NEW AND EMERGING INFECTIONS

The topic of emerging viruses has been widely publicized in recent years. It has been the subject of books (e.g., Laury Garrett's *The Coming Plague: Newly Emerging Diseases in a World Out of Balance*) and films and has generated a number of press releases. Most recently we've heard about the *Ebola* virus outbreaks in Gabon, and earlier in Sudan and Zaire. These diseases have caused 80 to 90% fatality rates and have been very fearsome indeed. But should we be truly concerned about these emerging infections, or are we just detecting things that have been around for a long time for which we now have more sensitive means of detection? Are these alarmist warnings from academics whose grants are on the line, or perhaps government scientists who would like a little more money in their budgets? Or are we getting exaggerated reports from the press to increase circulation?

I would like to reflect on a series of observations and concerns that culminated in August 1989 with a conference, called by Rockefeller University and the National Institutes of Health, on new and emerging infections. The conference marked the first time that many of us had actually sat down and thought about this issue. I had been asked to address the question of detecting and monitoring new infections, which was a real challenge: if you really don't know what you are looking for, how do you come up with some meaningful construct? I came away from that conference quite sobered and having concerns about the future.

I also want to highlight some of the events and problems that have surfaced since 1989, and touch on some man-made problems that have entered this arena. To conclude, I

will to take a brief look *back* and ask: Do we have any precedent in history for a microbial epidemic that in effect threatens civilization?

BACKGROUND

From the 1950s through the 1970s, the threat of infectious diseases in the United States, in particular, and in the industrialized world gradually receded. Sulfa drugs, penicillin, and many other antimicrobial drugs—wondrous antibiotics—had come into play. The feeling prevailed that if we didn't have a good antibiotic against a particular bacterial infection, one certainly would be forthcoming very soon. With advanced and basic science, as well as our understanding of microbial metabolism and pharmacology, we'd solve these problems without great difficulty. It was also felt that we were doing so well with the antimicrobials that certainly antiviral drugs would be next.

We then went on to the vaccines. In 1949, Enders, Robbins, and Weller used tissue culture to grow poliovirus in large quantity, and really laid the groundwork for producing many of our antiviral vaccines, going from polio to measles to rubella to mumps to many others. Simultaneously during this period, the standard of living throughout the country was improving, housing was better, nutrition was better, etc. In effect, infectious diseases seemed to have disappeared. In fact, the surgeon general, reflecting the common view of many, said in the early 1960s that the battle against infectious diseases was over, and it was time to turn our attention to the chronic diseases like cancer and heart disease.

Also during this time we found that the number of hospital residencies in infectious disease decreased sharply. Many of the research centers around the world—even in the developing countries—began to fold up, particularly with the end of colonialism, and departments of microbiology, which once were quite strong in a number of medical schools, closed altogether or became very much smaller. Indeed, there was a feeling of self-confidence (some might say arrogance) which conveyed the attitude that we could deal with any infectious disease agent that threatened us.

SHAKE-UP OF THE STATUS QUO

Then in the early 1980s we had a problem—the human immunodeficiency virus (HIV). Health and Human Services Secretary Heckler, announcing in a press conference that the virus had been identified, announced at the same time that we would have a vaccine within two years. Many years later, and with a budget exceeding a billion dollars devoted solely to this disease, we had no vaccines and none in field trials. We found ourselves debating whether to proceed with perhaps one or two "first-generation" vaccines. None of the drugs worked all that well. They were only marginally effective in deferring death for a period of time, but they were not curative by any means. In fact, we saw the disease spreading steadily across the world and tried to control it with various behavioral interventions. This, as we know, is very difficult. These circumstances were the genesis of the 1989 conference, i.e., the frustrations and realization that we had a great deal to be humble about when it came to looking at various organisms, with viruses being of particular concern.

Other problems arose in the early 1980s. The Lhasa fever hemorrhagic disease, which emerged in the late 1970s in West Africa with what looked like a very high case fatality rate, had never been seen or described before. Then we had the outbreak of *Ebola* virus. Around 1976, reports indicated that this outbreak was associated with one particular hospital; 80% of the hospital staff was dead. No one knew what this hemorrhagic disease with profuse bleeding was. Carl Johnson and Joel Breman flew down with no idea about how it was being spread and no idea about what they were dealing with. A capsule was also flown over from the United States so that if they became infected they would be evacuated back to a high-level biologic containment facility at Fort Detrick for care. As it turned out, Johnson and Breman were able to determine that the virus was spread by fairly close contact—a fairly simple barrier mechanism—and stopped the spread. Yet despite a huge amount of effort, we still have no idea where that virus is when it's not occurring in humans. We've not been able to identify it in any animal species.

In 1983 there was a mild influenza virus in chickens, which suddenly mutated a bit; within six months, 17 million chickens were dead. Another example was Lyme disease (Fig. 1), which had only recently been discovered due in large part to reforestation and a rather extensive spread of the deer population. A problem with raccoon rabies (Fig. 2) also emerged, which was initially contained within a relatively small area but then spread across the whole eastern seaboard. It has still not been effectively stopped. In 1988, a plague affecting seals around Great Britain killed a third of the seal population. This turned out to be a virus of the measles-type family.

Again, during that 1989 conference, we were sobered, having gained an appreciation that countless number of microbes were constantly growing, mutating, and endeavoring to secure their own niche within the whole biological matrix by whatever advantage could be exerted. For viruses to replicate they must involve themselves with the genetic and metabolic mechanisms of the cell of the animal they are infecting. So viruses are inextricably woven with the genetic mechanisms of man, animals, etc.

Suppose HIV had had a different set of characteristics with regard to transmission? Suppose, for example, it had been a very rapidly spreading respiratory disease like influenza rather than one with a very long latency period. With influenza, virtually everyone is exposed and infected within a 12- to 24-month period. Suppose that had happened with HIV? What guarantee did we have that that *wouldn't* happen?

In looking at these emerging infections at the time, many of us realized that we were not well prepared for them. We also became concerned that the situation could be grossly exaggerated or seen as an Andromeda strain scenario, as it was being portrayed in this press. And so the decision was made to ask a panel from the Institutes of Medicine to take two years to review all the evidence. The panel's 1992 report, *Emerging Infections: Microbial Threats to Health in the United States,* focused mainly on viruses but has since been expanded to include other agents as well.

Since 1990 we have had yet more problems. For example, the Hantavirus Pulmonary Syndrome (Fig. 3) suddenly emerged. The hantaviruses are a set of viruses, one of which is responsible for the Korean hemorrhagic fever, and there is a variant in Europe which causes a kidney-uremic syndrome. In the United States, curiously, the only evidence we had of hantavirus was in certain port cities. Research sponsored by Fort

Detrick, some of it done at the JHU School of Public Health, showed that the virus could be detected in rats that were being trapped in Baltimore. We wondered then if we would see patients in hospitals that we could identify as dying or having died of a mysterious hemolytic-uremic syndrome.

Then a hantaviruses causing a pulmonary disease emerged in the west, mainly among young adults. No hantavirus had caused this particular syndrome before. Eventually this was linked to small field rodents and seemed to spread as a result of the dust of rodent feces and urine being kicked up and inhaled by humans. But what was thought to be a fairly limited spread of the infection turned out to be much more far reaching (Fig. 4). By 1994, the fatality rate was just over 50%, but because of its mode of spread, we didn't expect this to result in a massive epidemic.

In 1993 a multistate outbreak of *e. coli* 157 occurred, connected with fast-food hamburgers. *E. coli* was first recognized as a pathogen only in 1982 and continues to be a problem (Table 1).

Table 1. *E. coli* 0157:H7 chronology.

Year	Event
1982	First recognized as a pathogen
1985	Associated with hemolytic-uremic syndrome
1990	Outbreak from drinking water
1991	Outbreak from apple cider
1993	Multistate outbreak from fast-food hamburger

Also in 1993 we saw infection caused by the parasite *cryptosporidiosis* (the first human cases were diagnosed in 1976), culminating in the largest recorded waterborne outbreak in U.S. history with 400,000 cases in Milwaukee, Wisconsin (Table 2).

Table 2. *Cryptosporidiosis* chronology.

Year	Event
1976	First human case diagnosed
1984	First well water outbreak
1987	First river water outbreak
1992	Multiple municipal water supply outbreak
1993	Largest recorded waterborne out break in U.S. history

The parasite comes through drinking water that is not well treated with chlorine or standard mechanisms, thus reflecting contamination in the watershed.

Rather more dramatic is nosocomial enterococci, which a CDC report found to be increasingly resistant to Vancomycin (Fig. 5) between 1989 and 1994. Vancomycin is important because it is the antibiotic of last resort. Today the percentage of resistant organisms is rapidly climbing, particularly in intensive care units. This is a real concern. At the time, pharmaceutical companies were making very limited investment in the development of antibiotics. Only in 1995–1996 was there some resurgence of interest, but it will take about 5 to 10 years more before these new classes of antibiotics are used. Recently, we've seen a new strain of cholera that has emerged in Bangladesh and spread into India. *None* of the vaccines have any effect on this disease, which appears to be the more virulent Asian-type strain.

This is certainly by no means an exhaustive list of problems that have come up, but it gives some sense of where we are.

MAN-MADE FACTORS FAVORING THE EMERGENCE AND SPREAD OF NEW AGENTS

Why are we having problems? And if we are having more problems, what has changed? One of the most significant factors has been population growth. Population growth and population problems have always existed. What is not so well appreciated is that population growth in urban areas today is going on at 3 to 5 times the rate that it is in the entire country. In 1950, only two urban areas in the world had populations greater than 7.5 million, London and New York. In the year 2000, 28 cities have populations of 7.5 million, and some of those have greater than 15 million (Fig. 6).

Interestingly, many of these large cities are in tropical areas with very limited or no sanitation, with people densely packed in as never before, and with very limited health facilities. If you wanted to find conditions that would facilitate an organism mutating a little bit and finding a receptive host, this situation provides a unique opportunity. Because much of the population is so concentrated, the opportunity for spread from one infected individual to others is enormous. In addition, many of these people, because of nutrition and other factors, have a compromised immune system. So the potential for an organism to establish itself and spread is greater than ever before.

Not only are urban centers the problem. Civil disorders and the number of refugees are mounting year by year. Here again you have a series of unique opportunities

for organisms to grow and proliferate, often in rather remote areas where the chance of contacting a whole new range of microorganisms becomes possible.

Hospitals also contribute to the spread of infection. Those in developing countries have very limited facilities. Standards for sanitation and sterility are very poor. One particular hospital during an *Ebola* virus outbreak had only five syringes per day for all patients. The syringes were sterilized by dipping them in water between patient use. More than that, sick people were being brought into the hospital that were contacting others already there who were susceptible to the disease. This problem was seen during the smallpox program as well.

We have more incursions into remote areas today than ever before. Take, for example, attempts to identify monkey pox in tropical rain forests. The population of the rain forest was scattered, living in groups of about 50. Their main source of protein was monkeys. Regularly they shot the monkeys, brought them into the center of the village, skinned them, and participated in cutting them up. It's not surprising when you see this to figure out how HIV might have found its way into a broader population.

Finally, we have seen the internationalization or industrialization of our food supply. Enormous quantities of food are shipped into the United States from all over the world, making distribution difficult to police. For example, we had an episode in Minnesota at a fruit kitchen where sandwiches contaminated by *Shigella* were being prepared for one of the airlines. Calculations were that there were 20,000 cases of *Shigella* from that one occurrence involving airlines across the world. This points up a potential that we have little means of controlling.

Where are we now with AIDS in the United States? Infections peaked in 1982. By the time we began doing anything in the way of control in this country in about 1986–1987, we were seeing approximately 40,000 new cases of infection. This was a major epidemic, spread particularly through the homosexual population, and later through tainted blood supplies and drug use. It has now stabilized at around 40,000 (Fig. 7), although it had been feared that it would affect millions in the United States.

But this is *not* the case with AIDS around the world. Documentation indicates that there are actually six different strains of the AIDS virus. In the United States we have almost entirely what is known as the B strain. In northern Thailand, they seem to have a totally different strain with very rapid, mostly heterosexual spread. Similarly, in Africa, where it is likewise spreading heterosexually and much more rapidly based on our experience, it is not the B strain. The belief is that the other strains may spread with greater rapidity.

TAKING A LESSON FROM HISTORY?

Have we ever had an episode(s) in history where indeed the very fabric of civilization was stressed owing to microbes? We're dealing with our first agricultural settlements only about 10,000 years ago, when people were so dispersed that even small outbreaks were not impossible. We believe that viral diseases really didn't get started until about the time when these first agricultural settlements arose.

Only about 500 years ago the entire population of the Americas was totally separated from other populations. Those in the Far East were pretty much separated from

those in Eurasia. Travel and transportation were fairly limited at that point. Until about the mid-1300s, Europe had been experiencing a 300-year period of growth, fairly good stability, and few deaths from infectious disease. But then there was a change: 1346 saw the beginning of the Black Death (Fig. 8). The Mongol armies came in through the Crimea and quickly moved across central Asia. The great Silk Route became established, bringing with it the black rat.

Remember that during the four-year period of 1346 to 1350, a third to a half of the population of Europe—scholars, peasant, leaders, etc.—died. Agricultural production diminished, starvation became common, construction ceased, and a period of true stagnation ensued. The plague did not stop either after those four years; epidemics continued to recur. It was 300 years before the population of Europe reached its pre-1350 level. Plagues still had a potential as recently as 1898, when 6 million died in Bombay during an epidemic.

A more dramatic problem was that of smallpox. Smallpox came from Hispañola in 1516 to the Americans, where it very quickly and literally decimated the Amerindian population. The Spanish began bringing in African slaves simply because they needed to make up for the loss of Amerindian manpower. In fact, after four years, Cortés went to Mexico to see if he could recruit more Amerindians to work the mines, etc., for the Spaniards. And so in April 1520, he landed in Mexico, and with him came smallpox, which by autumn had made its way to the great city of the Aztecs, Mexico City. The Spaniards did not develop the disease. They were survivors, having encountered it in Europe.

The population of the Americas, primarily located in Central America and the Andean region, was said to be around 20 to 40 million at that time, about half the population of Europe. Seventy-five years after Cortés entered Mexico with about 500 troops, and Pizarro entered the Andean region with a little less than 500 troops, between 70 and 95% of the Indians were dead.

A description of Peru at the time reported that whole villages were depopulated, corpses were scattered over the fields or piled up in houses and huts, all industrial activity was paralyzed, the fields were uncultivated, herds were unattended, and the workshops and mines were without laborers. The price of food rose to the point where it became unattainable. Some escaped the foul disease, only to be wasted by famine.

For reasons that are unclear, the American population, both north and south, seemed to be unusually susceptible to smallpox. Indeed in eastern North America, the settlers had very little trouble with the Indians, not because they were such good neighbors or because the Indians loved them, but because there just weren't that many Indians! Smallpox had wiped out whole tribes, so that region was settled with great ease.

Finally, in 1830s, concerns turned to quieting problems on the great frontier. From an 1838 letter, we have the following report on the effects of the smallpox epidemic:

> We have, from the trading posts on the western frontier of the Missouri, the most frightful accounts of the ravages of smallpox among the Indians. The number of the victims within a few months is estimated

at 30,000, and the pestilence is spreading...The vast preparations for the protection of the western frontier are superfluous. Every thought of war was dispelled and the few [Indians] that are left are as humbled as famished dogs. No language can capture the scene of desolation which this country presents.

CONCLUSION

One problem that is now emerging is our concern over terrorism and biological weapons. In 1979, an episode in central Russia occurred: a small amount of anthrax bacilli being used at a biological weapons installation escaped into the air, went downwind, and was subsequently traced. About 100 people died. Animals died as much as 50 kilometers downwind from where it was released. The pattern of spread was a very narrow plume that could be traced by the location of the deaths along that 50 kilometers. The amount of release, although not clear, is believed to have been about 100 milligrams.

As you know from Dessert Storm, the Iraqis were involved in developing biological weapons—they were producing anthrax bacilli in ton quantities. Those bacilli were weaponized in shells. We also had a Japanese religious cult that was producing both bacillinous toxin and anthrax. Today between 12 to 20 countries are actively involved with experimentation into biological warfare defense, up from only about 2 countries 25 years ago.

Should we be devoting resources against these microorganisms? How big is the problem? One way to look at these questions is to consider that in the 20th century,

between 100 and 150 million Americans died as a result of armed conflict. How does this compare to deaths from microbes? Table 3 puts these figures in perspective and perhaps gives a justification for expending resources against these microbes.

Table 3. Deaths from various causes in the United States.

Cause	Number of deaths (million)
Armed conflict (average per year, 20th century)	1.0–1.5
Influenza (1918)	21.0
Smallpox (1967)	2.0–2.5
Diarrhea (1993)	3.0
TB (1993)	2.7
Malaria (1993)	2.0
Measles (1985)	3.0
(1993)	1.2

I close with a quote from Joshua Lederberg, the Nobel Laureate and former President of Rockefeller University: "It is clear that man's only competitors for the dominion of the planet are the viruses—and the ultimate outcome is by no means fore-ordained."

Figure 1

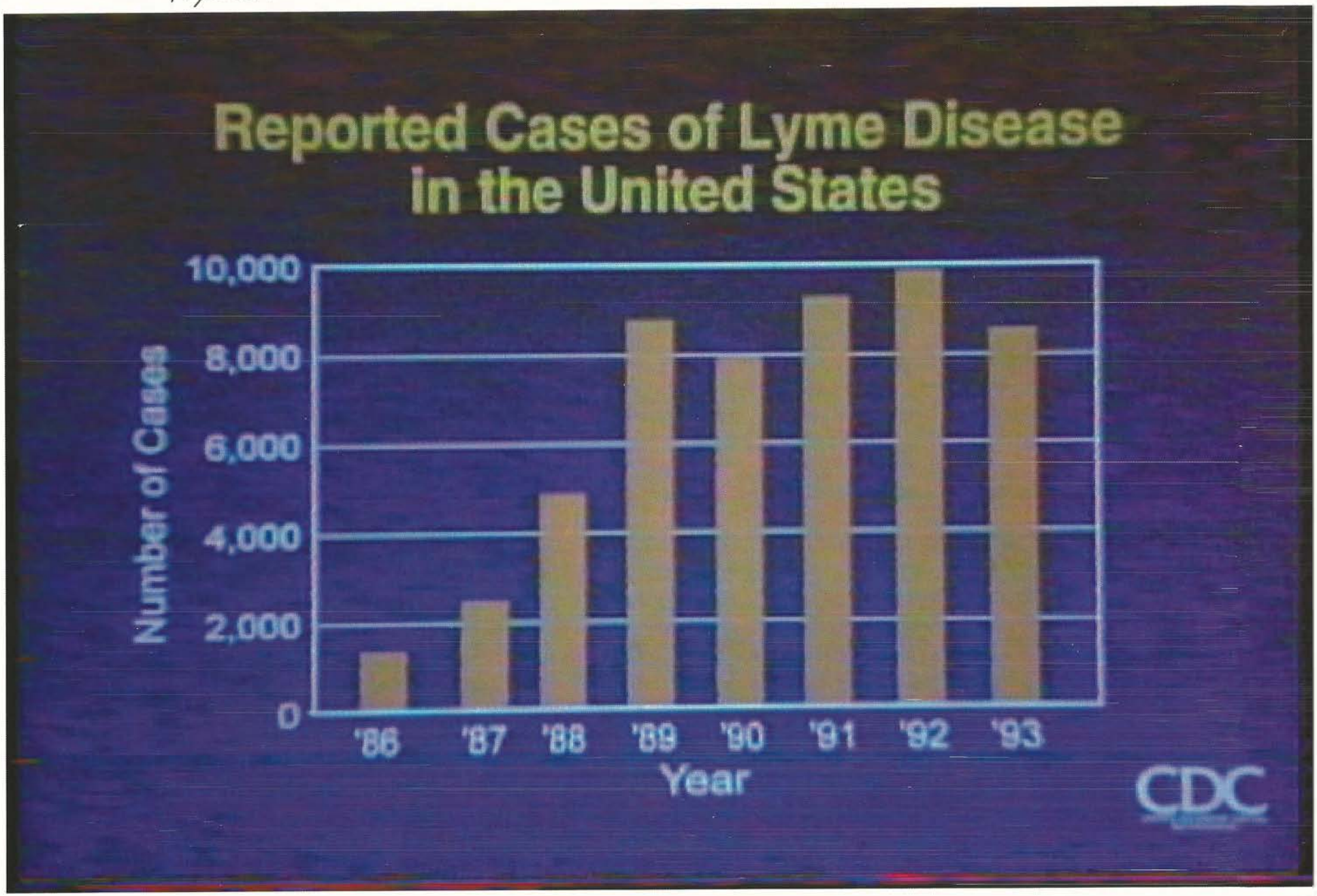
Reported Cases of Lyme Disease
in the United States
Number of Cases
10,000
8,000
6,000
4,000
2,000
0
'86
'87
'88
'89
'90
'91
'92
'93
Year
CDC

Figure 2

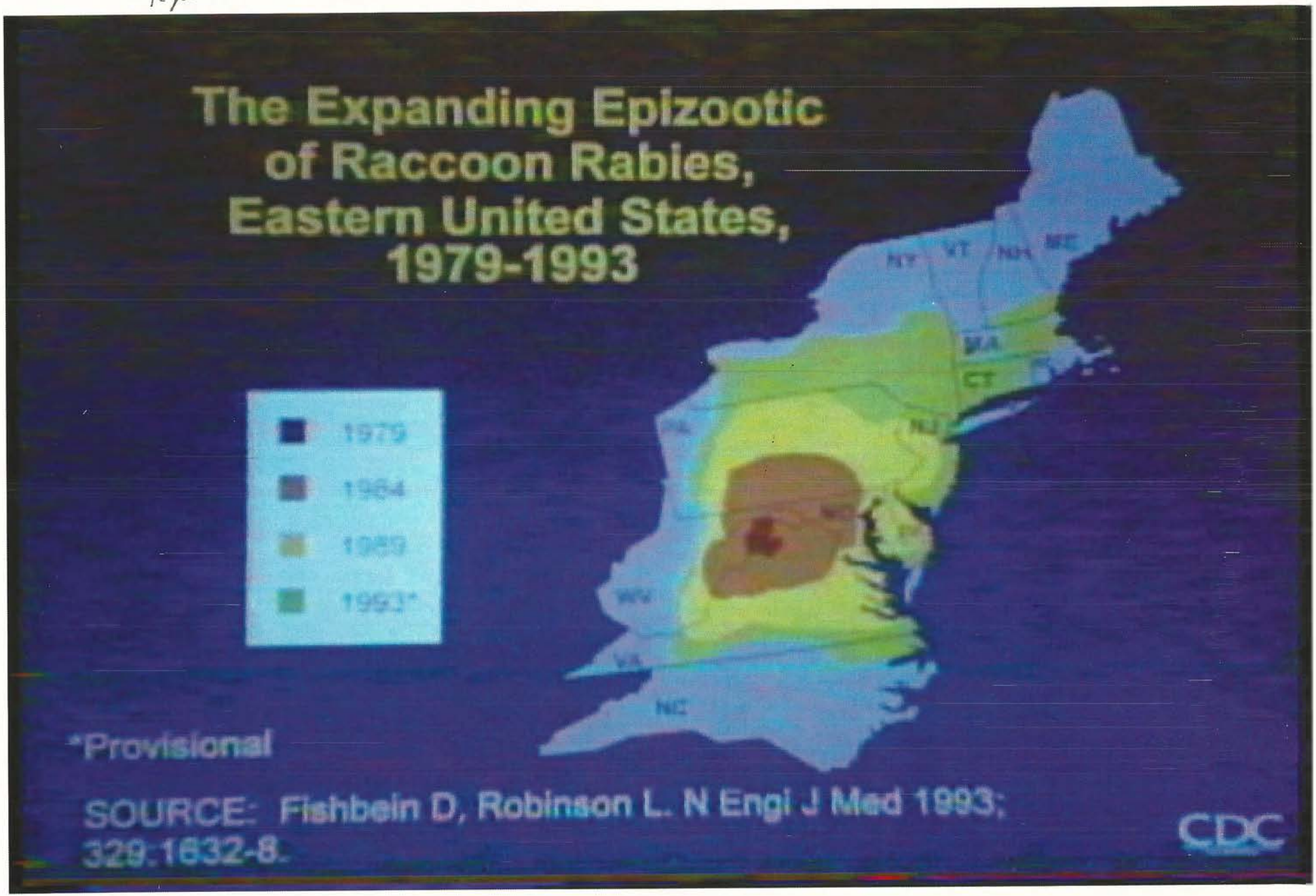
The Expanding Epizootic of Raccoon Rabies, Eastern United States, 1979-1993
1979
1984
1989
1993*
NY
VT
NH
ME
MA
CT
NJ
PA
WV
VA
NC
*Provisional
SOURCE: Fishbein D, Robinson L. N Engl J Med 1993; 329:1632-8.
CDC

Figure 3

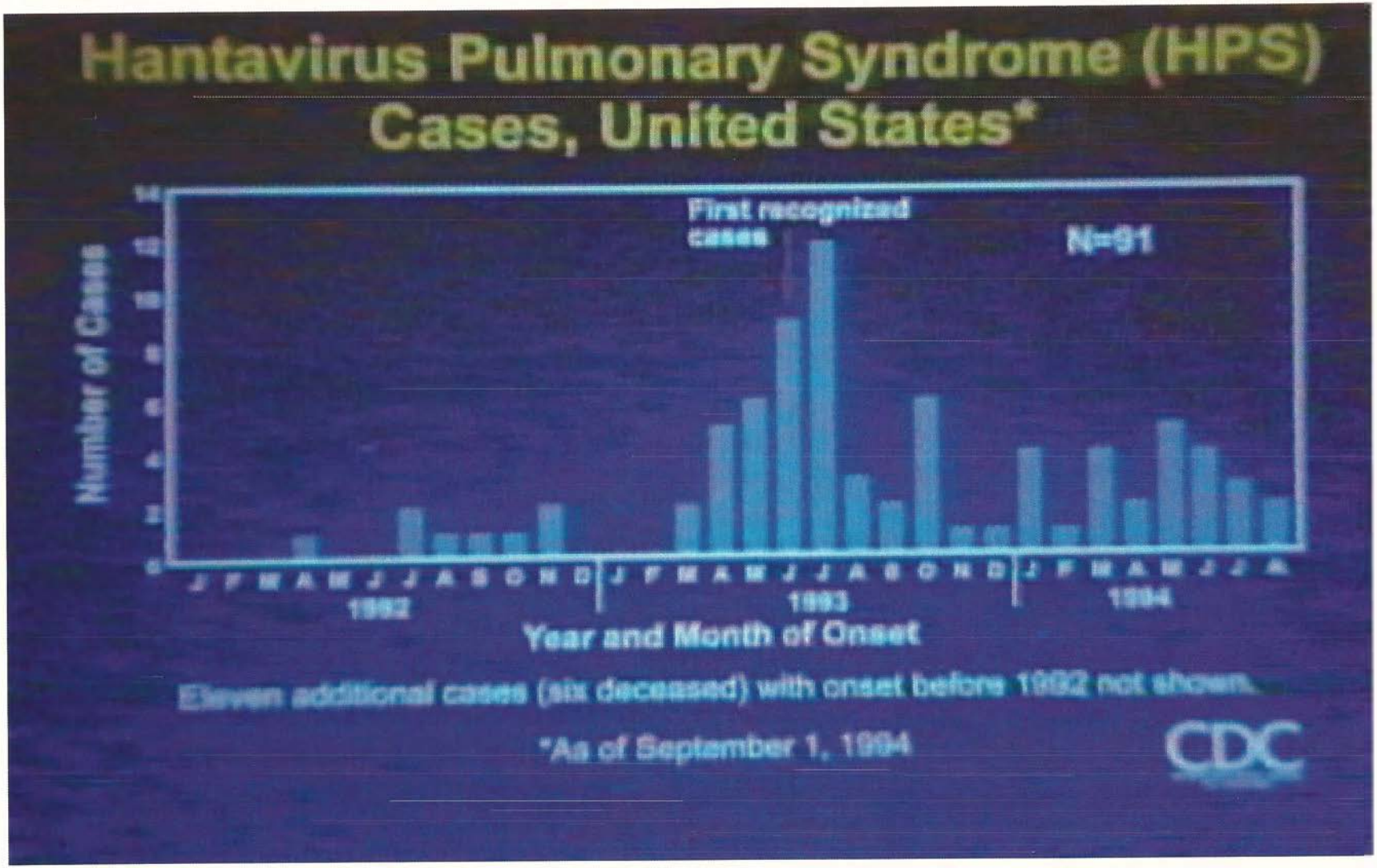
Hantavirus Pulmonary Syndrome (HPS)
Cases, United States*
First recognized cases
N=91
Number of Cases
J F M A M J J A S O N D J F M A M J J A S O N D J F M A M J J A
1992
1993
1994
Year and Month of Onset
Eleven additional cases (six deceased) with onset before 1992 not shown.
*As of September 1, 1994
CDC

Figure 4

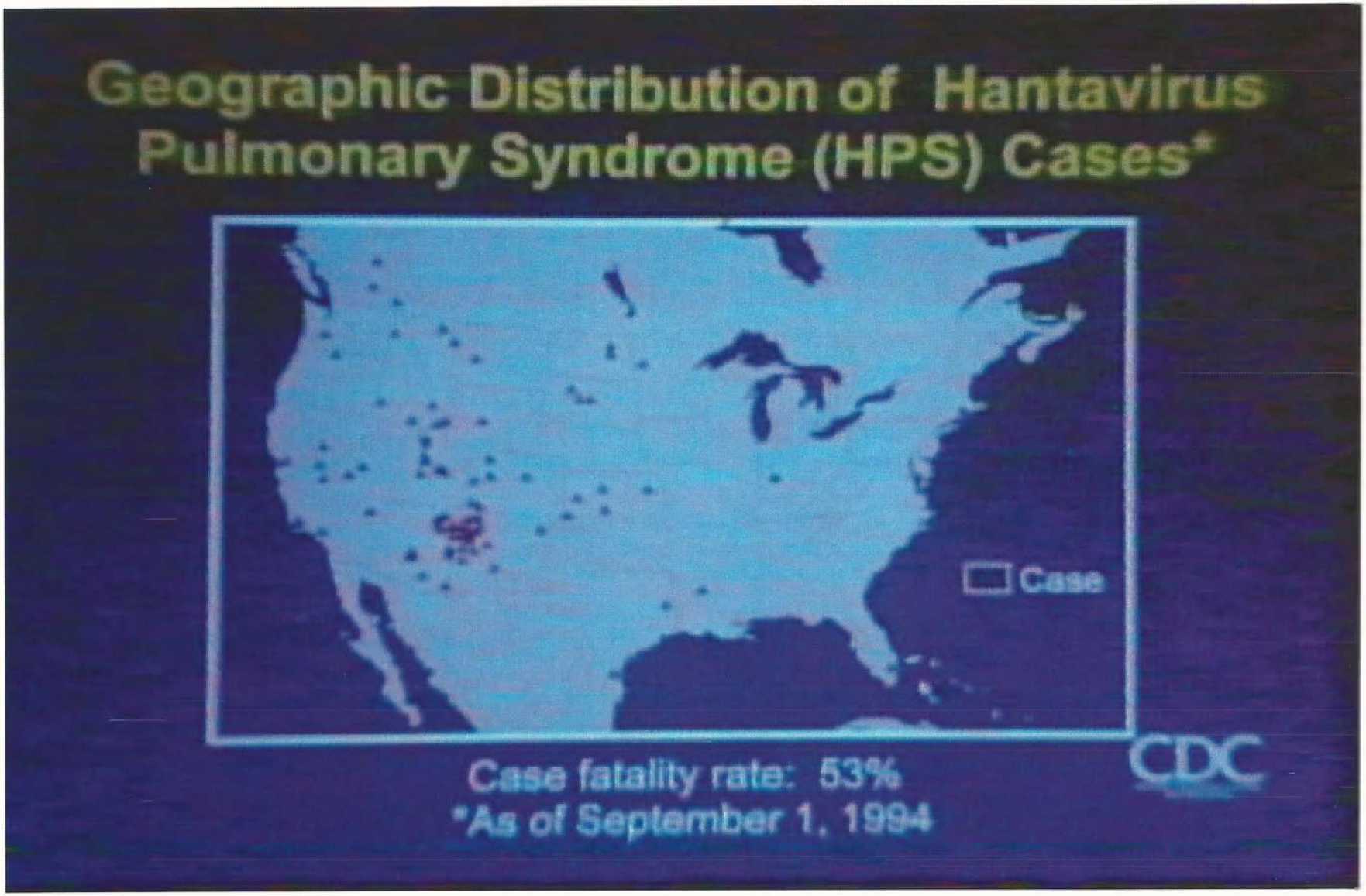
Geographic Distribution of Hantavirus Pulmonary Syndrome (HPS) Cases*
Case
Case fatality rate: 53%
*As of September 1, 1994
CDC

Figure 5

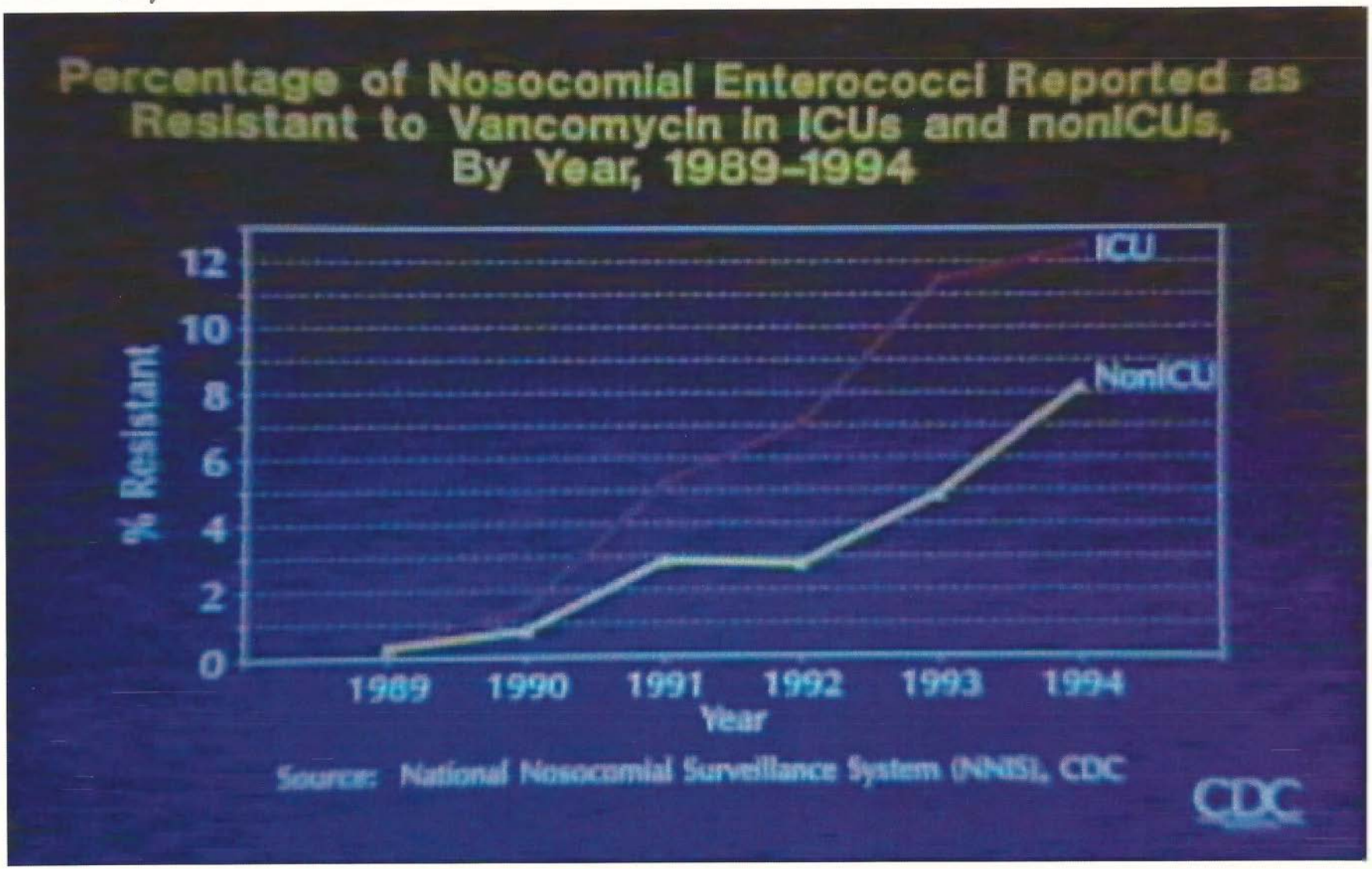
Percentage of Nosocomial Enterococci Reported as Resistant to Vancomycin in ICUs and nonICUs, By Year, 1989–1994
% Resistant
0
2
4
6
8
10
12
ICU
NonICU
1989
1990
1991
1992
1993
1994
Year
Source: National Nosocomial Surveillance System (NNIS), CDC
CDC

Figure 6

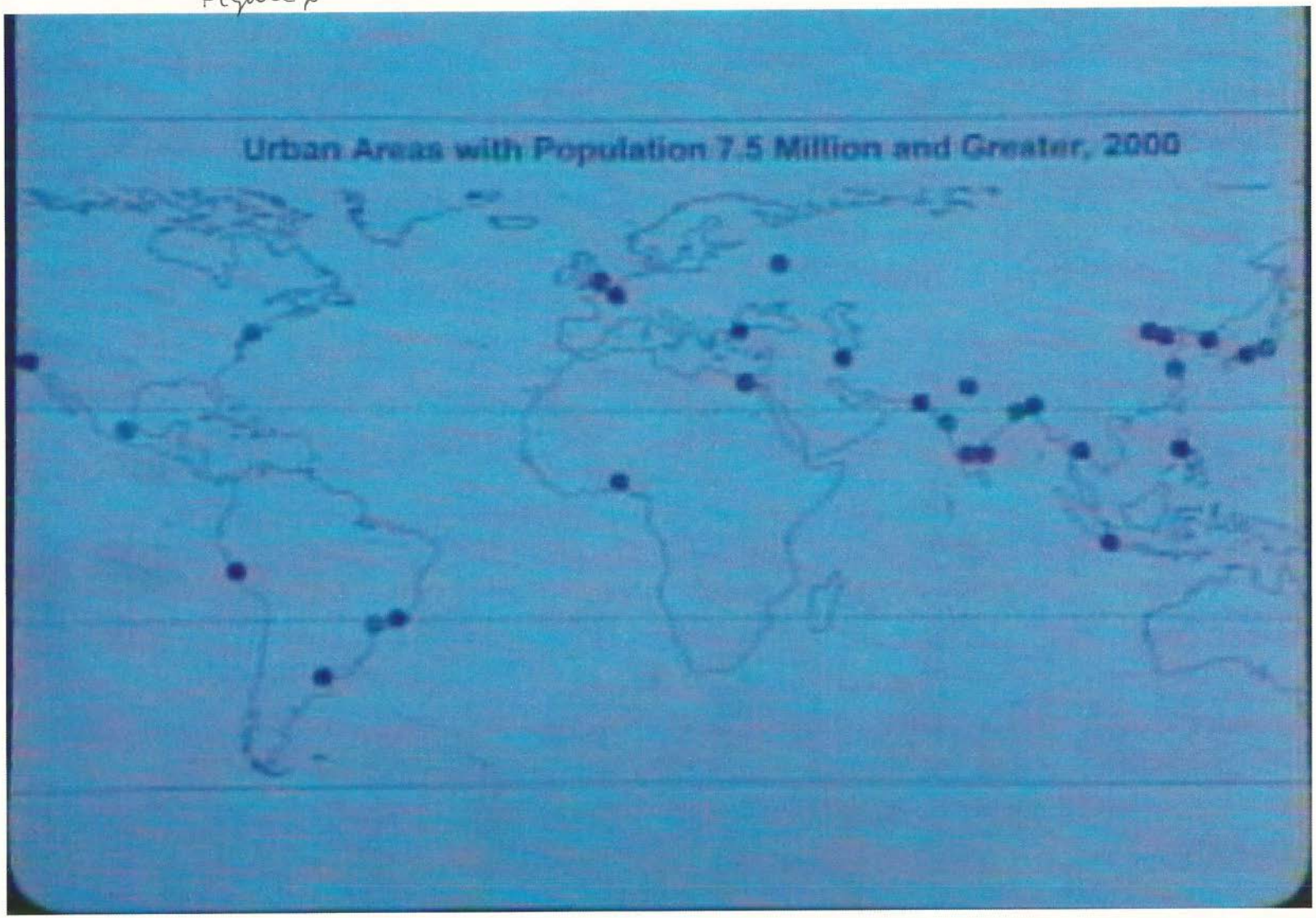

Figure 7

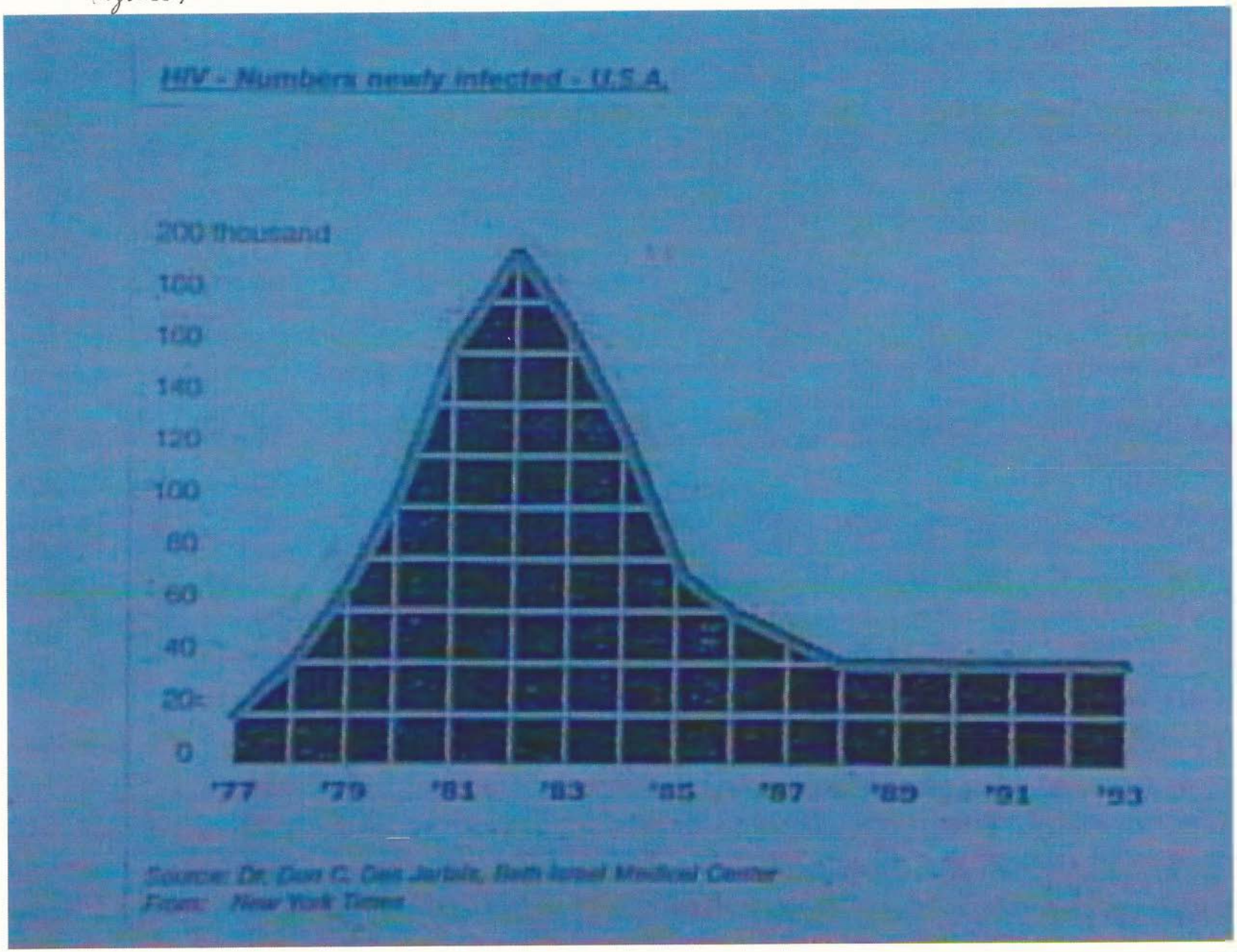
HIV - Numbers newly infected - U.S.A.
200 thousand
160
140
120
100
80
60
40
20
0
'77
'79
'81
'83
'85
'87
'89
'91
'93
Source: Dr. Don C. Des Jarlais, Beth Israel Medical Center
From: New York Times

Figure 8


THE SPREAD OF THE BLACK DEATH IN EUROPE
PARTIALLY OR TOTALLY STAMPED BY THE PLAGUE
ATLANTIC OCEAN