a single microbial

BOTH: PHOTODISC

sea

By Doug McInnis

Many of the great contagions of history still ravaged the globe's human inhabitants well into the 20th century. Smallpox killed millions each year. The 1918 flu epidemic left tens of millions dead.

Anyone, anywhere could be struck down. Wilbur Wright perished of typhoid nine years after he made aviation history at Kitty Hawk. Franklin Roosevelt, struck by polio in his late thirties, spent his presidency in a wheelchair. Tuberculosis (TB) killed residents of crowded cities and rural retreats alike. In 1901, if you had gathered 100 New Hampshire residents in a room, one of them, on average, could expect to die of tuberculosis within five years and 10 would be dead of TB before 1950.

Yet by 1975, dramatic advances in medicine had made typhoid, polio, and tuberculosis increasingly rare. Even smallpox, which had killed more than 300 million people in the previous 100 years, was close to being eradicated, thanks to a global campaign mounted by the World Health Organization. Vaccines, antibiotics, and improved public health strategies had worked: the age of infectious disease seemed near its end, at least for the planet's prosperous nations.

Then came AIDS.

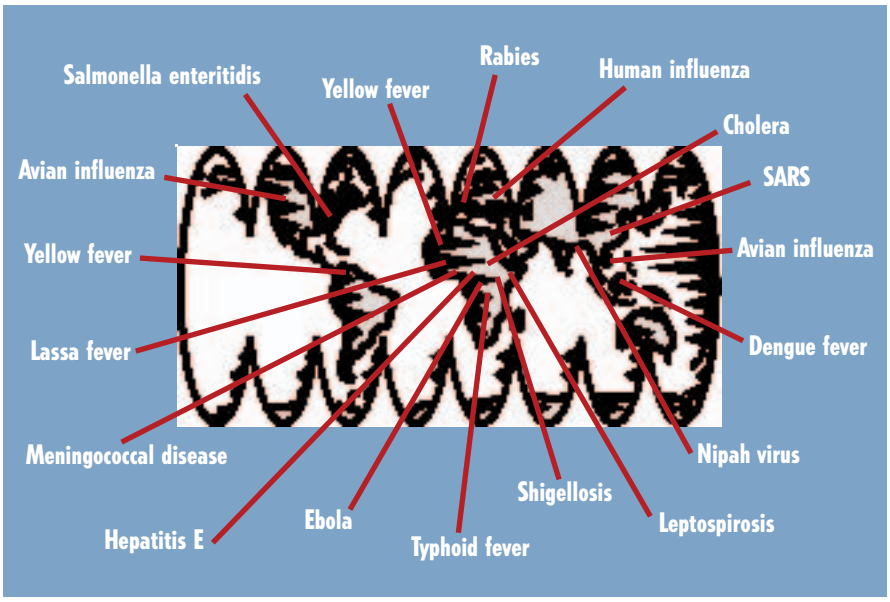
AIDS was the vanguard of a new group of emerging diseases that also now includes SARS, mad cow, avian influenza, and Ebola. These contagions joined antibiotic-resistant strains of tuberculosis and West Nile virus as increasingly worrisome threats to Europe and North America. Once, such diseases would likely have remained isolated in remote, undeveloped nations. But no place on Earth is remote in this age of global commerce and tourism.

"The one that brought this home to everybody was SARS," says Susan Dentzer, a 1977 Dartmouth College alumna who tracks global disease as the health correspondent for the PBS *NewsHour with Jim Lehrer*. "Even though it was highly localized in a few countries, there were nonetheless enough people who traveled from these countries that

Once upon a time, the developed world thought infectious diseases had been more or less wiped out by vaccines and antibiotics. But today we're battling AIDS and SARS and bird flu. And tomorrow we may be contending with contagions as yet unknown. What happened? And, more to the point, what can we do about it?

McInnis is a freelance writer based in Casper, Wyo., who specializes in science, agriculture, and business. His work has appeared in publications ranging from the New York Times *to the* Corn and Soybean Digest, *from* Harvard Magazine *to the alumni magazine of Oberlin College, his alma mater.*

What do Singapore's harbor (above) and Sao Paulo's skyline (left) have to do with infectious diseases in the U.S.? Everything, say experts at Dartmouth and elsewhere—global trade, travel, and urbanization have changed the way we must look at contagions.



In 2004, the World Health Organization reported outbreaks of these infectious diseases. The diagram above shows the main regions where they occurred.

"When AIDS came along," says senior associate dean David Nierenberg, "it took doctors with the spirit of inquisitiveness to discover something they hadn't seen before. The greatest challenges are the diseases that exist that we don't know about."

[there was] a serious impact on Canada. It was a miracle that nobody died in the U.S.

"The universal view of epidemiologists is that you can expect more outbreaks of new foreign diseases—it's only a matter of time," adds Dentzer, who is also a longtime member of Dartmouth Medical School's Board of Overseers.

"AIDS and SARS are prime examples of the fact that infectious disease is really a global phenomenon," agrees Fordham von Reyn, M.D., chief of infectious disease at Dartmouth-Hitchcock Medical Center. "This has a number of implications—first and foremost that control or even eradication of infectious diseases is now a global issue, not a local issue. Here at DHMC, we frequently see patients who've picked up diseases overseas. We see malaria, ulcerative skin disease, and numerous gastrointestinal infections. We also treat a number of people who acquired HIV in their country of origin.

"Global disease will be a constant threat," he maintains. "Microbes have the ability to develop resistance. New ones develop as the old ones are eradicated."

That all this poses a challenge for doctors and public-health experts goes without saying. But it also poses a conundrum for medical schools: How do you train medical students to recognize and treat diseases that don't yet exist? The short answer is that no medical school can do this, but they can train students to respond to the unexpected.

"We're stretching our students' skills for searching for answers to things that don't make sense," explains David Nierenberg, M.D., DMS's senior associate dean for medical education. "After all, when AIDS came along, it took doctors with the spirit of inquisitiveness to discover something they hadn't seen before. The greatest challenges are the diseases that exist that we don't know about. We encourage our students to read about them after they are discovered, or even discover them themselves." In fact, a graduate of DMS made a seminal contribution to the recognition of AIDS: the first report of a cluster of seemingly unexplained opportunistic infections in gay men in San Francisco came from Andrew Saxon, M.D., a 1970 graduate of Dartmouth Medical School.

Perhaps the great challenge is to control the rapid spread of diseases without shutting down the world's trade-based economy, which increasingly relies on air travel. "If you stopped air travel, it would stop the world's economy, which would lead to political instability, which can lead to disease," explains Paul Batalden, M.D., director of the leadership preventive medicine program at DMS. Such a drastic step, he states, "is not an option."

At one time, North America's location—separated from Europe and Asia by two great oceans—usually provided a sufficient margin of safety. "In the past, the length of travel long exceeded the incubation periods for many infectious diseases," points out John Modlin, M.D., the chair of pediatrics at DMS and former head of the federal Advisory Committee on Immunization Practices. Those who were infected often either died aboard ship or were so obviously sick by the time they got here that they could be quarantined before entering the general population. "That's no longer the case with air travel," Modlin says.

"There are more than two million people crossing international borders every single day," explains Nils Daulaire, M.D., a DMS Overseer who used to be a member of the faculty and is now the president of the Global Health Council, a worldwide advocacy group for health initiatives. "It's no longer a hermetically sealed world."

One way to understand the problem is to look at the explosion of computer viruses. New Internet viruses originate all over the globe. They can zip through cyberspace and infect millions of computers before anyone even figures out what they are or how to "treat" them. Like their biological counterparts, computer viruses spread by finding new "bodies" to infect; all they have to do is slip into a computer's address book and harvest a new batch of e-mail addresses. And also like their biological counterparts, they are a product of globalization.

One has only to look at relations between the United States and China to see how globalization has changed the world. President Nixon's 1972 visit to China shattered the bamboo curtain that had effectively separated East from West. His diplomatic overtures led to a renewal of trade with China. Two-way commerce between the U.S. and China totaled $12 billion in 1990 and more than $175 billion by 2003—most of it in the form of Chinese goods headed west. Furniture, toys, pots and pans, consumer electronics, clothes, and artificial flowers are among the myriad items in U.S. stores that are stamped "Made in China."

This flow of goods is made possible by human contact—at West Coast docks, at hotels, at airports, and at trade conferences. Each contact brings the risk of transmitting a new disease such as SARS or the latest variation of influenza, which, like many of the new diseases, often jumps species from animals to humans.

Global travel leading to the spread of disease is not a new phenomenon. To cite just one example from the past, the native populations of the Americas were decimated by the arrival of European diseases to which they had no immunity. But the scope of the problem has been magnified by air travel. There are now more than 500 million international border crossings each year by air. And jets make it easy for business travelers and tourists to get to places they'd never have visited in the past. Rain forest tourism, for example, may expose travelers to new, unknown organisms spawned in the fertile DNA-mixing factories of those hot, moist environments. AIDS is believed to have originated in Africa's rain forests; in another era, it might have remained there.

Similarly, say some experts, West Nile virus once caused a relatively mild disease and was found only in Africa. Then it jumped to the Middle East and Europe, and by the time it got to the U.S. it had become a powerful pathogen that has debilitated many of its victims and killed others.

The speed and scope of travel in the 21st century mean the U.S. (or any other country, for that matter) may get an outbreak under control one day, only to have new cases deplane the next day. And travel is just one factor. Three others are at work, according to D.A. Henderson, M.D., M.P.H., who headed the World Health Organization's successful drive to wipe out smallpox. They are urbanization, the internationalization of the world's food supply, and the increasing number of hospitals in developing countries.

"In 1955, there were two cities with populations greater than five million—New York and London," he says. "The number of urban areas with more than 15 million people now numbers more than 15. Many of these are in developing countries, where nutrition is poor, sanitation is poor, and there are minimal health resources. So if an organism mutates to become more lethal and more contagious, it can really get a foothold and spread rapidly.

PHOTODISC

Global tourism (right) means disease anywhere can travel to anyone. Dartmouth's Ford von Reyn (above, far right) helps open an AIDS clinic in Tanzania.

"The quantities of food coming from abroad are prodigious," he continues. "And that food may carry the same pathogens as if you had bought it in, say, Indonesia. I tell people you don't have to travel to get these diseases. You can get them right at home."

It's ironic that the growth in the number of Third World hospitals has worsened the problem of global disease transmission. Henderson says that's because hospitals in resource-poor nations lack essential equipment, so syringes and needles are routinely reused. "It's reasonable to think HIV was spread by this practice," he adds.

Many Americans still think of AIDS as a disease that afflicts gay men. They may also think of it as a disease that has put the U.S. health system under financial stress. But the biggest threat of AIDS is that it is destabilizing large sectors of the developing world, particularly sub-Saharan Africa, where the disease is spread in part through heterosexual prostitution and regional trade. A Rand Corporation examination of globalization and disease cites studies that tracked the spread of AIDS along African trucking routes. A sampling of 68 truck drivers and their assistants found that more than a third were HIV-positive. The disease then spreads from trucking routes to nearby settlements. As in-

"Control or even eradication of infectious diseases is now a global issue, not a local issue," says Ford von Reyn, chief of infectious disease at DHMC. "Microbes have the ability to develop resistance. New ones develop as the old ones are eradicated."

Dartmouth expertise is advancing two approaches to a tough problem

Infectious diseases don't yield to easy solutions because both the players and the playing field are constantly changing. Globalization has tilted the playing field, at least temporarily, in favor of the pathogens. That's because our opponents have the ability to constantly change "uniforms" by mutating.

Even so, infectious-disease specialists know there are things that can be done. There are two approaches. One uses incremental change—new vaccines or new public-health strategies, for instance. These methods have quelled some of nature's worst killers, most notably smallpox. The other approach looks at the world as an interconnected whole and attempts to formulate a big-picture strategy. Both are being advanced at Dartmouth.

The incremental approach

A traditional tactic is to take a single problem related to a single disease and try to solve it. When the disease is AIDS, the potential payoff is enormous. Scientists know HIV does its damage in part by unhinging bits of the immune system. That leaves sufferers open to a wide variety of illnesses that can infect them and ultimately kill them.

"We want to be able to buy strawberries in New York in January," says DMS's Sharon McDonnell.

Tuberculosis (TB) is among the worst of these opportunistic killers. That's because the virus that causes AIDS attacks cells in the immune system that are critical to controlling TB, says Fordham von Reyn, M.D., chief of infectious disease at DHMC. This makes anyone infected with HIV far more likely to develop TB. Von Reyn is the principal investigator of a four-year study of the efficacy of a tuberculosis vaccine booster for HIV-positive individuals. The vaccine, now being tested in Tanzania, is designed to supplement the TB vaccines that are routinely given to African children and add an additional layer of protection for the huge number of HIV-infected Africans.

The production of flu vaccines is another arena where new strategies are being sought. "We need a different system," says John Modlin, M.D., former chair of the federal Advisory Committee on Immunization Practices and DMS's chair of pediatrics. "I'm not sure I have the answer. But what is likely to be required is a high degree of public-private partnership, which offers incentives to bring private vaccine manufacturers into the marketplace. Since vaccines are much more expensive to produce than drugs, there isn't a strong incentive to make vaccines. Many, if not most, of the vaccine makers have dropped out of the market."

Imported foods are another source of disease. Public-health specialists say this problem can be mitigated by watching—or washing very well—what we eat, particularly fruits and vegetables. Some imported fruits, for example, carry parasites that can produce severe gastrointestinal illness in people with compromised immune systems, according to Sharon McDonnell, M.D., M.P.H., an adjunct associate professor of community and family medicine at DMS and an instructor in the School's M.P.H. program. "Imports are how we get much of our fruit in the off-season," she says. "We want to be able to buy strawberries in New York in January. But we have certain expectations of how food will be handled. Those expectations may not be met with imported food."

The systems approach

The other approach to global disease is systems thinking, which looks at the whole picture, not just its component parts. Paul Batalden, M.D., the resident systems thinker at DMS, explains that humans "are a fundamental force in nature. We are one of the reasons for globalization and disease. Therefore, if we are part of the problem, we have to change what we're doing. You can't keep doing what you're doing and muck your way through. But if you begin by understanding that we're all part of the problem, you begin to see options that you haven't seen before.

"The temptation is to say some single answer will solve the problem, but that won't work. We must continually change what we're doing. You have to recognize that as you take steps to deal with global disease, the disease organisms are interacting with the steps you're taking. It's part of living systems that they morph; bugs have the capacity to change." To deal with mutations, Batalden suggests we think like a member of a jazz quartet, where successful improvisation requires that all the players work together. "A good jazz player knows how he will sound in conjunction with the other members. And he has to listen very carefully to what they are doing."

Batalden says we also need to delve deeply enough to avoid solutions that may at first glance look appealing but that will ultimately fail. So in the case of globalization and disease, we can't shut down air travel, he says. But there are other options. "What if we made an investment in the vitality of our population by keeping people healthier? If they were healthier, they would be less likely to succumb from disease." (And, he adds, a healthier populace would help tame the spiral of health-insurance costs.)

Systems thinking evolved from the work of industrialists who wrestled with complex issues and often came up with contrarian solutions. In 1914, for instance, Henry Ford introduced an unheard-of $5-a-day pay scale at a time when other carmakers were trying to pay workers as little as possible. But Ford's move attracted the best workers and cut employee turnover. And with their fatter paychecks, Ford workers made enough to afford Ford cars. W. Edwards Deming came along later and developed a theory of effective workplaces that he called total quality management.

Batalden has been a pioneer in applying such thinking to medicine—especially globalization and infectious disease. "Every system is perfectly designed to get the results it gets," is Batalden's mantra. "If we don't like the results, and we don't redesign the system to produce different results, then we've deluded ourselves."

fected individuals sicken and die, leaving families destitute and children orphaned, the economic and social fabric of the society begins to disintegrate.

Facts like these may seem of little import to well-off Westerners. "The average American doesn't give a damn about AIDS in Africa," says James Strickler, M.D., former dean of DMS and longtime cochair of the board of the International Rescue Committee, a global relief agency. The average American's attitude, Strickler continues, is "'What's AIDS in Africa to me.' Well, it isn't just that AIDS is a worldwide disease that could eventually affect them and their friends. It's that AIDS in Africa creates enormous instability that could affect our national security.

"That's because social and political instability can lead to internal strife within a country," he explains, "and then spread into a conflict that may suck us in militarily."

As civil order breaks down, so, too, does the health-care system, and this breakdown opens the door to wider outbreaks of disease, which can all too easily spread to the U.S. "If we allow health to break down in other countries, and political turmoil results, we may get pulled into armed conflict," agrees the Global Health Council's Daulaire. "But as their health systems break down, we may also be victimized by the pathogens that get out of hand as global trade and travel bring them here."

There are three wild cards on the global disease scene. One is global warming, which many scientists blame on emissions from factories and automobiles of so-called greenhouse gases. Some scientists believe that even incrementally warmer temperatures could make the upper latitudes of the Northern Hemisphere more hospitable to the diseases of the Tropics, such as malaria and dengue fever. But other scientists argue that the conditions for some of these diseases—standing water, warm summers, and mosquitoes—already exist and that public-health initiatives have kept them at bay and can continue to do so.

There is also the chance that a new pathogen might be unwittingly generated in one of the industrial world's laboratories and spread through global travel. "There are mutations everywhere," says D.A. Henderson. "The question is when does it take off and become a problem to man? We compound this problem by the fact that we've now taught a lot of people how to manipulate bacteria and viruses. These techniques are being taught at the high school level. There are a lot of situations in which we might accidentally create a new bug."

Bioterrorism is the third wild card. A bioweapon released in any major city could quickly spread around the globe. There is a danger, for example, that terrorists could obtain smallpox virus from one of the bioweapons centers that retained samples in case they were needed to combat a future outbreak. (Smallpox has been considered eradicated worldwide since 1977.) Or terrorists could engineer their own pathogen. "You can do it in a small amount of space, and it can be done much easier than creating chemical weapons, which require a lot of equipment and supplies," says Henderson, who is senior advisor of the Center for Biosecurity at the University of Pittsburgh.

PHOTODISC

Cargo containers (right) can carry germs as well as goods, so disease knows no borders. DMS's James Strickler (above, right) delivers care in Cambodia.

Even if none of the wild cards play out, there are still ample threats from bugs already out there. "Lots of Americans are coming back from overseas with malaria," says DMS's Strickler. "We run the risk of people bringing back drug-resistant tuberculosis. The other example that's timely is the whole flu business. We are constantly worried about a pandemic caused by a new mutant flu virus. I read that if there is a pandemic, about one percent of the people who get it will die."

That's the same as the 1 in 100 chance that a person living in New Hampshire in 1901 would die of TB within five years. A century of advances may have put us right back where we were. The dream of someday eradicating infectious disease has given way to the realization that evolution will forevermore create new pathogens. We can try to flee from them as the people of 14th-century Europe fled from the plague, but in the end we have nowhere to hide. "Thanks to globalization," says Daulaire, "we all paddle in a single microbial sea." ■

"If we allow health to break down in other countries, and political turmoil results," explains DMS Overseer Nils Daulaire, president of the Global Health Council, "we may also be victimized by the pathogens that get out of hand as global trade and travel bring them here."