A Midcourse Assessment of Hantavirus Pulmonary Syndrome

Our understanding of infectious diseases follows a natural course—the initial discovery of the cause, the exploration of the natural history and biology of the etiologic agent, and finally the cure or solution. The discovery of Sin Nombre virus (SNV), one of the viruses causing hantavirus pulmonary syndrome (HPS), is unparalleled in terms of the rapid progress of the scientific investigation leading to its description. A cluster of cases of fatal adult respiratory syndrome was recognized in the Four Corners region of the United States in May 1993, and within a few days serologic evidence confirmed hantavirus infection (1). The outbreak occurred in the wake of the Institute of Medicine's report Emerging Infections: Microbial Threats to Health in the United States, in which acute respiratory disease was first on the list of clinical syndromes requiring high-priority surveillance (2).

The scientific community has now entered the midcourse phase of HPS research, including the exploration of the natural history of the American hantaviruses. Seven articles in this issue describe studies of rodent reservoirs of Sin Nombre and related viruses. They illustrate the multidisciplinary nature of such studies, which require ecologic methods, in addition to the newer molecular biology techniques that have helped hantavirologists detect and characterize the viruses.

These and other studies have elucidated much about the natural host relationships of hantaviruses. Multiple hantavirus genotypes exist in virtually all parts of North and South America; each hantavirus genotype has a single rodent species as its principal reservoir. Evidence exists that the virus and rodent have evolved together. Each hantavirus variant is focal in distribution. Prevalence of antibody is high in some regions, and low or absent in others, even when the same species of rodent is found in both places. Rodents are not infected at birth; they acquire the virus from other rodents. Once infected, the animals develop antibody, but many, or maybe all, infected rodents remain infected. Because of rapid turnover of the rodent population (as older antibody-carrying animals die and nonimmune animals are born), antibody prevalence can vary greatly, from 0% to 50%, with prevalence often lower than 20%.

The studies also have raised new questions. Why and by what route are animals infected? The articles in this issue suggest that contamination of wounds when animals fight may be an important route of infection, while allowing for the possibility of secondary mechanisms, such as venereal transmission or close association during communal nesting. Although textbooks state that people become infected by inhaling aerosols created by the rodents, we need better information. If the animals create infectious aerosols, why are only a small proportion of susceptible animals infected, even in enclosed colonies of the rodents (3)? Why is human infection so rare, even among forest workers and mammalogists (4)? Are some animals supersecretors of virus? Are individual virus-carrying rodents infectious for life or only periodically? If periodically, what makes them shed and stop shedding virus?

Classic pathogenesis studies are required to answer these questions. Two technologic advances—reverse transcription-polymerase chain reaction (RT-PCR) and enzyme-linked immunosorbent assay (ELISA)—have revolutionized science but at the same time lured us away from other time-tested methods. Before the RT-PCR technique was developed, virologists measured infectious virus by isolating it in cell cultures or laboratory animals. Although we need information about the infectivity of rodent blood, urine, throat secretions, feces, and organs, few investigators attempt to isolate infectious hantaviruses. The reasons are obvious. Virus isolation is tedious, technically difficult, and (without biosafety level three or four facilities) dangerous. Because detecting nucleic acid by RT-PCR is safe and easily accomplished, most investigators are satisfied with that method. Safe isolation of hantaviruses in the Americas will require additional investment in physical biocontainment facilities for university and government laboratories.

Many compelling reasons exist for isolating hantaviruses. How else will serotype specificity, animal models, pathogenic potential, replication, transmission, and other phenotypic properties be studied? I cannot emphasize too strongly the importance of propagating and preserving this biologic material. To isolate hantaviruses from rodent tissues will require new approaches. The technical difficulty now in isolating hantaviruses is analogous to that encountered 30 years ago with dengue viruses. The solution for dengue was to use a natural host, the mosquito (5). Colonized, virus-free rodent reservoir hosts of hantaviruses could possibly provide the increased sensitivity to infection needed to facilitate routine isolation of hantaviruses. This approach has been successful on a limited scale in Europe (6).

Only two serologic methods—ELISA and, to a lesser extent, immunofluorescence assay—are used on a large scale in the Americas for testing rodent sera for hantavirus antibody. CDC developed a recombinant antigen product of the small RNA segment of SNV (7), which was produced in large quantity and distributed gratis to state health departments and to collaborators in both North and South America for use in ELISA. The antigen is broadly cross-reactive and entirely safe. Before the advent of ELISA, classic virologists surveyed for antibody with one test and then confirmed a portion of the antibody-positive and -negative serum specimens with a different test, often the neutralization test. Such confirmatory tests are desirable in the studies of rodents for hantavirus antibody but are rarely done. The neutralization test, used to a limited extent (8), is not practical for study of large numbers of rodent serum specimens or for work with biosafety level four agents. An alternate to this test is the hemagglutination-inhibition test. Asian and European hantaviruses agglutinate goose cells (9,10); it should be feasible, therefore, to develop the hemagglutination-inhibition test for American hantaviruses.

What will it take to cure or prevent HPS? The only proposed antihantavirus drug is ribavirin, which although still under trial, has not been efficacious in treating HPS (11). Supportive emergency care can save lives, but diagnosis must be made early, clinical expertise is concentrated in only a few medical centers, and HPS cases are often dispersed. Approaches to hantavirus human vaccines have been developed (12), but such vaccines are probably not commercially feasible in the Americas, which have a low incidence of disease caused by focal genotypes. Rodent control does not seem practical because of the immense geographic range of hantaviruses. Ongoing rodent studies may eventually determine whether a wildlife vaccine analogous to that used successfully for rabies will be practical (13).

For the immediate future, we must depend on education to prevent human exposure. To design an effective education program, we must know much more about the rodent reservoir and the mode of virus transmission, both among rodents and to people. The publication of these ecologic studies in a medical journal represents important changes in the medical and ecologic sciences. These studies have required collaboration of ecologists, epidemiologists, and virologists. Their successful continuation, as well as the conception, design, and conduct of future studies, requires the spirit of innovation best achieved in a multidisciplinary atmosphere, as well as a long-term commitment to collect data for several years.

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