

# The Emergence of New Diseases

*Lessons learned from the emergence of new diseases and the resurgence of old ones may help us prepare for future epidemics*

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As recently as 25 years ago, the threat of plague seemed old-fashioned, even medieval. Death from infectious disease was thought to be the result of poor hygiene and a lack of good antibiotics and vaccines, problems that by the mid-1970s had been largely overcome in the United States and most other industrialized nations. Medical practitioners were confident that infectious disease would represent a vanishingly small percentage of their concern. Wrote one prominent biologist in 1975, "During the last 150 years the Western world has virtually eliminated death due to infectious disease."

At the time, his optimism seemed justified. Smallpox had nearly been eradicated; tuberculosis and polio were on the decline and, with the exception of malaria, so were all of the other major infectious health threats of the 20th century. Scientists believed that, thanks to improved hygiene and sanitation, immunizations and antibiotics, all remaining infections of human beings and domestic animals would soon be eradicated.

Of course, skepticism was expressed

even then. Agents of disease ranging from bacteria to insects had started to show resistance to the drugs and chemicals that had once so successfully killed them. And the optimistic projections were not consistent with what scientists knew to be true about the remarkable malleability of pathogens. For example, scrapie, a relatively mild disease of sheep, could somehow be transmitted to cattle, where it is devastating. Plants were also known to become afflicted with new diseases as old ones were eliminated. But the enthusiasm of the medical profession in general was not dampened by these examples, which after all, came from other disciplines and seemed too remote from the urgencies of medical practice.

Then came Lyme disease (1975), Legionnaire's disease (1978), toxic-shock syndrome (1978) and, more recently, AIDS (1981), chronic-fatigue syndrome (1985), and hantavirus (1993). The seventh cholera pandemic began in Indonesia in 1961, spread to Africa in the 1970s and reached South America in 1991, and now a new variant has emerged. Malaria reemerged in regions where it had been eliminated. Dengue and yellow fever are spreading. The incidence of tuberculosis started to climb in countries that had previously reported declines. Diphtheria reemerged in adults in the former Soviet Union. Suddenly, the proclamation of freedom from infection seemed, at best, premature.

These days, scientists no longer predict that the history of human infection will progress steadily toward the total elimination of infectious disease. More likely, the pattern will be one of disease turnover. With a new acceptance that infectious diseases will always be part of the human experience comes the realization that scientists will have to adopt a

new approach to understanding the patterns of disease evolution. Rather than place sole confidence in measures we would use to fight infectious diseases after they arise, we, the members of the Harvard Working Group on New and Resurgent Diseases, are trying to identify the factors that encourage the emergence and spread of new diseases. To do that, we integrate complex social, epidemiological, ecological and evolutionary processes to understand how events in these various dimensions interact under changing circumstances to produce radically new health problems. In exploring potential threats to human health, we examine recent trends as part of epidemiological history and explore the progression of human diseases, as well as those of plants and animals. In order to anticipate new disease problems, including diseases that have not yet emerged, we have to examine the patterns of existing diseases and vectors and also look at the gaps in epidemiology. We apply current concepts and reexamine the conceptual framework that guides our present strategy of disease control. It is one of our principles that the emergence of new diseases can not be fully understood without understanding the social context in which they emerge.

## What Is a New Disease?

At the start of our work we had to make two major decisions. First we had to define when a disease would be considered "new." Toward that end we identified ways in which a new disease may be recognized. A disease is recognized as new when its symptoms are distinct from any disease that has come before, or when a previously tolerated condition becomes unacceptable, as was the case with chronic exhaustion. A disease also becomes recognized when a previously marginal

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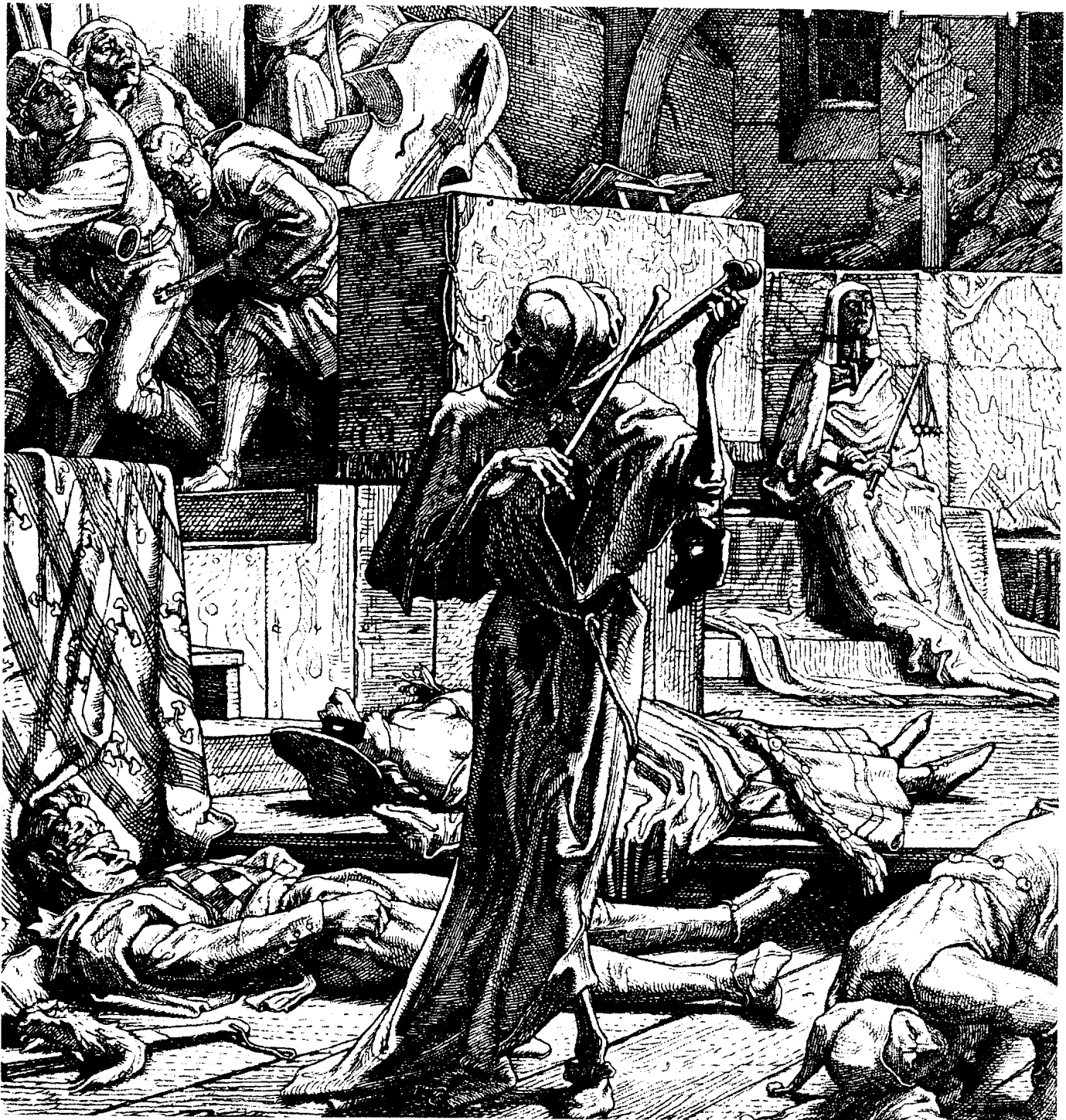


Figure 1. -Macabre images of plague-as-killer, such as this one from an 1845 wood carving by European artist Alfred Rethel, seemed, by the mid 1970s, old-fashioned. The near-elimination of smallpox and many other infections made many scientists confident that death from infectious disease was a thing of the past. Then came the emergence of new diseases and the resurgence of some old ones, and many scientists began to reassess the importance of infection in the future of human medical history.

population gains a public voice, which is what happened with black-lung disease. Diseases that are slow to develop may be newly identified in a population whose life span is increasing. In addition, conditions are identified as new when a local disease becomes widespread, a rare disease becomes common or a mild disease becomes severe. Diseases also become recognized when cases cluster in a locality

or social group, which was the situation with Legionnaire's disease. Sometimes a disease is identified as new when a new human population is medically examined or when improved diagnostic techniques allow a unique infectious agent to be seen.

We also had to settle on a definition of infectious disease. We agreed that it would be defined as a disease in which infection is brought about by one or

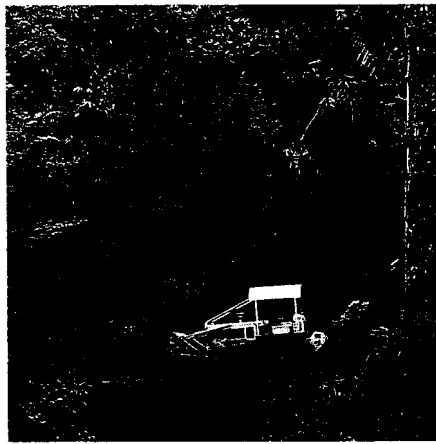
more kinds of parasite invading a susceptible animal. These parasites, commonly called pathogens (literally, the origin of suffering) can be microorganisms such as bacteria and viruses, or they can be multicellular organisms, such as worms. In spite of their diverse classifications, they all contribute to disease by a similar mechanism. They all carry out part of their life cycle inside another ani-

Recent New Diseases		
viruses: newly identified agents		
1957 India	Kyasanur Forest	severe systemic infection and fever; transmitted by tick
1959 Uganda	O'nyong-nyong	explosive outbreaks of acute illness with fever and severe joint pain; transmitted by mosquito
1983	HIV-1	Acquired Immunodeficiency Syndrome
1989	Hepatitis C virus	transfusion-related and sporadic hepatitis
1990	Hepatitis E virus	acute hepatitis water-borne epidemics and sporadic hepatitis
1991	Venezuelan hemorrhagic fever Guanarito virus	outbreaks of severe hemorrhagic illness
viruses: old agent, new location		
1992-1993 Kenya	Yellow fever	severe hepatitis and hemorrhagic fever; mosquito-borne virus
1993 southwestern U.S.	Hantavirus	new syndrome with pulmonary distress
ricketsial diseases: newly identified agent		
1986	<i>Ehrlichia chaffeensis</i>	moderate to severe systemic infection with fever, headache, low white-blood-cell count
bacterial diseases: newly identified agents		
1975	<i>Borrelia burgdorferi</i>	Lyme disease manifestations include arthritis and skin rashes
1976	<i>Legionella pneumophila</i>	Legionnaire's disease typically severe pneumonia. water-associated bacterium
1978	<i>Staphylococcus aureus</i>	toxic-shock syndrome; profound shock, kidney failure
1983	<i>Afipia felis</i>	cat-scratch disease; mild infection with enlarged, tender lymph nodes usually; acquired from cat
1992	<i>Vibrio cholerae</i> 0139	new variant of cholera

Figure 2. In spite of antibiotics and vaccines, a number of new diseases have emerged in the past 40 years. Here, a partial list demonstrates that the future of human health history will be one of disease turnover. New diseases come about through a complex interaction of biological, social, economic, evolutionary and ecological factors.



M. Courtney-Clarke (Photo Researchers, Inc.)



Alan D. Carey (Photo Researchers, Inc.)

*Rapid urbanization is one of the socioeconomic factors that puts people in contact with an unknown vector or pathogen*

*Creating new habitats—for example, by bulldozing forests—permits rare or remote microorganisms to become abundant and gain access to people*

mal—the host—where, for a time, they live, eat and reproduce. Disease is often a by-product of these activities. The parasite may produce a chemical that is toxic to the host, or it may damage the cells it infects. In addition, the host's own response may damage tissues.

But the parasite is actually only one of many factors that contribute to disease. Many parasites require an accomplice to facilitate their spread from host to host. Often this accomplice, called a vector, is an insect. Frequently the vector bites an infected animal and ingests some of its blood. It then bites a second animal and deposits into that animal's tissues some of the parasite-ridden blood from the first. Sometimes insect vectors themselves require carriers. Rodents, in addition to harboring pathogens, can also serve as hosts to fleas, ticks or other insects in which the pathogens reside. An animal's contact with parasites and vectors will obviously be an important factor in determining whether it will become sick. A potential host's general state of health and nutrition as well as its genetic predisposition to control infection will also determine the outcome of an encounter with a pathogen. Furthermore, social processes shape pathways of infection and disease. In the end, it is likely that the classification of diseases into infectious, environmental, psychosomatic, autoimmune, genetic and degenerative will prove to be applicable only to a sample of cases where one factor overwhelms all others. The more accurate viewpoint will encompass full complexity of this network of factors that leads to recognizable disease.

#### Identifying the Pathogen

Most bacteria are not pathogens, most arthropods are not disease vectors and most mammals are not a source of human disease. What, then, are the charac-

Recognizing New Diseases
• a previously tolerated condition becomes unacceptable (chronic exhaustion)
• a marginal population acquires public voice (black lung)
• increase of life span allows a slow disease to develop
• a local disease becomes widespread
• a rare disease becomes common
• a mild disease becomes severe
• symptoms are clearly distinctive
• contagion is high and latency short, so that cases cluster in a locality or social group
• health service examines a new population
• diagnostic techniques permit visualization of a new pathogen

Figure 3. Criteria for recognizing a disease as "new" include changing attitudes as well as changes in the organisms responsible for disease.

teristics of a successful pathogen or vector, and where should we look for them?

The potential for a nonpathogenic species to become a pathogen can be assessed by examining the present distribution of diseases, symptoms and virulence across groups of pathogens. We call this field systematic epidemiology and focus on ecological and social processes that influence disease emergence.

Systematic epidemiology asks, for example, questions about the range of hosts a particular pathogen can infect as well as the types of pathogen a particular host can support. It also explores unique and shared characteristics among related species of pathogen, symptom variability for the same pathogen in different hosts, modes of transmission and the

epidemiological potential for different species groups.

For a sample of 247 infections, we note that, relative to other pathogens, fungi are less common in serious primary human infections, but are prominent pathogens of fish and plants. We also note that viruses depend much more on arthropod vectors than other groups, while fungi typically require no vectors at all. Viruses are smaller and more fragile than fungal spores, which probably accounts for their reliance on vectors.

Will Kastens, a student at the Harvard School of Public Health, prepared a preliminary survey of 412 human infections. Of these, 180 were exclusively human diseases, 118 were primarily hu-

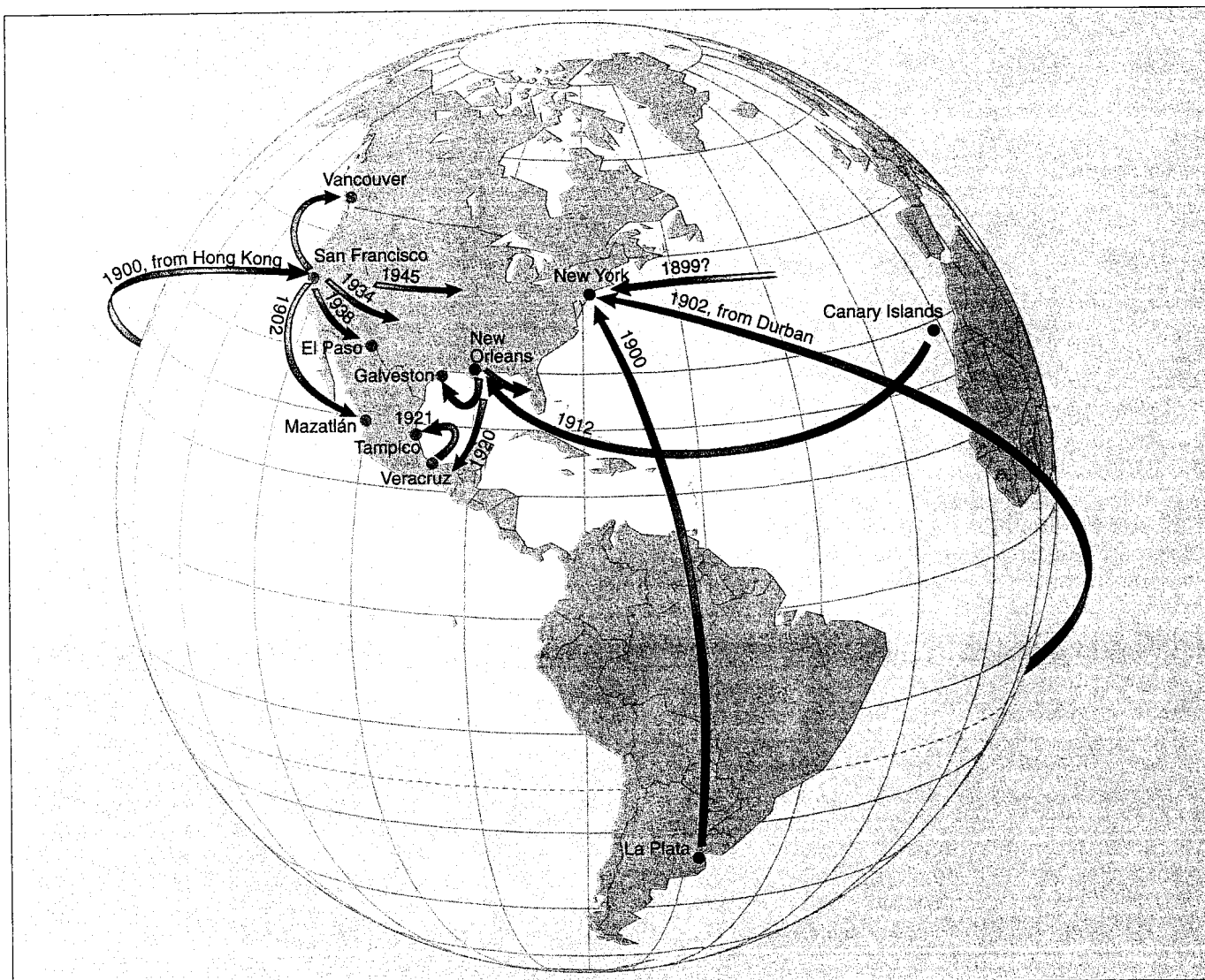


Figure 4. Map of the spread of bubonic plague in the early 20th century demonstrates how modern, rapid transportation can turn a local disease into a worldwide pandemic. When travel time is shorter than the incubation time of the disease, pathogens are more likely to move between countries and even continents. The spread of disease shown on this map would have been improbable during Christopher Columbus's time.

man diseases but could be found in other animals and 62 are principally found in other animals but can occasionally be found in people. The remaining pathogens are not normally pathogens of people or animals. Usually they are free-living microbes that cause disease when a chance encounter places them in contact with people. Of the diseases shared between people and other animals, 35 are widespread among mammals, about a dozen are shared with livestock and domestic animals, and approximately seven are shared with non-human primates. A few are shared between people and birds, and a smattering of pathogens can infect fish, people, shellfish and insects. Finally, at least two species of *Vibrio*, the microorganism that causes cholera, can be associated with plankton.

Kastens's data also show some inter-

esting trends with regard to virulence. Those pathogens that mostly affect animals but sometimes invade human populations include a greater proportion with high virulence. We speculate that this is because their evolution is dominated by selection in their nonhuman hosts. On the other hand, diseases that are commonly or exclusively human have evolved in part in the human context, and some of them evolve to be gentler to people. Paul Ewald of Amherst College has suggested that vector-borne diseases tend to be more virulent than those requiring direct contact between people. His argument is that where the mobility of the patient is a requirement for transmission, it is to the pathogen's advantage that the infected person remain mobile, even if this limits the pathogen's rate of reproduction. But these are only tendencies.

More detailed examinations of natural selection in pathogens reveal many exceptions to these examples.

#### Adaptive Potential

Although we give names to different species of pathogens, vectors, reservoirs and their associated diseases, these are not static entities. Pathogens as organisms undergo natural selection both within the host and in the course of transmission between hosts. And a pathogen's success in adapting to conditions within and between hosts will determine, in part, its success in spreading throughout a population.

A pathogen is confronted with three sometimes conflicting demands. It must obtain its nourishment to develop and reproduce, avoid being killed by the body's defenses and find a satisfactory exit to another host. Meeting these de-



John Gerlach (Animals Animals)



Wide World Photos

*A pathogen is introduced to a human population, as when carrier rodent populations increased and exposed people to hantavirus*

*People moving into a new country may encounter pathogens against which they have no resistance*

mands may require that a pathogen localize to a particular site in the body. For example, the blood is an optimal site for feeding, but it is a site of high immune activity. A pathogen in the central nervous system is relatively secure from destruction by the immune system but has no easy exit. The skin is also relatively safe from the immune system and can be exited fairly easily, but it is not a good site for reproduction.

Some pathogens adopt strategies for dealing with the immune system, so they are freer to choose sites in the body where immune activity is high. The human immunodeficiency virus, which causes AIDS, can remain in the blood because it destroys part of the immune system. Trypanosomes, which cause sleeping sickness, can also remain in the blood because they are adept at changing their protein coat, and in this way dodge detection by the immune system.

From the point of view of the pathogen, the symptoms suffered by the host are merely by-products of the pathogen's life-style. For example, in diarrheal diseases, the most obvious symptom arises when the pathogen exits one host in search of another. The pathogens remaining in the original host invade the gastrointestinal mucosa so they are not whisked away during the diarrheic episode.

Pathogens face other strategic decisions as well. Should they reproduce rapidly and exit quickly, or should they prolong the infection in the face of uncertain success in infecting someone else? The strategy adopted will depend on the relative rates of pathogenic reproduction, contagion possibilities and the danger of strong and effective treatment of the infection.

The role of drugs—antibiotics and antivirals in particular—in directing natural selection in the pathogen makes

the intervenor a part of the system being intervened in. The host's behavior in effect becomes part of the selection pressure and affects the characteristics of the pathogen in the next outbreak. For example, if the host uses antibiotics, some of the pathogens may develop resistance to the drugs. During future outbreaks, these drug-resistant pathogens may predominate, and other antibiotics will have to be used to eliminate them.

Vectors, like pathogens, also undergo evolutionary change. Currently, a new biotype (or possibly, sibling species) of the whitefly *Bemisia tabaci*, carrier of bean golden mosaic virus, is spreading at the expense of the previous biotype. The new biotype has a wider range of host plants to feed on and is therefore spreading viruses to new plant species. In this case, a change in host range of the vector makes new species of plants serve as reservoirs for infections of crop plants. Reservoirs can maintain pathogens at low levels in small wild populations without being noticed, until a change in the environment or vector opens up new opportunities.

#### **Pathogens on the Move**

To cause a disease, a pathogen must first find a potentially receptive population of hosts. Sometimes the pathogen is required to travel. Various measures have been proposed to indicate the likelihood of a disease invading a population, among them the number of new cases derived from a given case, which epidemiologists refer to as the reproductive rate.

We have identified several key factors affecting the introduction of diseases into new populations. When diseases are carried from one area to another, it is important to establish the travel time needed to reach the new population relative to the rate of progression of the disease. For example, in Columbus's

time, crossing the Atlantic was slow compared to the progression of smallpox. Since all carriers of the virus manifest symptoms of the disease, most of the infected travelers would have either become sick and died or recovered before reaching the New World. As a result, smallpox probably did not reach the Americas until several decades after Columbus's voyage. If Columbus were to begin his journey today, the situation might be different. Modern transportation has cut travel time to almost anywhere in the world to a few days at most, less than the average incubation time of many pathogens. Travel time, therefore, presents a less significant barrier to the spread of disease than it once did.

So does travel itself. Populations are much more easily moved than before. Left to their own devices, species spread into new areas very slowly. It has taken just over a century for rodent-borne plague to reach Mississippi from the West Coast. Fire ants spread at a rate of only a couple of miles a year. But man-made transport can speed the process so that pathogens can travel many thousands of miles in a few days. Political and economic oppression and opportunity are prime motivators for large-scale movements of people across countries and continents. The net effect of so much human migration is that diseases once confined to small regions of the globe can potentially spread to many regions.

Large-scale global commerce increases the probability of introducing vectors (often insects) and nonhuman carriers of disease to naive populations—a situation that may have touched off and accelerated the seventh cholera pandemic. For example, a freighter is thought to have transported the cholera vibrio in its ballast water from China to Peruvian coastal waters. *Vibrio* flourished in al-



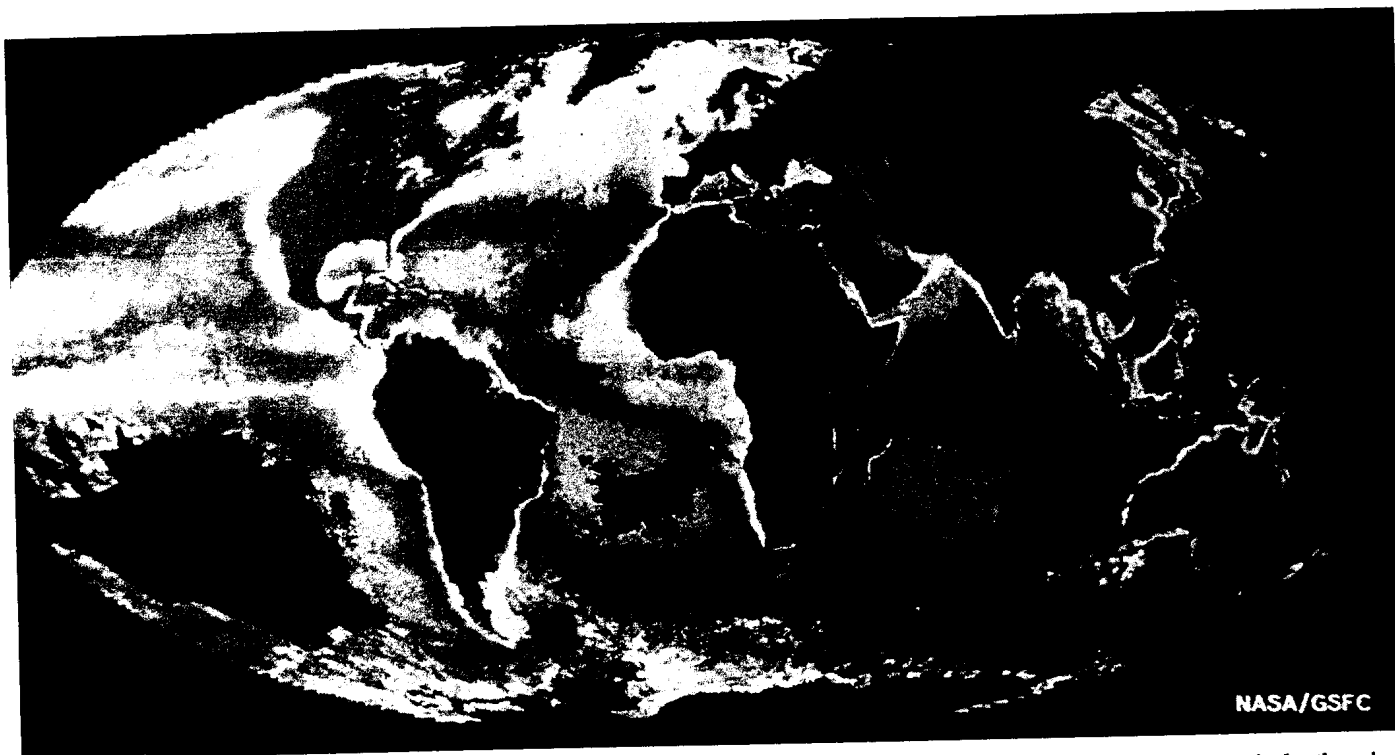


Figure 5. Satellite image shows the global distribution of coastal algal blooms, which are breeding grounds for pathogens, in particular the microorganism that causes cholera. Sewage and fertilizer pouring into marine ecosystems, overharvesting of fish and shellfish and the loss of wetlands, combined with climatic changes, have conspired to cause a worldwide explosion in the number of such blooms. (Photograph courtesy of NASA.)

gal blooms enriched with nitrogen and phosphorus from sewage and fertilizers. Algae are filtered and eaten by molluscs, crustaceans and fish that are, in turn, eaten by people. Once it entered, the infection in Latin America spread rapidly, as social and economic conditions provided a fertile environment for infection. Rapid urbanization, foreign debt and political changes strained the economy made sanitation and public health low priorities and paved the way for the epidemic spread of cholera. As of August 1992, more than 500,000 Latin Americans had become ill, and 5,000 of those people had died.

#### Changing Ecosystems

Just arriving in a new location does not ensure that a pathogen will take hold there. In fact, most introductions do not result in colonization because the species does not land in a hospitable niche. To successfully colonize new terrain, the invader must find a suitable environment and, if it is a pathogen, a receptive host population.

In general, invasion is easiest in regions of low biological diversity, where the invader faces less competition from native species. Oceanic islands are notoriously vulnerable to invasion. They have been known to be devastated by invasions of rats, goats or weeds, because their few native species could not compete.

Also vulnerable to invasion are habitats that have been disturbed by natural events or human activity. These events eliminate predators and competitors and create opportunities for new species to take up residence. For example, the spread of Lyme disease in New England is related to a number of human activities that have dramatically altered the region's ecology. During the past century, the forests were cleared to make way for agriculture. This eliminated from the area both the deer and their predators. The forests returned eventually, as did the deer. But the deer's predators did not. The deer tick, carrier of the infection, could spread, unimpeded, throughout the deer population and into the human populations that came into contact with them.

Vectors of human disease generally thrive in newly established habitats. Piles of used tires around the edges of rapidly growing cities collect water in which the mosquito *Aedes aegypti*, a vector for the organism that causes dengue and yellow fever, reproduces. Irrigation ditches, borrow pits, construction sites, poorly drained water pumps and puddled river bottoms each may serve as breeding sites for the mosquitoes that carry malaria. The pathogens carried by the mosquitoes can feed in these man-made habitats without being diverted to other animals, who are less successful in shuttling

the pathogen to human hosts. In this manner, whole new niches have been created beyond the original geographic and ecological range of the vectors.

Of course, the successful spread of a human pathogen requires a vulnerable human population. The vulnerability of a group of people to a pathogen depends, on one hand, how contagious the pathogen is and how quickly it is transmitted from person to person, versus the population's immunity on the other. In this equation, all environmental changes are potentially reflected epidemiologically since conditions can affect the opposing processes of contagion and recovery, acquisition and loss of immunity.

The contagion rate depends on the number of pathogens that leave an infected individual and enter the environment. It also depends on the number that survive in that environment and gain contact to and ultimately infect other people. Each of these steps is complex and combines biological and social factors that are not constant. For example, no two people are equally susceptible to infection. A person's general state of health is as much determined by social, nutritional, age and gender factors as by genetics. Personal habits, such as smoking, sexual practices, alcohol consumption and food availability and preferences can also contribute to a person's susceptibility to a particular disease.



Bruce Brander (Photo Researchers, Inc.)



Renee Lynn (Photo Researchers, Inc.)

In addition, there is now widespread concern about the potential effects of climatic change on disease. Changes in global temperature would carry with them changes in wind and precipitation patterns, humidity, soil composition and vegetation. All of these affect human activity and movement of populations.

Finally, the environment of a pathogen includes other parasites. In developing countries, it is not uncommon for people to harbor two to four simultaneous infections. Within their shared host, these pathogens may interact in familiar ecological patterns. They may compete for nutrients, or they may alter immune function in such a way as to benefit one while deterring another. They may alter their shared environment by causing fever or by damaging cells. The symptoms of one infection, say, sneezing, may facilitate the spread or mask the symptoms of the other. What this suggests is that the most effective way to deal with disease in the clinic is to consider the entire epidemiological profile, rather than consider one disease at a time.

### Hantavirus

The emergence of a disease within a changing ecosystem was dramatically

illustrated when a mysterious illness emerged in the Four Corners region of the southwestern United States earlier this year. In August 1993, a 37-year-old farmer who worked in the Four Corners area sought medical help when an illness he had had for six days took a turn for the worst. At first, the farmer experienced flu-like symptoms, including fever, nausea and vomiting, which progressed to coughing and shortness of breath. An xray showed fluid in both of the farmer's lungs. After 12 hours, he developed acute respiratory distress and died. Several weeks and several cases later, scientists at the Centers for Disease Control in Atlanta linked the mysterious disease to a new strain of hantavirus, viruses that have been associated with hemorrhagic fevers and renal disease in Europe and Asia, but that had not previously been known to cause disease in North America. Where had the virus come from, and why did it suddenly emerge?

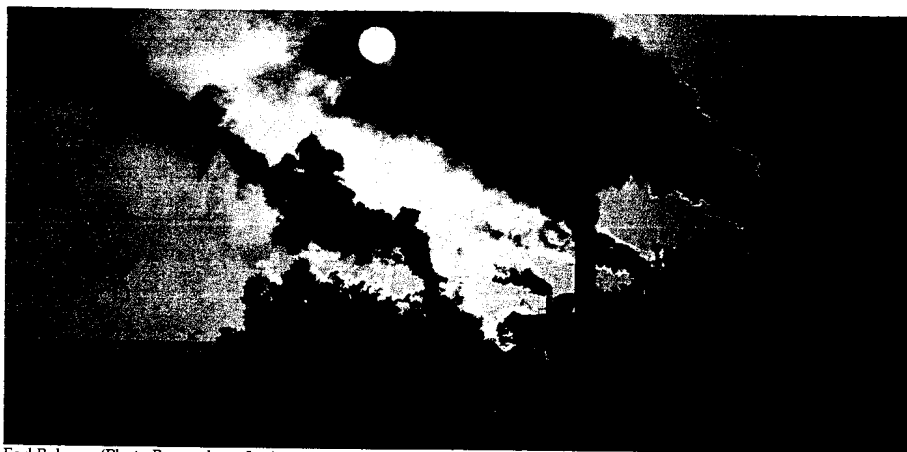
That answer came serendipitously from studies conducted by Robert Parmenter and colleagues at the University of New Mexico. Parmenter and his team had been interested in the sudden increase in deer mice, which, as it turns

*Malnutrition, as well as immunosuppressive drugs and environmental stressors, makes people vulnerable to infection*

*Animal pathogens mutate and acquire the ability to infect people; the human immunodeficiency virus may have evolved from a monkey virus*

out, are carriers of the hantavirus. Six years of drought ended in the spring of 1992, when heavy rains deluged the area. The abrupt change disturbed the ecological balance in the region, producing an abundance of piñon nuts and grasshoppers, food for the mice. The deer-mouse population flourished, but the drought had virtually eliminated all of the mouse's predators. In the year between May 1992 and May 1993, the deer-mouse population increased ten fold. By October 1993, the deer-mouse population had declined sharply, and the epidemic apparently came to an end. It had taken its toll. Forty-two cases of hantavirus pulmonary syndrome were reported in 15 states, mostly clustered in the Southwest. Twenty-six of those cases were fatal.

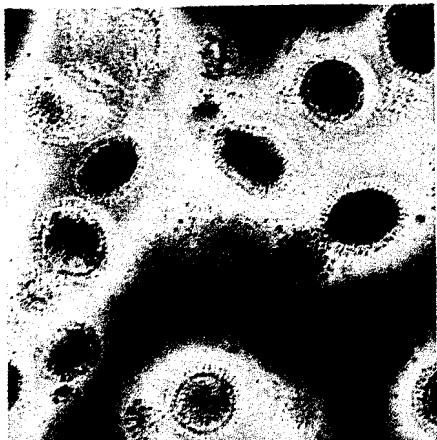
One of the lessons to be learned from such case studies is how disruption of stable ecosystems can alter an existing disease and facilitate its spread. For that reason, we are particularly concerned with recent disruptions of marine ecosystems, which are undergoing dramatic changes. Sewage and fertilizer pouring into marine ecosystems, overharvesting of fish and shellfish and the loss of wetlands, combined with climatic changes, have conspired to cause a worldwide ex-



Earl Roberge (Photo Researchers, Inc.)

*Pollutants or radiation increase the mutation rate of pathogens*





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## *Influenza virus and other pathogens may evolve toward greater virulence*

*Although it has not happened yet, bioengineered organisms may contribute to infection in the future*

plosion in coastal algal blooms around coastal regions, providing a rich environment for diverse communities of microorganisms. The sea-surface temperatures in these environments are frequently elevated, which shifts organisms towards more toxic species, possibly by increasing their mutation and reproduction rates.

Among the new species that have been identified in these algal blooms is a new variant of the cholera vibrio. Now present in 10 Asian nations, this new variant seems to be distinct from previous forms of cholera, based on immunological tests. Antibodies that recognize other known variants do not recognize this one. This newly emergent, environmentally hardy form of cholera threatens to become the agent of the eighth pandemic. Monitoring algae and other microscopic marine organisms for vibrios offers the opportunity for establishing an early warning system for this new pathogen. Images from remote-sensing satellites can help guide this operation.

### **Confronting Uncertainty**

The ultimate goal of these types of analyses is to anticipate the onset of new diseases and to eliminate the situations that facilitate their spread. In meeting these challenges, however, we confront a high degree of uncertainty. We can make some short-term predictions about new disease outbreaks by recognizing conditions that favor outbreaks of known disease and by anticipating ecological changes associated with human activity. We are developing models based on evolutionary ecology that would allow us to make some longer-range predictions about new disease outbreaks.

Just as organisms adapt rapidly to a new condition, we too can respond

rapidly to new disease threats. But to do that, we have to recognize them quickly. An analysis of the factors facilitating or delaying recognition along with improved diagnostic techniques, might allow us to recognize problems sooner than is now possible.

We also must be very general in our response to disease. Our current therapeutic tools—immunization and antibiotics—are highly specific for the diseases they fight and can be developed only after the pathogen has been studied. Other organisms develop very non-specific resistances that confer protection against a range of threats. For human beings, measures could be taken to boost the body's defenses in general. These would include good nutrition, pollution control, biodiversity for vector control and social arrangements that ensure these measures reach the entire population.

We advocate a mixed strategy, which offers back-up protection in case the first plan turns out not to be the best. A mixed strategy combines the tried-and-true approaches with newer ones. It may rely on some short-range predictions and monitoring, but it encourages longer-range ecological and evolutionary surveillance. It may concentrate on public health measures and seek to create healthful social systems that renegotiate our relations with the rest of nature.

Ultimately, we may have to reevaluate our notion of disease. We must see disease as the outcome of multiple conditions arising from changes not only within cell nuclei, but also around the globe, including changes in climate, economic patterns and communities of species. Any effective analysis of emerging diseases must recognize the study of complexity as perhaps the central general scientific problem of our time.

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