. One of their collaborators, however, talked to the popular press, and in no time headlines appeared announcing the discovery of HIV3. An uproar ensued. The Centers for Disease Control intervened, arguing that the claim for an HIV3 was nonsense. The researchers applied for NIH funding but were turned down.

"I learned how difficult it is to be a Paul Revere where infectious disease is involved," Gelman says. "Eventually, we were proven one hundred percent correct. There is now a subgroup of AIDS classified as outliers, which aren't identified by standard tests."

Obtaining funding to study the emerging disease of AIDS was difficult enough when thousands were dying in this country and abroad; finding funds for the study of bioterrorism agents such as anthrax or smallpox was nearly out of the question. Only a handful of academic researchers were active in the area, according to Gelman. At Mount Sinai, the faculty didn't teach a single class in the microbiology of possible bioterror agents.

Then came 9/11 and the subsequent anthrax attacks. The sight of a white powder on a newspaper at Mount Sinai led to a full alert with police, troops, and a shutdown (it was sugar from a doughnut). The faculty put together a course on bioterrorism agents and illnesses. Nationally, funding for research increased exponentially to $1.5 billion a year.

In July 2004 Congress approved Project Bioshield, which allocates $5.6 billion over 10 years to biodefense. This infusion of money has not come without controversy. On Feb. 28 of this year, more than 700 scientists sent a petition to the director of the National Institutes of Health, arguing that the government is erring by shifting funds away from the pathogens that cause major public health problems, such as tuberculosis and syphilis, toward obscure microbes that might be used in a bioterrorist attack. The petition, according to the New York Times, claims that funding for research on anthrax and five other rare diseases has increased fifteenfold since 2001, while support of research in areas more critical to public health has declined.

The dispute pits many of the nation's top microbiologists against the government over the proper focus of biodefense spending. Dr. Anthony S. Fauci, director of the National Institute of Allergy and Infectious Diseases, which controls about 95 percent of NIH biodefense spending, argued that biodefense research will benefit public health efforts to protect against natural emerging diseases. Acknowledging that a flu pandemic would pose a more serious threat than bioterrorism, Fauci maintained that NIH funds for biodefense would support influenza research as well.

Michael McAlear, associate professor of molecular biology and biochemistry at Wesleyan, doubts that terrorists would turn to molecular biology in hopes of developing a novel weapon. Engineering superbugs remains a largely hypothetical and difficult task to accomplish in the lab, even though he points out that some nasty tricks could be performed fairly easily, including developing a strain of anthrax resistant to Cipro, the antibiotic approved to treat inhaled anthrax.

"I think emerging diseases are a bigger health threat," he adds. "Nature is so sophisticated and is always throwing out variants of bacteria and viruses. Anthrax would be bad news, but the unknown is more of a threat than the known."

The Prion Puzzle

Emerging infections can be insidiously difficult to identify, and mad cow disease is a case in point, says Michael McAlear, associate professor of molecular biology and biochemistry.

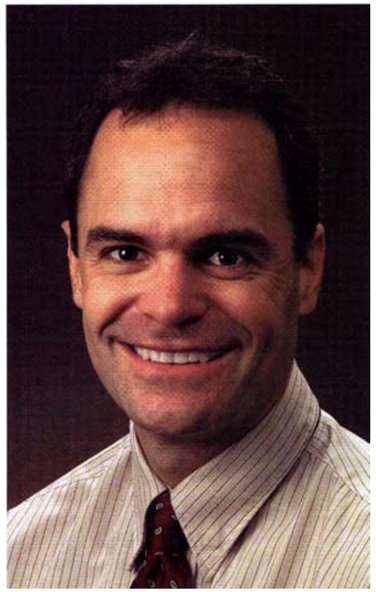
In the 1700s, sheep began dying from an unknown illness called scrapie, one symptom of which was that they rubbed up against posts, wearing off their skin.

In the 1920s, doctors in Germany identified a rare but fatal human disease that opened holes in the brain. It was named Creutzfeld-Jacob Disease after the discovering doctors, but the cause remained undiagnosed.

In the 1950s, physicians observed that individuals in an isolated New Guinea tribe developed neurological problems after cannibalizing deceased relatives. A researcher in London who saw an exhibit about this tribe connected the problem to Creutzfeld-Jacob disease, but another 20 years would pass before scientists finally pinned down the cause.

The answer that linked all of these incidents was met first with disbelief, then with astonishment. Transmissible spongiform encephalopathy—the class encompassing scrapie, Creutzfeld-Jacob disease, and the more recent manifestation of mad cow disease—is caused not by a virus nor by a bacteria, but by a protein that occurs naturally in the brain. Stanley Prusiner, a Nobel-winning neurologist at U.C. San Francisco, identified the cause in 1982 as a protein, called a prion, which causes diseases merely by folding into the wrong shape. As the mass of misshapen prions grow, holes appear in the brain along with fibrous plaques resembling those in Alzheimer's disease.

"This was just brand new for science," says McAlear. "It didn't fit the paradigm and took a long time to figure out."



Scott Dowell '85, M.D., an expert on influence with the CDC, is stationed in Bangkok on the front line of emerging diseases.

Who would have guessed, he suggests, that within five years West Nile virus would have spread from a few cases in the New York area to become endemic throughout the United States and Canada.

Influenza is a perfect example of nature's wiles. Its genetic material (RNA, specifically) is organized into eight segments that, like plasmids, can be exchanged. So chicken influenza and pig influenza could trade large chunks of genetic material, like shuffling cards, and produce an entirely new variant that might not infect humans at all or might be deadly.

The latter prospect terrifies public health officials. At a meeting last month in Vietnam, an official from the World Health Organization contended that the world is now in "the gravest danger of a pandemic." No one has immunity to avian flu, and absent a vaccine, the world health community is unprepared for an onslaught. Although the virus has killed only 42 people so far, that represents three-quarters of known avian-flu infections in humans—an alarmingly high mortality rate. Avian flu has already killed hundreds of millions of animals in Asia and has affected a more diverse group of animals than any other type of flu, ranging from blue pheasants to clouded leopards, pigs, and tigers. When Tommy Thompson announced his resignation as Health and Human Services Secretary in the Bush administration, he cited avian flu as one of the greatest health dangers facing the United States.

In so many respects, molecular

biology has revolutionized the study of pathogens. Scientists can take a single strand of DNA, multiply it a millionfold in the lab and identify it, sometimes within less than an hour. They can sequence the DNA bases quickly and compare the laboratory findings to vast electronic databases of genetic sequences to look for matches. That's how investigators determined that West Nile virus arrived in New York from Israel in 1997 and how Scott Dowell learned so quickly that the virus that killed the Thai girl and her mother was genetically pure avian flu.

For all the power of new techniques, however, emerging diseases still have secrets that are hard to unlock. Vaccines are often elusive. They have to meet a high standard of safety and effectiveness in the incredibly complex human immune system. Years of research have yet to yield an HIV vaccine, and no vaccine exists for one of the newest of emerging diseases, the SARS virus. The natural host of Ebola, one of the most deadly and feared of all viruses, remains a mystery. Identifying the cause of mad cow disease required 20 years of research before scientists found the culprit: neither a virus nor a bacteria but a protein that produced havoc merely by changing its shape.

The CDC recognized the threat posed by emerging diseases when it sent Dowell to Thailand to establish the first CDC program of its kind for controlling emerging infections in a developing country. He was present in March of 2003 when SARS, not yet named, broke out of China, where officials initially suppressed information that a killer was in their midst. That experience was personal. His colleague, Carlo Urbani, a World Health Organization physician stationed in Hanoi, came to Bangkok feverish. In two weeks he was dead of SARS. Dowell and others saw from behind the window of a hospital isolation room the virulence of this then-mysterious disease.

In a remarkably short time, scientists identified SARS as a novel variant of the common Corona virus. Once again, nature had jumbled genes and handed humans a deadly surprise. Politics and money are at work here as well. Only four small outbreaks have occurred since SARS spread like wildfire in 2003, and three of those were the result of labs failing to contain the virus. In the absence of wider outbreaks, there is no market for therapeutics and companies are reluctant to invest resources. To this day, the only effective response is quarantine.

Would a quarantine work if avian flu acquires human influenza genes and starts to spread from person to person? Dowell is not sure; influenza moves much more rapidly through a population than SARS.

"The SARS outbreak highlighted for us that even a highly dangerous and readily transmissible pathogen could be contained with traditional quarantine if you can identify it quickly enough and if the global health community can move quickly enough to contain hot spots," he says. "For a number of reasons avian influenza would be more challenging. Yet it's certainly worth a try."

Given nature's skill at concocting emerging diseases, Dowell probably will get his chance.

Do you have an opinion about this topic? Please write us at letters@wesleyan.edu.

Irwin Gelman '80 at the Roswell Cancer Institute in Buffalo knows firsthand how politics and the media mix with science over volatile issues related to bioterror and emerging diseases.

Studying Microbes for 47 years

Faculty members hold office

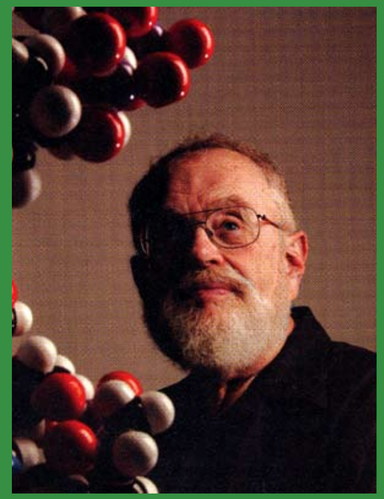
hours for students, but William Firshein, just retired as professor of molecular biology and biochemistry, holds them for his colleagues. After an early morning run, he's at the office by 7:45 a.m. By mid-morning, he's ready to receive whoever stops by.

Firshein will "talk science, offer advice, console you if the world has hurt or harassed you, or give you an earful, on politics or life," said Don Oliver, professor of molecular biology and biochemistry. Speaking at a retirement gala for his colleague, Oliver told an audience of 250 people, "Bill has learned those hard lessons: about limitations, growing up and growing old, losing loved ones, and yes, paying too many taxes, and everything we humans face. He has reflected on what they mean, and he is willing to help you in the finest mentoring tradition of Wesleyan."

Firshein has been an animating presence on campus for 47 years. He's taught more than 8,000 students, among them 12 doctoral candidates. More than 100 undergraduates have worked with him on research projects, and 25 have co-authored papers with him. He has raised approximately $3 million in external grant funds. Lately, as public attention has focused on the capacity of microorganisms to inflict harm, he has taught courses on emerging diseases and bioterrorism.

He has retired with the longest tenure of anyone on the faculty. During his 47 years at Wesleyan, he has seen the technology of teaching change greatly as textbooks have improved and classrooms have been equipped with computer and video technologies.

"Nevertheless," he says, "my own experience with thousands of students has not changed—namely, that I connect to them best and they to me when I 'stand and deliver' by lecturing. The moment of recognition of some concepts by students after I have sweated mightily to explain is still awe-inspiring.



"In 1958, we were at the beginning of understanding the nature of the gene, how genes control cell functions, how a cell is organized and divides, how the macromolecules in the cell are synthesized and organized, how organisms develop, how pathogens cause diseases, how the immune system works, how the brain works, how cancer is induced, etc. Advances in three basic fields have enabled life scientists to reach today's rarefied heights: molecular biology, genetics, and biochemistry (plus one interdisciplinary field, biophysics). And yet, none of us today can adequately cover these fields by ourselves. We have learned to divide our courses into parts, with faculty having expertise in one field sharing the teaching. In order to understand our own disciplines and teach them effectively, however, we must be aware of knowledge in all of these fields. Thus, the interchanges among faculty (and students) in team-taught courses have helped us all.

"I wish sometimes I could be around in years to come to see how all of this turns out. These are exhilarating times for life scientists."