Hantavirus Pulmonary Syndrome: An Emerging Infectious Disease

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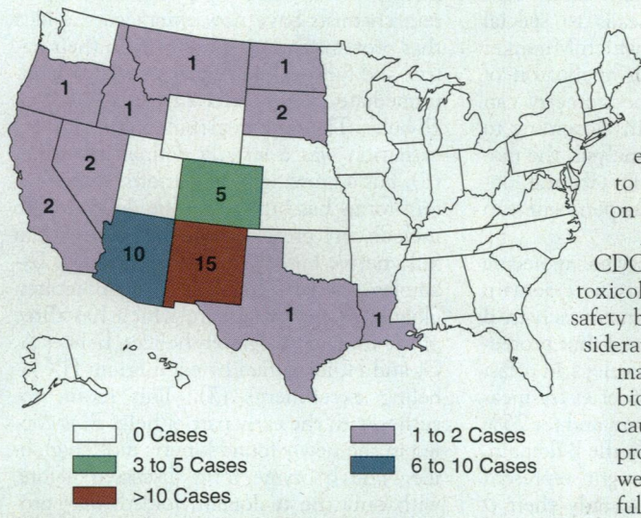
"Pathogenic microbes can be resilient, dangerous foes. Although it is impossible to predict their individual emergence in time and place, we can be confident that new microbial diseases will emerge." A recent report (*1*) by an Institute of Medicine Committee included this warning about infectious diseases in the United States, and emphasized the complacency that has developed regarding their control. The Committee recommended measures of increased vigilance to ensure that such diseases are detected early and investigated rapidly.

Since publication of this report in October of 1992, U. S. public health officials have confronted a number of emergent infectious diseases, including an outbreak of hemorrhagic colitis and hemolytic-uremic syndrome in several western states, caused by foodborne *Escherichia coli* 0157 (*2*); a large outbreak of cryptosporidiosis in Milwaukee, caused by contaminated water (*3*); infections in children attending day-care centers, caused by multiple drug-resistant pneumococci (*4*); bloodstream infections in New York hospitals, caused by vancomycin-resistant enterococci (*5*); influenza, caused by a new strain (A/Beijing/32/92) of influenza A virus (*6*); and, as discussed here, a lethal pulmonary disease in the southwestern United States, caused by a new rodent-borne hantavirus. The sequence of events leading up to the identification of this hantavirus provides several important lessons about the critical role of the public health system in an era of health care reform.

The first suspicion of this disease can be traced to the observations of an Indian Health Service (IHS) clinician knowledgeable about the spectrum of illnesses in his community. In mid-May, this clinician treated a patient suffering from an unusual respiratory illness. He contacted other practicing physicians and the Office of Medical Investigations (OMI) of the state of New Mexico, which resulted in identification of four additional patients with similar symptoms.

On 27 May, the IHS and the New Mexico Department of Health requested assistance in the investigation from the Centers for Disease Control and Prevention (CDC), and on 29 May, four CDC epidemiologists traveled to the area to join an investigation that included personnel from the Health Departments of the Four Corner states (New Mexico, Arizona, Colorado, and Utah), the IHS, the Navajo Nation Division of Health, and the University of New Mexico Medical Center.



Distribution of hantavirus pulmonary syndrome in the United States, as of 14 October 1993. (Data source is the Division of Viral and Rickettsial Diseases, National Center for Infectious Diseases, Centers for Disease Control and Prevention.)

Investigation of the initial patients indicated that the disease affected healthy young adults and was first manifested as a fever, accompanied by muscle aches and other nonspecific symptoms. Hospitalization was often prompted by the sudden onset of interstitial pulmonary edema, which rapidly progressed to respiratory failure and, in most cases, death. Other organ systems were minimally involved, although severely affected patients showed evidence of shock. Leukocytosis and other hematological abnormalities were common, and mild renal insufficiency was seen in a few. Patients with similar symptoms were scattered over a large geographic area in the southwest.

Extensive laboratory studies by the State Health Departments and the University of New Mexico soon eliminated the most likely candidate etiologic agents, such as *Yersinia pestis* (the pathogen responsible for pneumonic plague), *Legionella*, *Mycoplasma*, and influenza virus. When separate meetings were held in New Mexico and Atlanta over the Memorial Day weekend to review these findings, no known toxic or infectious agent satisfactorily explained the clinical and epidemiological findings. Immediately, a broad-based laboratory investigation began at CDC to search for both recognized and novel infectious agents and toxins. At the same time, additional CDC epidemiologists were dispatched to the Four Corner's area to assist in accelerated clinical and epidemiological studies and to formulate new hypotheses on etiology.

As samples were sent to CDC for microbiologic and toxicologic investigations, biosafety became another major consideration. Clinical material was manipulated with enhanced biosafety level 3 (BSL-3) precautions, and attempts to propagate the suspected agent were performed under carefully controlled conditions, including animal inoculation at maximum containment levels (BSL-4).

By 4 June, serologic tests conducted by the Special Pathogens Branch, Division of Viral and Rickettsial Diseases, National Center for Infectious Diseases (NCID), CDC, provided the first lead to disease etiology. Antibodies cross-reactive with recognized hantaviruses were identified in sera from patients meeting a provisional case definition, and the pattern of reactivity suggested that the pathogenic agent was a previously unrecognized hantavirus.

Hantaviruses are negative-stranded RNA viruses belonging to the family *Bunyaviridae* (*7*). Hantaviral disease first became a U.S. public health concern in the 1950s, when soldiers serving in the Korean conflict developed an illness referred to as Korean hemorrhagic fever or hemorrhagic fever with renal syndrome (HFRS) (*8*). The causative agent, Hantaan virus, was not isolated until the late 1970s (*9*). HFRS is characterized by severe renal failure and prominent hemorrhage, and is therefore quite distinct from the new disease (provisionally named hantavirus pulmonary syndrome or HPS), with its severe, noncardiac pulmonary edema and shock. Other hantaviruses include Puumala virus, which causes a mild form of HFRS common in Europe; Prospect Hill virus, a North American virus that has not been associated with human disease; and Seoul virus, antibodies

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to which have been associated with hypertensive end-stage renal disease in patients in Baltimore (*10, 11*).

Once a hantavirus was suspected, scientists incorporated state-of-the-art molecular virology methods into their investigations. Oligonucleotide primers based upon conserved sequences of known hantaviruses were designed for use in the polymerase chain reaction (PCR) to amplify hantavirus-specific RNA from tissues of patients dying from the disease. Subsequent serological and PCR studies implicated the deer mouse (*Peromyscus maniculatus*) as the virus reservoir (*12*). Identification of hantaviral antigens in capillary endothelium of the lung provided an important pathogenetic link to the dramatic clinical manifestation of pulmonary edema (*13*). NCID scientists then cloned, sequenced, and expressed large parts of the genome of the new virus from human autopsy tissues (*14*). Phylogenetic studies based on these sequences firmly established that a new hantavirus causes HPS. Remarkably, these advances, as well as production of candidate diagnostic reagents, have been achieved even though the virus has not yet been propagated in cell culture.

The rapid identification of this hantavirus was greatly facilitated by the background information acquired from studies on HFRS, a project that received continual support from the Department of Defense since the 1950s. These studies led to the isolation of Hantaan virus (9), adaptation of the virus to cell culture (*15*), and characterization of the virus (*7*) at the U.S. Army Medical Research Institute of Infectious Diseases. Without this previous experience with hantaviruses, the present investigation would have been delayed considerably.

Public health efforts have now shifted to defining the clinical aspects of the disease and identifying possible risk factors for infection. Person-to-person transmission does not occur with other hantaviruses, and there is no evidence of virus transmission to health care workers in this investigation. Over 5000 specimens a month, from humans and wild rodents, have come to CDC laboratories in the course of these studies, and geographic mapping of the disease and virus is in progress (figure). The broad distribution of *P. maniculatus* (*16*) suggests that sporadic cases may occur over much of the United States if the virus is distributed wherever the reservoir is found. Indeed, the disease has been identified in most western states. Interestingly, a patient with a similar clinical picture has been identified in Louisiana, where *P. maniculatus* is not found. Genetic sequences obtained from autopsy lung tissue revealed that another previously unrecognized hantavirus may be associated with HPS in that location.

Current prevention strategies are focused on minimizing the risk of contact with the rodent reservoir and rodent excreta (*17*). The antiviral drug ribavirin is being evaluated as a therapeutic agent. The possibilities for vaccine development await further definition of the geographic extent of the disease and identification of high-risk groups.

Many questions remain to be addressed. What is the origin of the virus? Did it evolve recently through genetic reassortment or has it existed in rodent populations in the epidemic area for a long time? What is its geographic distribution? Are there additional, previously unrecognized hantaviruses in rodents in other parts of the United States? Why did the epidemic occur this year? Are there behaviors, occupations, or other factors that affect risk of infection? Why is the lung primarily affected? What are the optimal treatment and prevention strategies? Answers to these and other questions will require continued investigations of the epidemic by a multidisciplinary team of federal, state, and local public health officials, clinicians, biomedical researchers, behavioral scientists, and public education specialists, working in collaboration with the Navajo Nation and other groups.

Recognition of the HPS epidemic underscores the importance of implementing the recommendations in the Institute of Medicine report (*1*) and serves as a reminder of the challenges that microbial agents will continue to pose. Investigations of future infectious diseases are likely to benefit from the same combination of epidemiologic and laboratory expertise that proved so essential in establishing the hantaviral etiology of HPS.

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