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Emerging Infectious Diseases

Emerging Infectious Diseases is published four times a year by the National Center for Infectious Diseases, Centers for Disease Control and Prevention (CDC), 1600 Clifton Road., Mailstop C-12, Atlanta, GA 30333, USA. Telephone 404-639-3967, fax 404-639-3039, e-mail EIDEDITOR@CIDOD1.EM.CDC.GOV.

Editorial Policy and Call for Articles

The goals of *Emerging Infectious Diseases* (EID) are to promote the recognition of new and reemerging infectious diseases and to improve the understanding of factors involved in disease emergence, prevention, and elimination. EID has an international scope and is intended for professionals in infectious diseases and related sciences. We welcome contributions from infectious disease specialists in academia, industry, clinical practice, and public health as well as from specialists in economics, demography, sociology, and other disciplines whose study elucidates the factors influencing the emergence of infectious diseases.

EID will be published in English and will feature three types of articles: *Perspectives*, *Synopses*, and *Dispatches*. The purpose and requirements of each type of article are described in detail below.

Instructions to Authors

Editorial Material: Manuscripts should be prepared according to the "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" (JAMA 1993:269[17]: 2282-6).

Begin each of the following sections on a new page and in this order: title page, abstract, text, acknowledgments, references, each table, figure legends, and figures. On the title page, give complete information about each author (full names and highest degree). Give current mailing address for correspondence (include fax number and e-mail address). Follow Uniform Requirements style for references. Consult *List of Journals Indexed in Index Medicus* for accepted journal abbreviations. Tables and figures should be numbered separately (each beginning with 1) in the order of mention in the text. Double-space everything, including the title page, abstract, references, tables, and figure legends. Italicize scientific names of organisms from species name all the way up, except for vernacular names (viruses that have not really been speciated, such as coxsackievirus and hepatitis B; bacterial organisms, such as pseudomonads, salmonellae, and brucellae).

Perspectives: Contributions to the *Perspectives* section are welcome from scientists and professionals in all disciplines and should address factors known to contribute to the emergence of infectious diseases, including microbial adaption and change; human demographics and behavior; technology and industry; economic development and land use; international travel and commerce; and the breakdown of public health measures. Articles should be approximately 3,500 words and should include references, not to exceed 40. The section should begin with an introduction outlining the relationship of the issues discussed in the paper to the emergence of infectious diseases. Use of additional subheadings in the main body of the text is recommended. If detailed methods are included, a separate section on experimental procedures should immediately follow the body of the text. Photographs and illustrations are optional. Provide a short abstract (150 words) and a brief biographical sketch.

***Synopses*:** Submit concise reviews of infectious diseases or closely related topics. Preference will be given to reviews of new and emerging diseases; however, timely updates of other diseases or topics are also welcome. Synopses should be approximately 3,500 words and should include references, not to exceed 40. The section should begin with an introduction outlining the relationship of the issues discussed in the paper to the emergence of infectious diseases. Use of additional subheadings in the main body of the text is recommended. If detailed methods are included, a separate section on experimental procedures should immediately follow the body of the text. Selective use of illustrations is encouraged. Provide a short abstract of no more than 150 words and a brief biographical sketch.

Dispatches: Provide brief updates on trends in infectious diseases or infectious disease research. Dispatches (1,000 to 1,500 words of text) should be in a "letter to the editor" format and should not be divided into sections. Dispatches should begin with a brief introductory statement about the relationship of the topic to the emergence of infectious diseases. Include methods development; references, not to exceed five; and figures or illustrations, not to exceed two.

All articles will be reviewed by independent reviewers. The Editor reserves the right to edit articles for clarity and to modify the format to fit the publication style of *Emerging Infectious Diseases*.

Send documents in hardcopy (Courier 10-point font), on diskette, or by e-mail. Acceptable electronic formats for text are ASCII, WordPerfect, AmiPro, DisplayWrite, MS Word, MultiMate, Office Writer, WordStar, or Xywrite. Send graphics documents in Corel Draw, Harvard Graphics, Freelance, .TIF (TIFF), .GIF (CompuServe), .WMF (Windows Metafile), .EPS (Encapsulated Postscript), or .CGM (Computer Graphics Metafile). The preferred font for graphics files is Helvetica. If possible, convert Macintosh files into one of the suggested formats. Submit photographs in camera-ready hardcopy.

Send all manuscripts and correspondence to the Editor, *Emerging Infectious Diseases*, National Center for Infectious Diseases, Centers for Disease Control and Prevention, 1600 Clifton Road, Mailstop C-12, Atlanta, GA 30333, USA or by e-mail on the Internet to EIDEDITOR@CIDOD1.EM.CDC.GOV.

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Emerging Infections: Getting Ahead of the Curve

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The early history of infectious diseases was characterized by sudden, unpredictable outbreaks, frequently of epidemic proportion. Scientific advances in the late 19th and early 20th centuries resulted in the prevention and control of many infectious diseases, particularly in industrialized nations. Despite these improvements in health, outbreaks of infectious disease continue to occur, and new infections emerge. Since 1987, the National Academy of Science's Institute of Medicine (IOM) has published three reports that have identified erosion of the public health infrastructure among the factors contributing to new and reemerging infectious diseases. In partnership with many public and private organizations in the United States and abroad, the Centers for Disease Control and Prevention (CDC) has developed a strategic plan that addresses the priorities set forth in the IOM reports and serves as a guide for CDC and its partners to combat emerging microbial threats to health. Laboratory-based surveillance, better communication networks, and improvements in the public health infrastructure are the cornerstones of the strategy. Emerging Infectious Diseases, *a new periodical produced by CDC, will serve as a forum for exchange of information about incipient trends in infectious diseases, analysis of factors contributing to disease emergence, and development and implementation of prevention measures.*

"Nothing in the world of living things is permanently fixed."

Hans Zinnser—Rats, Lice and History, 1935

Early History of Infectious Diseases

Infectious diseases have plagued humans since the dawn of civilization (1-5). The history of these diseases provides a valuable perspective for evaluating current trends. Humans are presumed to have originated in tropical climates and to have been affected by the same parasitic diseases as other primates in these areas. As available supplies of game diminished, early hunters migrated into temperate zones which were free of tropical parasites. Historians speculate that humans were relatively safe from infectious diseases during that period. Later, however, as agriculture began to provide a substantial portion of the human diet, populations stabilized and grew. Eventually, populations reached a size that would support persistent person-to-person spread of infectious microorganisms. With this newly established mode of transmission, infectious diseases soon became widespread. The exact origins of many infectious agents remain obscure, but with the advent of large populations, humans eventually became the established reservoir of many agents. Infected animals and contaminated food and water were additional sources of infectious microorganisms.

Dissemination of infectious diseases intensified as civilizations progressed. Caravans of traders carried new pathogens to unsuspecting and susceptible populations. Explorers and later conquering armies brought infectious microorganisms to new continents. Stowaway rats and other vermin in the holds of ships traveled down the moorings when the ships docked, bringing fleas, lice, and deadly pathogens to a new world. Sporadic epidemics of plague, smallpox, typhus, and measles ravaged cities, decimated armies, and altered the course of history.

19th Century Discoveries Lead to Infectious Disease Prevention and Control

Control of many infectious diseases became possible with the pioneering work of Robert Koch and Louis Pasteur and the introduction of the germ theory of disease. With bacteriologic cultivation techniques came the first isolation and identification of etiologic agents; virus cultivation and identification became available some decades later. Reservoirs of microorganisms and their life cycles were identified; the epidemiology and natural history of many infectious diseases were described, and successful control measures were initiated. Water

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treatment, vector control, and rodent reduction programs followed. By the beginning of the 20th century, the principles of vaccination, established empirically by Edward Jenner more than 100 years earlier, began to be realized in earnest. Antibiotics were discovered, and disinfectants were developed. Collectively, these control measures dramatically decreased the incidence and prevalence of many infectious diseases and their fatality rates. The early part of this century is appropriately regarded as a golden age in public health.

New and Reemerging Infectious Diseases—A Contemporary Problem

Compared with earlier generations, we possess an enormous scientific base, and the rate of acquisition of new information about infectious diseases is at a historic high. Moreover, thanks in large measure to effective childhood immunization programs, including the President's Childhood Immunization Initiative, many infectious diseases are under control, particularly in the industrialized world. The elimination of smallpox in 1977 stands as a towering achievement in the fight against infectious diseases. However, many infectious diseases have persisted and have displayed a remarkable ability to reemerge after lengthy periods of stability. Therefore, we must be ever mindful of the cyclical nature of disease trends.

A careful review of infectious disease trends shows a fragile equilibrium between humans and infectious microorganisms. Infectious diseases are still broadly endemic and maintain a large reservoir of agents that have the potential for rapid and widespread dissemination. Infectious diseases remain the leading cause of death worldwide, even as the International Code of Diseases places many infectious diseases in other categories. For example, meningitis and cirrhosis are classified as diseases of the nervous system and liver, respectively, and only 17% of deaths attributable to infections are actually included in the codes for parasitic and infectious diseases (6). In the United States, each year, approximately 25% of physician visits are attributable to infectious diseases, with direct and indirect costs, including those for human immunodeficiency virus (HIV) infection and related illnesses, estimated at more than $120 billion (7).

Persons living in tropical climates are still as vulnerable to infectious diseases as their early ancestors were. Each year more than one million children die of malaria in sub-Saharan Africa alone (8); worldwide, approximately 200 million people have schistosomiasis (9), and each year 35-60 million people contract dengue (10). Moreover, infectious diseases and their attendant problems are not confined to tropical climates. For example, an estimated 600,000 cases of pneumonia occur in the United States each year and cause 25,000 to 50,000 deaths (11). More than 10,000 cases of diphtheria have occurred in Russia since 1993 because of inadequate levels of immunization (12). Despite a century of scientific progress, infectious diseases still cause enormous human suffering, deplete scarce resources, impede social and economic development, and contribute to global instability. The potential for even greater dissemination looms as a continuous threat.

Recent outbreaks underscore the potential for the sudden appearance of infectious diseases in currently unaffected populations. In the United States, contamination of the municipal water supply in Milwaukee, Wisconsin, in 1993 resulted in an outbreak of cryptosporidiosis that affected an estimated 400,000 people; approximately 4,400 persons required hospitalization (13). In the 1990s, epidemic cholera reappeared in the Americas, after being absent for nearly a century; from 1991 through June of 1994 more than one million cases and nearly 10,000 deaths were reported (14). During the 1980s, tuberculosis reemerged in the United States after decades of decline, and drug-resistant strains have made its control more difficult (15,16). The increasing prevalence of antibiotic-resistant strains of gonococci, pneumococci, enterococci, and staphylococci portend of other serious treatment and control failures. Many other examples of emerging infections could be given (17,18).

New infectious diseases, often with unknown long-term public health impact, continue to be identified. Table 1 lists major diseases or etiologic agents identified just within the last 20 years (19-41). New agents are regularly added to the list, particularly with the availability of nucleic acid amplification techniques for detecting and identifying otherwise noncultivable microorganisms (40, 42).

In some cases, etiologic agents have been identified as the causes of known diseases or syndromes (e.g., rotavirus, parvovirus, human T-cell lymphotropic viruses I and II (HTLV I/II), and human herpesvirus type 6, (HHV-6); in other cases, diseases became better recognized or defined (e.g., Legionnaires' disease, Lyme disease, human ehrlichiosis). Still others are entirely new: with some parallels to medieval times, a previously unknown and deadly disease, acquired immunodeficiency syndrome (AIDS), originated from uncertain sources in one part of the world and became globally disseminated; this time the disease spread at a rate that would have been unthinkable in medieval times. Clearly, the complete history of infectious diseases remains to be written.

Getting Ahead of the Curve

Recent disquieting infectious disease trends have not gone unrecognized, and their similarity to earlier disease trends with immense global consequences has not gone unnoticed. Primary responsibility for addressing new and reemerging infectious diseases rests squarely with the custodians of public health. Indeed, the fundamental maxim of public health must guide current prevention programs: the health of the individual is best ensured by maintaining or improving the health of the entire community. Core functions necessary to ensure the health of the public were defined in the National Academy of Science's Institute of Medicine (IOM) report on *The Future of Public Health* (43):

- Assessment of health status, risks, and services
- Development of health policy
- Assurance of quality health services

Surveillance (assessment) is the *sine qua non* of infectious disease prevention programs; however, for surveillance to be effective it must be specific. Consider, for example, surveillance of viral hepatitis. Only after the various agents of viral hepatitis were identified and specific laboratory testing became available was it possible to explain trends in disease prevalence and establish the epidemiologic principles underlying the different modes of transmission. Specific laboratory testing is also the basis of screening programs that ensure the safety of the blood supply against hepatitis B and hepatitis C. Agent-specific surveillance is a critical component of many immunization programs. Vaccines to *Haemophilus influenzae* type b, (Hib), for example, were developed in response to laboratory-based surveillance that identified Hib as a major cause of invasive disease in children. The effectiveness of the Hib vaccination campaign in the United States has been dramatic (Figure 1). Similar approaches will ensure appropriate formulation of other developmental vaccines. Monitoring antibiotic resistance is yet another important example of the value of laboratory-based

Table 1. Major Etiologic Agents, Infectious Diseases Identified Since 1973*

Year	Agent	Disease	Reference
1973	Rotavirus	Major cause of infantile diarrhea worldwide	19
1975	Parvovirus B19	Fifth disease; Aplastic crisis in chronic hemolytic anemia	20
1976	*Cryptosporidium parvum*	Acute enterocolitis	21
1977	Ebola virus	Ebola hemorrhagic fever	22
1977	*Legionella pneumophila*	Legionnaires' disease	23
1977	Hantaan virus	Hemorrhagic fever with renal syndrome (HFRS)	24
1977	*Campylobacter* sp.	Enteric pathogens distributed globally	25
1980	Human T-cell lymphotropic virus-I (HTLV I)	T-cell lymphoma—leukemia	26
1981	*Staphylococcus* toxin	Toxic shock syndrome associated with tampon use	27
1982	*Escherichia coli* O157:H7	Hemorrhagic colitis; hemolytic uremic syndrome	28
1982	HTLV II	Hairy cell leukemia	29
1982	*Borrelia burgdorferi*	Lyme disease	30
1983	Human immunodeficiency virus (HIV)	Acquired immunodeficiency syndrome (AIDS)	31
1983	*Helicobacter pylori*	Gastric ulcers	32
1988	Human herpesvirus-6 (HHV-6)	Roseola subitum	33
1989	*Ehrlichia chaffeensis*	Human ehrlichiosis	34
1989	Hepatitis C	Parenterally transmitted non-A, non-B hepatitis	35
1991	Guanarito virus	Venezuelan hemorrhagic fever	36
1992	*Vibrio cholerae* O139	New strain associated with epidemic cholera	37
1992	*Bartonella* (= *Rochalimaea*) *henselae*	Cat-scratch disease; bacillary angiomatosis	38, 39
1993	Hantavirus isolates	Hantavirus pulmonary syndrome	40
1994	Sabiá virus	Brazilian hemorrhagic fever	41

*Compiled by CDC staff. Dates of discovery are assigned on the basis of the year the isolation or identification of etiologic agents was reported.

surveillance. Within this context, current discoveries of etiologic agents and diseases (Table 1) are reasons for optimism. The potential for improvements in assessment and prevention of these and other newly discovered diseases is reminiscent of the watershed years of Koch and Pasteur.

We cannot overstate the role of behavioral science in our effort to "get ahead of the curve" with emerging infections. Having the science or laboratory technology to control infectious diseases is not enough, unless we can influence people to behave in ways that minimize the transmission of infections and maximize the efforts of medical interventions. For example, even though HIV/AIDS does not have a vaccine or cure, it is almost entirely preventable. For many people, however, reducing the risk for HIV infection and AIDS requires important changes in lifestyle or behavior. We must use our knowledge of human behavior to help people make lifestyle changes and prevent disease.

Another illustration of the need to use behavior science is the problem of antibiotic resistance. To a great extent, this problem is related to the behavior of both physicians and patients. Physicians continue to use antibiotics inappropriately, and patients continue to demand antibiotic treatment when it is not indicated, for example, for the common cold. As society changes and institutions such as day care centers and prisons become more crowded, the spread of infectious diseases is exacerbated. For homeless and drug-dependent populations, completing a 6- to 9-month course of therapy for tuberculosis is difficult, and the failure to complete the therapy increases the risk for drug-resistant tuberculosis in the community.

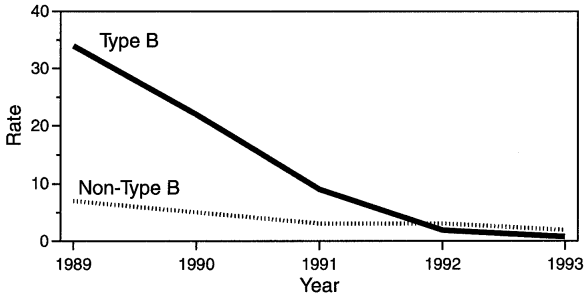

Figure 1. Race-adjusted incidence rate* of *Haemophilus influenzae* type b and non-type b disease detected through laboratory-based surveillance† among children aged <5 years — United States, 1989–1993

* Per 100,000 children aged <5 years.

† The surveillance area population was 10.4 million in four states (three counties in the San Francisco Bay Area, eight counties in metropolitan Atlanta, four counties in Tennessee, and the state of Oklahoma.

Source: CDC. Progress toward elimination of *Haemophilus influenzae* type b disease among infants and children — United States, MMWR 1994;43:144-8.

Microbiologists, infectious disease specialists, and other basic and clinical scientists must collaborate with behavioral scientists in an interdisciplinary effort to prevent and control emerging infections.

The Future of Public Health emphasizes the relationship between a sound public health infrastructure and infectious disease prevention programs. Infrastructure improvements must become a national priority: certainly they are among CDC's top priorities. Improvements in infectious disease surveillance are particularly needed (44). Enriching the capacity to respond to urgent threats to health and developing nationwide prevention strategies are also CDC priorities. To combat new and reemerging infectious diseases, CDC, in collaboration with other federal agencies, state and local health departments, academic institutions, professional societies, international organizations, and experts in public health infectious diseases and medical microbiology developed a plan—*Addressing Emerging Infectious Disease Threats: A Prevention Strategy for the United States* (7). The plan has four major goals:

- **Surveillance and Response**—detect, promptly investigate, and monitor emerging pathogens, the diseases they cause, and the factors influencing their emergence
- **Applied research**—integrate laboratory science and epidemiology to optimize public health practice
- **Prevention and control**—enhance communication of public health information about emerging diseases and ensure prompt implementation of prevention strategies
- **Infrastructure**—strengthen local, state, and federal public health infrastructures to support surveillance and implement prevention and control programs

CDC's plan provides a framework for the agency to work collaboratively with its many partners to identify and reverse worrisome trends in infectious diseases.

The need for implementing CDC's plan is urgent, given the extremely dynamic nature of disease trends and the complexity of factors contributing to disease emergence; these were outlined in detail in the 1992 IOM report—*Emerging Infections: Microbial Threats to Health in the United States* (45) and are discussed in a companion article by Stephen S. Morse, Ph.D., in this issue. The IOM report concludes that infectious diseases must be viewed as but one component of a dynamic and complex global ecology, which is shaped and buffeted by technologic, societal, economic, environmental, and demographic

changes, not to mention microbial change and adaptation.

Clearly, broader coalitions are needed, and communication must improve if we are to "get ahead of the curve." This new periodical is part of the overall strategy to draw worldwide attention to emerging infections and improve communication. Given the multiplicity of factors contributing to disease emergence, *Emerging Infectious Diseases* (EID) will present relevant concepts from professionals in multiple disciplines and disseminate information about emerging infectious diseases in order to develop and apply ecologically acceptable interventions that will benefit humankind. Prevention and control of new and emerging infectious diseases depend on the participation of scientists and other professionals in the public and private sectors.

CDC will make EID available by print and electronically to facilitate rapid communication. We hope that in the process EID will promote the exchange of infectious disease information through global electronic networks and bulletin boards.

Although there are many similarities between our vulnerability to infectious diseases and that of our ancestors, there is one distinct difference: we have the benefit of extensive scientific knowledge. Ultimately, our success in combatting infectious diseases will depend on how well we use available information. A recent report by the Carnegie Commission "Science, Technology, and Government for a Changing World," provides valuable insight in this regard (46). Commenting on the Earth Summit in Rio de Janeiro in 1992, the report emphasizes the need to shift from the "manifestations of environmental changes in the air, land, water, and plant and animal kingdoms to the causes of those changes." Indeed, the advice of that report challenges us all—"our capacity to generate, integrate, disseminate, and apply knowledge will determine the human prospect in the 21st century."

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Factors in the Emergence of Infectious Diseases

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"Emerging" infectious diseases can be defined as infections that have newly appeared in a population or have existed but are rapidly increasing in incidence or geographic range. Among recent examples are HIV/AIDS, hantavirus pulmonary syndrome, Lyme disease, and hemolytic uremic syndrome (a foodborne infection caused by certain strains of Escherichia coli*). Specific factors precipitating disease emergence can be identified in virtually all cases. These include ecological, environmental, or demographic factors that place people at increased contact with a previously unfamiliar microbe or its natural host or promote dissemination. These factors are increasing in prevalence; this increase, together with the ongoing evolution of viral and microbial variants and selection for drug resistance, suggests that infections will continue to emerge and probably increase and emphasizes the urgent need for effective surveillance and control. Dr. David Satcher's article and this overview inaugurate "Perspectives," a regular section in this journal intended to present and develop unifying concepts and strategies for considering emerging infections and their underlying factors. The editors welcome, as contributions to the Perspectives section, overviews, syntheses, and case studies that shed light on how and why infections emerge, and how they may be anticipated and prevented.*

Infectious diseases emerging throughout history have included some of the most feared plagues of the past. New infections continue to emerge today, while many of the old plagues are with us still. These are global problems (William Foege, former CDC director now at the Carter Center, terms them "global infectious disease threats"). As demonstrated by influenza epidemics, under suitable circumstances, a new infection first appearing anywhere in the world could traverse entire continents within days or weeks.

We can define as "emerging" infections that have newly appeared in the population, or have existed but are rapidly increasing in incidence or geographic range (1,2). Recent examples of emerging diseases in various parts of the world include HIV/AIDS; classic cholera in South America and Africa; cholera due to *Vibrio cholerae* O139; Rift Valley fever; hantavirus pulmonary syndrome; Lyme disease; and hemolytic uremic syndrome, a foodborne infection caused by certain strains of *Escherichia coli* (in the United States, serotype O157:H7).

Although these occurrences may appear inexplicable, rarely if ever do emerging infections appear without reason. Specific factors responsible for disease emergence can be identified in virtually all cases studied (2-4). Table 1 summarizes the known causes for a number of infections that have emerged recently. I have suggested that infectious disease emergence can be viewed operationally as a two-step process: 1) Introduction of the agent into a new host population (whether the pathogen originated in the environment, possibly in another species, or as a variant of an existing human infection), followed by 2) establishment and further dissemination within the new host population ("adoption") (4). Whatever its origin, the infection "emerges" when it reaches a new population. Factors that promote one or both of these steps will, therefore, tend to precipitate disease emergence. Most emerging infections, and even antibiotic-resistant strains of common bacterial pathogens, usually originate in one geographic location and then disseminate to new places (5).

Regarding the introduction step, the numerous examples of infections originating as zoonoses (7,8) suggest that the "zoonotic pool"—introductions of infections from other species—is an important and potentially rich source of emerging diseases; periodic discoveries of "new" zoonoses suggest that the zoonotic pool appears by no means exhausted. Once introduced, an infection might then be disseminated through other factors, although rapid course and high mortality combined with low transmissibility are often limiting. However, even if a zoonotic agent is not able to spread readily from person to person and establish itself, other factors (e.g., nosocomial infection) might transmit the infection. Additionally, if the reservoir host or vector becomes more widely disseminated, the microbe can appear in new places.

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Table 1. Recent examples of emerging infections and probable factors in their emergence

Infection or Agent	Factor(s) contributing to emergence
Viral	
Argentine, Bolivian hemorrhagic fever	Changes in agriculture favoring rodent host
Bovine spongiform encephalopathy (cattle)	Changes in rendering processes
Dengue, dengue hemorrhagic fever	Transportation, travel, and migration; urbanization
Ebola, Marburg	Unknown (in Europe and the United States, importation of monkeys)
Hantaviruses	Ecological or environmental changes increasing contact with rodent hosts
Hepatitis B, C	Transfusions, organ transplants, contaminated hypodermic apparatus, sexual transmission, vertical spread from infected mother to child
HIV	Migration to cities and travel; after introduction, sexual transmission, vertical spread from infected mother to child, contaminated hypodermic apparatus (including during intravenous drug use), transfusions, organ transplants
HTLV	Contaminated hypodermic apparatus, other
Influenza (pandemic)	Possibly pig-duck agriculture, facilitating reassortment of avian and mammalian influenza viruses*
Lassa fever	Urbanization favoring rodent host, increasing exposure (usually in homes)
Rift Valley fever	Dam building, agriculture, irrigation; possibly change in virulence or pathogenicity of virus
Yellow fever (in "new" areas)	Conditions favoring mosquito vector
Bacterial	
Brazilian purpuric fever (*Haemophilus influenzae*, biotype *aegyptius*)	Probably new strain
Cholera	In recent epidemic in South America, probably introduced from Asia by ship, with spread facilitated by reduced water chlorination; a new strain (type O139) from Asia recently disseminated by travel (similarly to past introductions of classic cholera)
Helicobacter pylori	Probably long widespread, now recognized (associated with gastric ulcers, possibly other gastrointestinal disease)
Hemolytic uremic syndrome (*Escherichia coli* O157:H7)	Mass food processing technology allowing contamination of meat
Legionella (Legionnaires' disease)	Cooling and plumbing systems (organism grows in biofilms that form on water storage tanks and in stagnant plumbing)
Lyme borreliosis (*Borrelia burgdorferi*)	Reforestation around homes and other conditions favoring tick vector and deer (a secondary reservoir host)
Streptococcus, group A (invasive; necrotizing)	Uncertain
Toxic shock syndrome (*Staphylococcus aureus*)	Ultra-absorbency tampons
Parasitic	
Cryptosporidium, other waterborne pathogens	Contaminated surface water, faulty water purification
Malaria (in "new" areas)	Travel or migration
Schistosomiasis	Dam building

*Reappearances of influenza are due to two distinct mechanisms: Annual or biennial epidemics involving new variants due to antigenic drift (point mutations, primarily in the gene for the surface protein, hemagglutinin) and pandemic strains, arising from antigenic shift (genetic reassortment, generally between avian and mammalian influenza strains).

Bubonic plague transmitted by rodent fleas and ratborne hantavirus infections are examples.

Most emerging infections appear to be caused by pathogens already present in the environment, brought out of obscurity or given a selective advantage by changing conditions and afforded an opportunity to infect new host populations (on rare occasions, a new variant may also evolve and cause a new disease) (2,4). The process by which infectious agents may transfer from animals to humans or disseminate from isolated groups into new populations can be called "microbial traffic" (3,4). A number of activities increase microbial traffic and as a result promote emergence and epidemics. In some cases, including many of the most novel infections, the agents are zoonotic, crossing from their natural hosts into the human population; because of the many similarities, I include here vector-borne diseases. In other cases, pathogens already present in geographically isolated populations are given an opportunity to disseminate further. Surprisingly often, disease emergence is caused by human actions, however inadvertently; natural causes, such as changes in climate, can also at times be responsible (6). Although this discussion is confined largely to human disease, similar considerations apply to emerging pathogens in other species.

Table 2 summarizes the underlying factors responsible for emergence. Any categorization of the factors is, of course, somewhat arbitrary but should be representative of the underlying processes that cause emergence. I have essentially adopted the categories developed in the Institute of Medicine report on emerging infections (12), with additional definitions from the CDC emerging infections plan (13). Responsible factors include ecological changes, such as those due to agricultural or economic development or to anomalies in climate; human demographic changes and behavior; travel and commerce; technology and industry; microbial adaptation and change; and breakdown of public health measures. Each of these will be considered in turn.

Ecological interactions can be complex, with several factors often working together or in sequence. For example, population movement from rural areas to cities can spread a once-localized infection. The strain on infrastructure in the overcrowded and rapidly growing cities may disrupt or slow public health measures, perhaps allowing establishment of the newly introduced infection. Finally, the city may also provide a gateway for further dissemination of the infection. Most successful emerging infections, including HIV, cholera, and dengue, have followed this route.

Consider HIV as an example. Although the precise ancestry of HIV-1 is still uncertain, it appears to have had a zoonotic origin (9,10). Ecological factors that would have allowed human exposure to a natural host carrying the virus that was the precursor to HIV-1 were, therefore, instrumental in the introduction of the virus into humans. This probably occurred in a rural area. A plausible scenario is suggested by the identification of an HIV-2-infected man in a rural area of Liberia whose virus strain resembled viruses isolated from the sooty mangabey monkey (an animal widely hunted for food in rural areas and the putative source of HIV-2) more closely than it did strains circulating in the city (11). Such findings suggest that zoonotic introductions of this sort may occur on occasion in isolated populations but may well go unnoticed so long as the recipients remain isolated. But with increasing movement from rural areas to cities, such isolation is increasingly rare. After its likely first move from a rural area into a city, HIV-1 spread regionally along highways, then by long distance routes, including air travel, to more distant places. This last step was critical for HIV and facilitated today's global pandemic. Social changes that allowed the virus to reach a larger population and to be transmitted despite its relatively low natural transmissibility were instrumental in the success of the virus in its newfound human host. For HIV, the long duration of infectivity allowed this normally poorly transmissible virus many opportunities to be transmitted and to take advantage of such factors as human behavior (sexual transmission, intravenous drug use) and changing technology (early spread through blood transfusions and blood products) (Table 1).

Ecological Changes and Agricultural Development

Ecological changes, including those due to agricultural or economic development, are among the most frequently identified factors in emergence. They are especially frequent as factors in outbreaks of previously unrecognized diseases with high case-fatality rates, which often turn out to be zoonotic introductions. Ecological factors usually precipitate emergence by placing people in contact with a natural reservoir or host for an infection hitherto unfamiliar but usually already present (often a zoonotic or arthropod-borne infection), either by increasing proximity or, often, also by changing conditions so as to favor an increased population of the microbe or its natural host (2,4). The emergence of Lyme disease in the United States and Europe was probably due largely to reforestation (14), which increased the population of deer and the deer tick, the vector of Lyme disease. The movement of people into these areas placed a larger population in close proximity to the vector.

Agricultural development, one of the most common ways in which people alter and interpose themselves into the environment, is often a factor

Table 2. Factors in infectious disease emergence*

Factor	Examples of specific factors	Examples of diseases
Ecological changes (including those due to economic development and land use)	Agriculture; dams, changes in water ecosystems; deforestation/reforestation; flood/drought; famine; climate changes	Schistosomiasis (dams); Rift Valley fever (dams, irrigation); Argentine hemorrhagic fever (agriculture); Hantaan (Korean hemorrhagic fever) (agriculture); hantavirus pulmonary syndrome, southwestern US, 1993 (weather anomalies)
Human demographics, behavior	Societal events: Population growth and migration (movement from rural areas to cities); war or civil conflict; urban decay; sexual behavior; intravenous drug use; use of high-density facilities	Introduction of HIV; spread of dengue; spread of HIV and other sexually transmitted diseases
International travel and commerce	Worldwide movement of goods and people; air travel	"Airport" malaria; dissemination of mosquito vectors; ratborne hantaviruses; introduction of cholera into South America; dissemination of O139 *V. cholerae*
Technology and industry	Globalization of food supplies; changes in food processing and packaging; organ or tissue transplantation; drugs causing immunosuppression; widespread use of antibiotics	Hemolytic uremic syndrome (*E. coli* contamination of hamburger meat), bovine spongiform encephalopathy; transfusion-associated hepatitis (hepatitis B, C), opportunistic infections in immunosuppressed patients, Creutzfeldt-Jakob disease from contaminated batches of human growth hormone (medical technology)
Microbial adaptation and change	Microbial evolution, response to selection in environment	Antibiotic-resistant bacteria, "antigenic drift" in influenza virus
Breakdown in public health measures	Curtailment or reduction in prevention programs; inadequate sanitation and vector control measures	Resurgence of tuberculosis in the United States; cholera in refugee camps in Africa; resurgence of diphtheria in the former Soviet Union

*Categories of factors (column 1) adapted from ref. 12, examples of specific factors (column 2) adapted from ref. 13. Categories are not mutually exclusive; several factors may contribute to emergence of a disease (see Table 1 for additional information).

(Table 2). Hantaan virus, the cause of Korean hemorrhagic fever, causes over 100,000 cases a year in China and has been known in Asia for centuries. The virus is a natural infection of the field mouse *Apodemus agrarius*. The rodent flourishes in rice fields; people usually contract the disease during the rice harvest from contact with infected rodents. Junin virus, the cause of Argentine hemorrhagic fever, is an unrelated virus with a history remarkably similar to that of Hantaan virus. Conversion of grassland to maize cultivation favored a rodent that was the natural host for this virus, and human cases increased in proportion with expansion of maize agriculture (15). Other examples, in addition to those already known (2,15), are likely to appear as new areas are placed under cultivation.

Perhaps most surprisingly, pandemic influenza appears to have an agricultural origin, integrated pig-duck farming in China. Strains causing the frequent annual or biennial epidemics generally result from mutation ("antigenic drift"), but pandemic influenza viruses do not generally arise by this process. Instead, gene segments from two influenza strains reassort to produce a new virus that can infect humans (16). Evidence amassed by Webster, Scholtissek, and others, indicates that waterfowl, such as ducks, are major reservoirs of influenza and that pigs can serve as "mixing vessels" for new mammalian influenza strains (16). Pandemic influenza viruses have generally come from China. Scholtissek and Naylor suggested that integrated pig-duck agriculture, an extremely efficient food

production system traditionally practiced in certain parts of China for several centuries, puts these two species in contact and provides a natural laboratory for making new influenza recombinants (17). Webster has suggested that, with high-intensity agriculture and movement of livestock across borders, suitable conditions may now also be found in Europe (16).

Water is also frequently associated with disease emergence. Infections transmitted by mosquitoes or other arthropods, which include some of the most serious and widespread diseases (18,19), are often stimulated by expansion of standing water, simply because many of the mosquito vectors breed in water. There are many cases of diseases transmitted by water-breeding vectors, most involving dams, water for irrigation, or stored drinking water in cities. (See "Changes in Human Demographics and Behavior" for a discussion of dengue.) The incidence of Japanese encephalitis, another mosquito-borne disease that accounts for almost 30,000 human cases and approximately 7,000 deaths annually in Asia, is closely associated with flooding of fields for rice growing. Outbreaks of Rift Valley fever in some parts of Africa have been associated with dam building as well as with periods of heavy rainfall (19). In the outbreaks of Rift Valley fever in Mauritania in 1987, the human cases occurred in villages near dams on the Senegal River. The same effect has been documented with other infections that have aquatic hosts, such as schistosomiasis.

Because humans are important agents of ecological and environmental change, many of these factors are anthropogenic. Of course, this is not always the case, and natural environmental changes, such as climate or weather anomalies, can have the same effect. The outbreak of hantavirus pulmonary syndrome in the southwestern United States in 1993 is an example. It is likely that the virus has long been present in mouse populations but an unusually mild and wet winter and spring in that area led to an increased rodent population in the spring and summer and thus to greater opportunities for people to come in contact with infected rodents (and, hence, with the virus); it has been suggested that the weather anomaly was due to large-scale climatic effects (20). The same causes may have been responsible for outbreaks of hantaviral disease in Europe at approximately the same time (21,22). With cholera, it has been suggested that certain organisms in marine environments are natural reservoirs for cholera vibrios, and that large scale effects on ocean currents may cause local increases in the reservoir organism with consequent flare-ups of cholera (23).

Changes in Human Demographics and Behavior

Human population movements or upheavals, caused by migration or war, are often important factors in disease emergence. In many parts of the world, economic conditions are encouraging the mass movement of workers from rural areas to cities. The United Nations has estimated that, largely as a result of continuing migration, by the year 2025, 65% of the world population (also expected to be larger in absolute numbers), including 61% of the population in developing regions, will live in cities (24). As discussed above for HIV, rural urbanization allows infections arising in isolated rural areas, which may once have remained obscure and localized, to reach larger populations. Once in a city, the newly introduced infection would have the opportunity to spread locally among the population and could also spread further along highways and interurban transport routes and by airplane. HIV has been, and in Asia is becoming, the best known beneficiary of this dynamic, but many other diseases, such as dengue, stand to benefit. The frequency of the most severe form, dengue hemorrhagic fever, which is thought to occur when a person is sequentially infected by two types of dengue virus, is increasing as different dengue viruses have extended their range and now overlap (25). Dengue hemorrhagic fever is now common in some cities in Asia, where the high prevalence of infection is attributed to the proliferation of open containers needed for water storage (which also provide breeding grounds for the mosquito vector) as the population size exceeds the infrastructure (19). In urban environments, rain-filled tires or plastic bottles are often breeding grounds of choice for mosquito vectors. The resulting mosquito population boom is complemented by the high human population density in such situations, increasing the chances of stable transmission cycles between infected and susceptible persons. Even in industrialized countries, e.g., the United States, infections such as tuberculosis can spread through high-population density settings (e.g., day care centers or prisons) (12,26-28).

Human behavior can have important effects on disease dissemination. The best known examples are sexually transmitted diseases, and the ways in which such human behavior as sex or intravenous drug use have contributed to the emergence of HIV are now well known. Other factors responsible for disease emergence are influenced by a variety of human actions, so human behavior in the broader sense is also very important. Motivating appropriate individual behavior and constructive action, both locally and in a larger scale, will be essential for controlling emerging infections. Ironically, as AIDS prevention efforts have demonstrated, human

behavior remains one of the weakest links in our scientific knowledge.

International Travel and Commerce

The dissemination of HIV through travel has already been mentioned. In the past, an infection introduced into people in a geographically isolated area might, on occasion, be brought to a new place through travel, commerce, or war (8). Trade between Asia and Europe, perhaps beginning with the silk route and continuing with the Crusades, brought the rat and one of its infections, the bubonic plague, to Europe. Beginning in the 16th and 17th centuries, ships bringing slaves from West Africa to the New World also brought yellow fever and its mosquito vector, *Aedes aegypti*, to the new territories. Similarly, smallpox escaped its Old World origins to wreak new havoc in the New World. In the 19th century, cholera had similar opportunities to spread from its probable origin in the Ganges plain to the Middle East and, from there, to Europe and much of the remaining world. Each of these infections had once been localized and took advantage of opportunities to be carried to previously unfamiliar parts of the world.

Similar histories are being repeated today, but opportunities in recent years have become far richer and more numerous, reflecting the increasing volume, scope, and speed of traffic in an increasingly mobile world. Rats have carried hantaviruses virtually worldwide (29). *Aedes albopictus* (the Asian tiger mosquito) was introduced into the United States, Brazil, and parts of Africa in shipments of used tires from Asia (30). Since its introduction in 1982, this mosquito has established itself in at least 18 states of the United States and has acquired local viruses including Eastern equine encephalomyelitis (31), a cause of serious disease. Another mosquito-borne disease, malaria, is one of the most frequently imported diseases in non-endemic-disease areas, and cases of "airport malaria" are occasionally identified.

A classic bacterial disease, cholera, recently entered both South America (for the first time this century) and Africa. Molecular typing shows the South American isolates to be of the current pandemic strain (32), supporting the suggestion that the organism was introduced in contaminated bilge water from an Asian freighter (33). Other evidence indicates that cholera was only one of many organisms to travel in ballast water; dozens, perhaps hundreds, of species have been exchanged between distant places through this means of transport alone. New bacterial strains, such as the recently identified *Vibrio cholerae* O139, or an epidemic strain of *Neisseria meningitidis* (34,35) (also examples of microbial adaptation and change) have disseminated rapidly along routes of trade and travel, as have antibiotic-resistant bacteria (5,36).

Technology and Industry

High-volume rapid movement characterizes not only travel, but also other industries in modern society. In operations, including food production, that process or use products of biological origin, modern production methods yield increased efficiency and reduced costs but can increase the chances of accidental contamination and amplify the effects of such contamination. The problem is further compounded by globalization, allowing the opportunity to introduce agents from far away. A pathogen present in some of the raw material may find its way into a large batch of final product, as happened with the contamination of hamburger meat by *E. coli* strains causing hemolytic uremic syndrome (37). In the United States the implicated *E. coli* strains are serotype O157:H7; additional serotypes have been identified in other countries. Bovine spongiform encephalopathy (BSE), which emerged in Britain within the last few years, was likely an interspecies transfer of scrapie from sheep to cattle (38) that occurred when changes in rendering processes led to incomplete inactivation of scrapie agent in sheep byproducts fed to cattle (39).

The concentrating effects that occur with blood and tissue products have inadvertently disseminated infections unrecognized at the time, such as HIV and hepatitis B and C. Medical settings are also at the front line of exposure to new diseases, and a number of infections, including many emerging infections, have spread nosocomially in health care settings (Table 2). Among the numerous examples, in the outbreaks of Ebola fever in Africa many of the secondary cases were hospital acquired, most transmitted to other patients through contaminated hypodermic apparatus, and some to the health care staff by contact. Transmission of Lassa fever to health care workers has also been documented.

On the positive side, advances in diagnostic technology can also lead to new recognition of agents that are already widespread. When such agents are newly recognized, they may at first often be labeled, in some cases incorrectly, as emerging infections. Human herpesvirus 6 (HHV-6) was identified only a few years ago, but the virus appears to be extremely widespread (40) and has recently been implicated as the cause of roseola (exanthem subitum), a very common childhood disease (41). Because roseola has been known since at least 1910, HHV-6 is likely to have been common for decades and probably much longer. Another recent example is the bacterium *Helicobacter pylori*, a probable cause of gastric ulcers (42) and some cancers (43,44). We have lived with these diseases for a long time without knowing

their cause. Recognition of the agent is often advantageous, offering new promise of controlling a previously intractable disease, such as treating gastric ulcers with specific antimicrobial therapy.

Microbial Adaptation and Change

Microbes, like all other living things, are constantly evolving. The emergence of antibiotic-resistant bacteria as a result of the ubiquity of antimicrobials in the environment is an evolutionary lesson on microbial adaptation, as well as a demonstration of the power of natural selection. Selection for antibiotic-resistant bacteria (5,36) and drug-resistant parasites has become frequent, driven by the wide and sometimes inappropriate use of antimicrobial drugs in a variety of applications (27,45,46). Pathogens can also acquire new antibiotic resistance genes from other, often nonpathogenic, species in the environment (36), selected or perhaps even driven by the selection pressure of antibiotics.

Many viruses show a high mutation rate and can rapidly evolve to yield new variants (47). A classic example is influenza (48). Regular annual epidemics are caused by "antigenic drift" in a previously circulating influenza strain. A change in an antigenic site of a surface protein, usually the hemagglutinin (H) protein, allows the new variant to reinfect previously infected persons because the altered antigen is not immediately recognized by the immune system.

On rare occasions, perhaps more often with nonviral pathogens than with viruses (49), the evolution of a new variant may result in a new expression of disease. The epidemic of Brazilian purpuric fever in 1990, associated with a newly emerged clonal variant of *Hemophilus influenzae*, biogroup *aegyptius*, may fall into this category. It is possible, but not yet clear, that some recently described manifestations of disease by group A *Streptococcus*, such as rapidly invasive infection or necrotizing fasciitis, may also fall into this category.

Breakdown of Public Health Measures and Deficiencies in Public Health Infrastructure

Classical public health and sanitation measures have long served to minimize dissemination and human exposure to many pathogens spread by traditional routes such as water or preventable by immunization or vector control. The pathogens themselves often still remain, albeit in reduced numbers, in reservoir hosts or in the environment, or in small pockets of infection and, therefore, are often able to take advantage of the opportunity to reemerge if there are breakdowns in preventive measures.

Reemerging diseases are those, like cholera, that were once decreasing but are now rapidly increasing again. These are often conventionally understood and well recognized public health threats for which (in most cases) previously active public health measures had been allowed to lapse, a situation that unfortunately now applies all too often in both developing countries and the inner cities of the industrialized world. The appearance of reemerging diseases may, therefore, often be a sign of the breakdown of public health measures and should be a warning against complacency in the war against infectious diseases.

Cholera, for example, has recently been raging in South America (for the first time in this century) (50) and Africa. The rapid spread of cholera in South America may have been abetted by recent reductions in chlorine levels used to treat water supplies (34). The success of cholera and other enteric diseases is often due to the lack of a reliable water supply. These problems are more severe in developing countries, but are not confined to these areas. The U.S. outbreak of waterborne *Cryptosporidium* infection in Milwaukee, Wisconsin, in the spring of 1993, with over 400,000 estimated cases, was in part due to a nonfunctioning water filtration plant (51); similar deficiencies in water purification have been found in other cities in the United States (52).

For our Future

In his accompanying article, Dr. David Satcher discusses the history of infectious diseases and the many infections that, from the dawn of history to the present, have traveled with the caravans and followed the invading armies. The history of infectious diseases has been a history of microbes on the march, often in our wake, and of microbes that have taken advantage of the rich opportunities offered them to thrive, prosper, and spread. And yet the historical processes that have given rise to the emergence of "new" infections throughout history continue today with unabated force; in fact, they are accelerating, because the conditions of modern life ensure that the factors responsible for disease emergence are more prevalent than ever before. Speed of travel and global reach are further borne out by studies modeling the spread of influenza epidemics (53) and HIV (54,55).

Humans are not powerless, however, against this relentless march of microbes. Knowledge of the factors underlying disease emergence can help focus resources on the key situations and areas worldwide (3,4) and develop more effective prevention strategies. If we are to protect ourselves against emerging diseases, the essential first step is effective global

disease surveillance to give early warning of emerging infections (3,12,13,56). This must be tied to incentives, such as national development, and eventually be backed by a system for an appropriate rapid response. World surveillance capabilities are critically deficient (12,56,57). Efforts, such as the CDC plan (13), now under way in the United States and internationally to remedy this situation are the essential first steps and deserve strong support. Research, both basic and applied, will also be vital.

This Journal and the "Perspectives" Section

Early warning of emerging and reemerging infections depends on the ability to identify the unusual as early as possible. Information is, therefore, essential. Hence this journal, which is intended as a peer-reviewed forum for the discussion of concepts and examples relevant to emerging infectious diseases and their causes, and to provide a channel for field reports and observations on emerging infections. The "Perspectives" section will provide general overviews dealing with factors in disease emergence, conceptual syntheses of information, approaches for studying or predicting emerging infections, and analyses that shed light on how and why infections emerge, and how they may be anticipated and prevented. Submissions for this section are warmly invited. In coming issues, Perspectives will deal in greater detail with many of the factors discussed in this overview article, and with ways to dissect steps in the emergence process. Discussion of technologies that are broadly applicable to the identification or control of emerging diseases are also appropriate for this section. Case studies are welcome if they are used to develop broader lessons.

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Unraveling Mysteries Associated with Cat-Scratch Disease, Bacillary Angiomatosis, and Related Syndromes

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The search for the infectious agents responsible for cat-scratch disease, bacillary angiomatosis, and related syndromes has a long and often circuitous history. Recognition of the etiologic agents and a new understanding of the fundamental features of the epidemiology and natural history of modern day Bartonella *(formerly* Rochalimaea*)-associated diseases culminate a multipartite story that combines clinical medicine, traditional microbiology, and novel technological approaches to solve a long-standing enigma.*

The quest for the etiologic agent of cat-scratch disease (CSD) has frequently been described as a mystery (1,2). Indeed, the search has many qualities of a mystery novel; the pursuit has spanned several decades and recently taken several unexpected turns. During this period of important discovery, major microbial suspects have undergone name changes, novel microbial culprits have been introduced, new groups of affected patients have been recognized, and yet significant questions remain to be answered. Scientific and medical interest has been high; approximately 900 publications have dealt with CSD since the first good clinical description of the disease in 1950 (3).

Clinical Features of CSD

Throughout the life of this evolving mystery, the clinical descriptions of "classical" CSD have remained remarkably consistent (Dalton MJ, et al. *Rochalimaea* antibody; a new era in the diagnosis of cat-scratch disease, submitted for publication; 4-6). CSD is typically a benign and self-limited illness lasting 6 to 12 weeks in the absence of antibiotic therapy. Regional lymphadenopathy (axillary, head and neck, inguinal) is the predominant clinical feature of CSD; affected nodes are often tender and occasionally suppurate (4-7). Between 25% and 60% of patients report a primary cutaneous inoculation lesion (0.5- to 1-cm papule or pustule) at the site of a cat scratch or bite (5,7). The skin lesions typically develop 3 to 10 days after injury and precede the onset of lymphadenopathy by 1 to 2 weeks. Low-grade fever and malaise accompany lymphadenopathy in up to 50% of patients; headache, anorexia, weight loss, nausea and vomiting, sore throat, and splenomegaly may develop. In addition, short-lived, non-specific maculopapular eruptions, erythema nodosum, figurate erythemas, and thrombocytopenic purpura have been observed (8).

Unusual manifestations of CSD, which occur in up to 14% of patients, include Perinaud's oculoglandular syndrome (6%), encephalopathy (2%), hepatic granulomas (0.3%), osteomyelitis (0.3%), and pulmonary disease (0.2%) (4,5,8). In general, these complications resolve without sequelae. Perinaud's oculoglandular syndrome is manifested by conjunctival granuloma, periauricular lymphadenopathy, and nonsuppurative conjunctivitis. Encephalopathy, manifested as fever and coma that progress to convulsions, may last for days to weeks; cerebrospinal fluid is unremarkable. Optic neuritis with transient blindness may also occur.

For many years, CSD has been clinically diagnosed when three of the following four criteria are met in a patient: 1) history of traumatic cat contact; 2) positive skin-test response to CSD skin-test antigen; 3) characteristic lymph node lesions; and 4) negative laboratory investigation for unexplained lymphadenopathy (8). Although biopsy confirmation of CSD has been rarely required (especially in lieu of a reliable serologic test—see below), a constant pathologic hallmark of CSD-affected tissues has been granuloma formation. With hematoxylin and eosin stains, the primary inoculation lesion of CSD reveals small areas of frank necrosis surrounded by concentric layers of histiocytes, lymphocytes, and nucleated giant cells (9). Affected lymph nodes are characterized by necrotizing granulomas ringed by lymphocytic infiltrates and multinucleated giant cells.

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Enter *Afipia felis*

During the past 44 years, a variety of microbial agents, including herpes viruses and bacteria of the genera *Chlamydia* and *Pasteurella*, have been suspected as the causes of CSD (3). A major chapter of the CSD saga unfolded with the 1988 announcement by the Armed Forces Institute of Pathology that a bacterial agent had been visualized within CSD-involved lymph nodes by using the Warthin-Starry silver stain (10), and a novel bacterial agent had been isolated from a CSD patient's lymph node (11). By 1992, this agent was characterized fully, given the name *Afipia felis* (*Afipia* being a latinized acronym for the source of the original isolate, the Armed Forces Institute of Pathology, and *felis* referring to the presumed vertebrate vector of the human infection), and proclaimed the agent of CSD (12).

Although *A. felis* was declared the putative CSD bacillus, evidence of convincing patient humoral or cellular immune responses to laboratory cultured *A. felis* antigen was not forthcoming. Despite numerous attempts, other laboratories were unable to recover additional isolates of *A. felis* from CSD patients. In addition, although the majority of patients with CSD reported exposure to a cat(s), no clear link between cats and *A. felis* was demonstrated.

Enter New Syndromes

The story of CSD took a significantly divergent path with the recognition that opportunistic infections were an important consideration for patients infected with human immunodeficiency virus (HIV). Bacillary angiomatosis (BA), a newly recognized disease characterized by cutaneous and subcutaneous vascular lesions containing bacillary organisms visualized by Warthin-Starry silver staining, was described predominantly among HIV-infected patients; however, bacterial isolates were not made or identified (13-15). Over the ensuing decade, the clinical spectrum of BA was expanded to include patients with single or multiple vascular lesions affecting virtually every organ system, including lymph node, bone, brain, liver (peliosis hepatis), and spleen (14-17). Independently, an unidentified gram-negative pathogen was isolated predominantly from HIV-infected patients with fever and bacteremia, however, these patients lacked cutaneous or parenchymal vascular lesions and were not recognized as BA patients (18).

Because silver staining and electron microscopy of both BA and CSD tissue sections revealed bacillary organisms indistinguishable from one another, several authors suggested that BA might represent disseminated CSD in the immunocompromised host (17,19-21). In addition, several anecdotal reports of BA described a history of cat contact preceding the onset of disease (22).

Ultimately, the relationships between possible environmental exposures and BA or CSD were systematically investigated. The first case-control study conducted among patients with BA found traumatic contact with a cat (bite or scratch) to be significantly associated with BA disease (22). BA patients were also more likely than controls to have a household kitten (a cat <1 year of age). A subsequent case-control study of CSD patients found that these patients were more likely than controls to have traumatic contact with a cat, to own at least one kitten, and to have kittens with fleas (7).

Despite the similarities in histochemical staining properties and epidemiology, serious reservations remained concerning a possible link between the causative agents of CSD and BA. The pathologic features of classical CSD (granuloma) and BA (proliferative vascular lesions without granuloma) were distinctly different, and the two diseases seemed to respond differently to antibiotic therapy. Although antimicrobial therapy for BA and CSD have not been systematically evaluated, the majority of BA patients evaluated responded quickly to single-agent therapy with either erythromycin or doxycycline (14,23), whereas the symptoms and signs of patients with CSD failed to show consistent rapid resolution following antibiotic therapy (5). In addition, clinicians' first choices of antibiotics for treating BA and CSD vary (5,6,14,23).

Enter *Rochalimaea henselae*

A breakthrough occurred when a novel approach was used to identify possible prokaryotic ribosomal DNA extracted from BA skin lesions. When prokaryotic ribosomal gene DNA extracted from BA lesions and amplified by polymerase chain reaction (PCR) was compared with sequenced ribosomal genes from other organisms, it become apparent that the agent associated with BA in this study was related to, but not necessarily identical to, the agent of trench fever, *Rochalimaea quintana* (24).

At nearly the same time in Oklahoma, *Rochalimaea*-like organisms were being isolated on blood agar from bacteremic patients (18). Independently in Houston, Texas, fastidious, slow-growing *Rochalimaea*-like isolates were recovered on several occasions from the blood of an HIV-infected patient with relapsing fever of unknown origin; like the isolates from the Oklahoma patients, the Houston isolate was recovered from a patient in the absence of BA or CSD lesions (25). The Houston isolate (Houston-1) was identified as the prototype isolate of a novel species of *Rochalimaea* by using traditional as well as genotypic methods, including ribosomal RNA gene analysis similar to that used to identify the nucleic acid found in BA patients' lesions (25). Almost simultaneously, the group from Oklahoma had

come to a similar conclusion by using DNA relatedness data (26); most of their isolates also consisted of the novel species, *R. henselae*. The new species designation, first officially used to describe the Houston-1 isolate, was coined in recognition of the contribution of Diane Hensel, a microbiologist who had isolated several of the initial organisms in Oklahoma (18,25,26). Subsequently, Koehler et al. isolated bacilli directly from cutaneous lesions of persons with BA (27); surprisingly, either *R. henselae* or *R. quintana* was isolated from BA lesions from different HIV-infected patients.

At this juncture, *R. henselae* infections had been described predominantly among immunocompromised patients with either BA or fever with bacteremia. The availability of isolates made it possible to develop a test for serologic evidence of *Rochalimaea* infection and to refine PCR methods for identification of *Rochalimaea* organisms in tissues and other samples. These methods, together with new techniques for recovering *Rochalimaea* species isolates, were crucial to obtaining a more detailed account not only of BA but also of CSD.

The Cat-scratch Connection: A Synthesis

A *Rochalimaea* genus-specific, indirect fluorescence antibody (IFA) test using irradiated whole cell antigen from the Houston-1 isolate of *R. henselae* was developed by the Centers for Disease Control and Prevention (CDC) to help identify risk factors for *Rochalimaea*-associated disease. Several blinded serum samples from both HIV-infected BA patients and HIV-infected controls residing in San Francisco were sent to CDC for serologic testing. High-titered antibodies were identified in serum samples from several of the BA patients (28). Similar high-titered antibodies were not detected for any of non-BA control patients with one exception; a serum sample from an HIV-infected patient with CSD also demonstrated strong serologic reactivity to *R. henselae* antigen.

Shortly thereafter, single sera collected from patients with suspected CSD to look for *A. felis* antibodies were evaluated with the new *R. henselae* serologic test; 36 (88%) of 41 sera were positive (29). None of the sera had significantly elevated titers to *A. felis* antigen. The same set of sera were coded and resubmitted along with sera taken from other well-characterized bacterial and viral diseases and tested again in a blinded manner. The IFA test accurately identified sera of case-patients with suspected CSD. In addition, 6 (6%) of 107 sera from ostensibly healthy persons, obtained from a commercial vendor, showed antibody by IFA testing (29). These serologic data were the first laboratory evidence suggesting that *R. henselae* was associated with CSD.

Data further substantiating the role of *R. henselae* in the etiology of CSD soon followed. The newly developed serologic test was used to help investigate a possible cluster of CSD cases in Connecticut; 38 (84%) of 45 suspected CSD cases had elevated *Rochalimaea* antibody titers, whereas 4 (3.6%) of 112 age-matched controls had detectable antibody titers (7). In another investigation, serum samples obtained from 600 prospectively evaluated patients with well-characterized CSD (i.e., persons with history of cat scratch, papule at site of inoculation, and enlarged regional lymph node) had a 95% correlation with positive *Rochalimaea* serology.

In 1993, *R. henselae* was isolated directly from the lymph nodes of two CSD patients and was identified by genotypic means; both patients had strong serologic responses to *Rochalimaea* antigen (30). Evidence of *R. henselae*-specific nucleic acid sequences were found in 21 (84%) of 25 CSD lymph node tissues submitted to CDC for evaluation (31).

Additional supporting evidence for a *Rochalimaea* as the cause of CSD came from archival sources. Skin-test antigen, used rather extensively in the past to help diagnose examples of CSD (4,8), consisted of pasteurized exudate collected from suppurative CSD lymph nodes. Among a cohort of CSD patients who were skin-test positive, 52 (93%) of 56 had positive IFA antibody titers to the defined *Rochalimaea* reagents (32). Furthermore, various lots of skin-test antigen were shown by PCR analysis to contain *Rochalimaea* nucleic acid sequences (33), and *R. henselae* sequences in particular (34). No *A. felis* DNA sequences could be detected by PCR. These data strongly indicated that microbiologically undefined skin-test reagents, which had been used for many years for the diagnosis and clinical characterization of CSD, were in fact *R. henselae* reagents.

Collectively, these data supported a *Rochalimaea* species etiology for both CSD and BA. Despite numerous attempts, recent efforts to implicate *A. felis* as a cause of either of these two clinical entities have repeatedly failed.

Felis domesticus: A Reservoir for *Rochalimaea henselae*

In addition to epidemiologic data, serologic evidence also implicated domestic cats with *Rochalimaea*-associated disease. *Rochalimaea*-specific IFA antibodies were demonstrated in 6 (46%) of 13 pet cats not associated with human disease and among 39 (81%) of 48 cats living in households reporting human CSD in Connecticut (7). Microbiologic evidence for the domestic cat as a reservoir for *R. henselae* soon followed. *R. henselae* was isolated over a 3-week period from the blood of a single cat not linked to human illness (35). Investigations by Koehler et al. established the cat as a reservoir for

R. henselae infection (36). *R. henselae* was established as the cause of cutaneous BA in three or four patients with the disease. *R. henselae* was isolated from the blood of all seven asymptomatic pet cats with which these four BA patients had prolonged contact. The prevalence of infection among cats in the greater San Francisco Bay region was also studied; 25 (41%) of 61 pet or impounded cats had asymptomatic *R. henselae* bacteremia (36). *R. henselae* was also detected by both direct culture and PCR from several cat fleas combed from these bacteremic cats (36).

The human body louse (*Pediculus humanus)* was established as a vector for human-to-human trench fever *R. quintana* transmission during the First World War (37). Likewise, *B. bacilliformis*, a closely related organism (see below) found in the mountains of South America, can be transmitted by another arthropod, the *Phlebotomus* sand fly (38). The observation that related microbes are vectored between humans by arthropods adds credence to the proposed role of arthropod vectors of CSD. Despite several suggestions that fleas or possibly ticks (7,36,39) are associated with *R. henselae* disease, no experimental data exist to clearly demonstrate that arthropods act as direct vectors.

Changes in Nomenclature: *Rochalimaea* becomes *Bartonella*

Genotypic evaluation of members of the genus *Rochalimaea* has led to the conclusion that members of the genus are closely related to *Bartonella bacilliformis*, the agent of Carrión disease, Oroya fever, and verruga peruana (40). Because of historical precedence, the genus designation *Bartonella* is now applied to all species of the old genus *Rochalimaea* and replaces the *Rochalimaea* designation (species names remain unchanged).

Physicians and researchers need to exercise care in using the term "bartonellosis." This term has classically been used to describe the frequently fatal syndromes caused by *B. bacilliformis*. To date, *B. bacilliformis* and its associated syndrome (bartonellosis) have been identified exclusively in South America (38,41).

Remaining Questions for Ongoing and Future Research

Although *B. henselae* is now regarded as the etiologic agent of CSD, as well as a cause of BA, endocarditis (42), and fever with bacteremia, many questions remain unanswered. For example, why did it take so long to isolate and identify *B. henselae*? Part of the answer probably stems from the requirements necessary for growth in vitro, including enriched, non-selective blood agar incubated over a prolonged period in a CO_2 atmosphere. Most hospital laboratories discard their bacteriological plates before primary isolates of *B. henselae* would be expected to appear (9-40 days). Extreme sensitivity to a wide variety of antibiotics, at least in vitro, suggests that residual levels of antibiotics in patients' blood or other tissues (such as lymph node biopsy) might inhibit *Bartonella* growth during primary isolation attempts in vitro. Selective medium has yet to be developed. Novel genotypic methods were crucial for identification of *B. henselae*; thus, isolates may well have been made in the past but remained unidentified.

As mentioned above, it has become apparent that in addition to *B. henselae*, *B. quintana* can also be another significant cause of BA disease, at least among immunocompromised patients in San Francisco (27). Another focus of *B. quintana* infections ("urban trench fever") has been identified among homeless alcoholics in Seattle (43,44). How common are *B. quintana* infections; are they louseborne and vectored strictly between humans, as was believed during World War I (37)? *B. quintana*-associated disease has no known link with an alternative vertebrate vector (such as cats).

Bartonella elizabethae is known only from a single isolate from a man surviving endocarditis following aortic valve-replacement surgery (45). Is there further public health significance to this organism? What additional *Bartonella* species have yet to be identified and what diseases may they cause?

Members of the genus *Bartonella* are exquisitely sensitive to antibiotics in vitro (30,46). Why then do CSD patients not respond as rapidly and consistently to antibiotic therapy as BA patients do? One hypothesis is that immunocompetent patients somehow sequester infectious organisms beyond the reach of antibiotics, whereas immunocompromised patients do not. An alternative hypothesis regarding differential antibiotic responsiveness recognizes that many of the signs of CSD are immune mediated; antibiotics, even if effective in neutralizing or killing bacteria, may not immediately alleviate long-duration immunologic tissue manifestations of antigen stimulation. Conversely, in the absence of the immunologic capability to react to bacterial infection by forming granulomas, as in the case of severely immunocompromised persons with BA, antibiotics are generally effective in alleviating the symptoms and signs of infection. Does this suggest that possible non-granulomatous manifestations of CSD (for example, neuroretinitis and encephalopathy) should respond well to the appropriate antibiotic therapy?

Although BA has been described in immunocompetent patients (15), the vast majority of BA patients are immunocompromised (14). What are the factors explaining why *B. henselae* and *B. quintana* induce vascular proliferative lesions, such as BA and

parenchymal bacillary peliosis, almost exclusively in severely immunocompromised patients?

What percentage of the relatively large numbers of undiagnosed febrile disease among HIV-infected persons is in fact due to *Bartonella* species infections? The answer to this important question may help alleviate significant morbidity among HIV-infected patients. The potential for selection for drug-resistance during long-term antimicrobial therapy deserves scrutiny.

Does the 4%-6% of IFA antibody-positive, ostensibly healthy "control" study populations suggest a relatively common undercurrent of undiagnosed, subclinical *Bartonella*-associated disease?

Is it possible to immunize cats and thereby interrupt *B. henselae* transmission to humans? Preliminary data suggest that asymptomatic bacteremia in cats can be successfully treated with antimicrobial therapy (36). Once cleared of bacteremia, are these cats routinely susceptible to reinfection?

Are the complications occasionally associated with CSD and BA associated with different strains of *Bartonella* species or are the variations in clinical presentation strictly functions of dose, route of inoculation, and immune status?

And finally, in what role, if any, will *A. felis* reappear as an agent of human disease? Is *A. felis* responsible for the relatively small number of cases of CSD-like lymphadenopathy that have no evidence of antibody to *B. henselae*? Or is there another explanation for the originally proposed association between *A. felis* and CSD that has not yet come to light?

The new recognition of the importance of *Bartonella*-associated diseases will continue to spawn a host of unanswered related questions. Whereas novel subplots will continue to unfold, the new puzzles are no longer totally shapeless, and answers to questions of natural history and epidemiology, enhanced diagnosis and treatment, and methods for disease intervention should now begin to unfold rapidly.

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Emergence of Barmah Forest Virus in Western Australia[1]

To the editor: Barmah Forest (BF) virus is a mosquito-borne alphavirus, found only in Australia, which causes outbreaks of polyarthritis in humans. The disease is very similar to epidemic polyarthritis caused by infection with Ross River virus, another Australian alphavirus. BF virus was first isolated from mosquitoes in the State of Western Australia in 1989. After this, small clusters of human cases were diagnosed in the arid northern and central regions of Western Australia in 1992, and the first substantial outbreak of human disease due to infection with BF virus (BF virus disease) occurred in the southwestern region of the state during the spring and summer (September-March) of 1993-94 (2). No evidence of BF virus activity had been found in these regions before these events, which suggests that the virus had only recently been introduced to Western Australia. This report describes the timing and distribution of BF virus disease in humans and the isolation of the virus from mosquitoes in Western Australia, which corroborate the view that BF virus is an emerging virus in this state.

The ecology of Australian arboviruses that cause human disease, including BF virus, has recently been reviewed (3). BF virus was first isolated from *Culex annulirostris* mosquitoes collected at the Barmah Forest in northern Victoria (southeastern Australia) in 1974 (4). It was first shown to infect humans in New South Wales (central-eastern and southeastern Australia) in 1986 (5) and was reported as a cause of clinical disease in humans in 1988 (6). The most common clinical features include polyarthritis, arthralgia, myalgia, fever, rash, and lethargy (7); in some cases, symptoms may persist for more than 6 months (2). Although the symptoms are similar to those caused by infection with Ross River virus, there is little cross-reaction between the two viruses in serologic tests (8), and differentiating between infections caused by either is generally not difficult. The first true outbreak of BF virus disease occurred concurrently with an outbreak of Ross River virus infection at Nhulunbuy in the Northern Territory in early 1992 (9).

The principal vectors of BF are believed to be mosquitoes, and although the vertebrate hosts of BF virus are not known, serologic surveys in eastern Australia have suggested that marsupials are involved in the natural cycle.

BF virus was first detected in Western Australia in 1989. Since then, 73 isolates of the virus have been obtained from mosquitoes trapped in several different regions of Western Australia (Table 1). The first human cases of BF virus disease in Western Australia were reported in 1992, and 67 serologically confirmed cases have now been diagnosed. The locations of towns where human cases have occurred or where mosquitoes that yielded BF virus were collected are shown in Figure 1.

Eight isolates of the virus were obtained from five different mosquito species (Table 1) collected at Billiluna, a small, remote aboriginal community in an arid area in the southeastern Kimberley region in April 1989 (10). The infected mosquitoes were collected 3 weeks after heavy local rains. Only moderate wet season rains were recorded in the remainder of the Kimberley region, and no cases of BF virus disease were reported from any region in Western Australia that year. There have been no subsequent isolations of BF virus from mosquitoes collected at Billiluna, despite annual collections in the region. No human cases have been reported from Billiluna.

The first cases of BF virus disease in Western Australian were reported almost 3 years later, either individually or in small clusters from towns in the arid East Kimberley, Pilbara, Gascoyne, Murchison and Southeast (Goldfields) regions between April and September (Autumn-Spring) 1992. Most activity was reported from the towns of Exmouth (six cases) and Carnarvon (four cases). All of these cases occurred during or just after much larger outbreaks of disease caused by Ross River virus. This suggested that BF and Ross River viruses may have similar mosquito vectors and require similar environmental conditions for successful transmission. The main environmental factor contributing to the 1992 outbreaks of Ross River virus disease was extremely heavy rain in these normally arid regions during autumn and winter (11).

BF virus was isolated from five species of mosquito in the Fortescue region of the Pilbara and from three species in the West Gascoyne, just prior to, and during, these arid-region outbreaks. In coastal regions of the Pilbara, the main vector of BF virus appears to be *Aedes vigilax*, a salt marsh-breeding species. Large numbers of this species develop after very high tides or heavy rains on salt marshes. It is also the main vector of Ross River virus in these regions (12). Several other temporary freshwater ground pool-breeding species in the subgenus *Ochlerotatus*, particularly *Ae. eidsvoldensis* and *Ae.* EN Marks' species #85, were found to be infected with the virus in inland areas or coastal areas where such pools develop. These preliminary investiga-

[1] This report is adapted from and expands on a previous bulletin. (1)

Table 1. Mosquito species from which BF virus was isolated in Western Australia by region and date, 1989–1993*

Region†	Locality†	Species	Date	Isolates
East Kimberley	Billiluna	*Ae. bancroftianus*	22 Apr 1989	1
East Kimberley	Billiluna	*Ae. eidsvoldensis*	22 Apr 1989	3
East Kimberley	Billiluna	*Ae. pseudonormanensis*	22 Apr 1989	1
East Kimberley	Billiluna	*An. amictus*	22 Apr 1989	2
East Kimberley	Billiluna	*An. annulipes* s.l.	22 Apr 1989	1
East Kimberley	Halls Creek	*Cx. annulirostris*	11 Feb 1993	1
West Kimberley	Broome	*Ae. vigilax*	10-16 Feb 1993	9
West Kimberley	Fitzroy Crossing	*Cx. annulirostris*	13 Feb 1993	1
West Kimberley	Willare	*Ae. normanensis*	16 Mar 1993	1
Pilbara (Fortescue)	Onslow	*Ae.* EN Marks' sp. #85	13-14 Jun 1992	3
Pilbara (Fortescue)	Onslow	*Cx. annulirostris*	13 Jun 1992	1
Pilbara (Fortescue)	Onslow	*An. amictus*	13-14 Jun 1992	2
Pilbara (Fortescue)	Exmouth	*Ae. vigilax*	16 Jun-11 Jul 1992	7
Gascoyne (West)	Minilya	*Ae. eidsvoldensis*	7 Jul 1992	5
Gascoyne (West)	Minilya	*Ae. eidsvoldensis* (bloodfed)	7 Jul 1992	1
Gascoyne (West)	Minilya	*Ae.* EN Marks' sp. #85	7 Jul 1992	1
Gascoyne (West)	Carnarvon	*Ae. eidsvoldensis*	12 Jul 1992	3
Gascoyne (West)	Carnarvon	*Ae.* EN Marks' sp. #85	12 Jul 1992	1
Gascoyne (West)	Carnarvon	*Cx. quinquefasciatus*	12 Jul 1992	1
Gascoyne (West)	Carnarvon	Unidentifiable mosquitoes	12 Jul 1992	1
Central Coastal	Karnup	*Cx. annulirostris*	4 Jan 1993	1
Central Coastal	Karnup	*Cq.* species near *linealis*	4 Jan 1993	4
Central Coastal	Perth	*Cx. annulirostris*	6 Jan 1993	1
South Coastal	Australind	*Ae. camptorhynchus*	6 Jul 1993	1
South Coastal	Mandurah (Peel)	*Ae. camptorhynchus*	5 Aug-5 Oct 1993	10
South Coastal	Busselton	*Ae. camptorhynchus*	1 Sep-15 Nov 1993	9
South Coastal	Busselton	*Cx. globocoxitus*	1 Nov 1993	1
				Total 73

*Numbers of mosquitoes trapped and processed and estimated minimum field infection rates for each region will be published in detail elsewhere.
† Refer to Figure 1 for location of regions and towns from which isolates of BF virus were obtained.

tions also suggested that both BF and Ross River virus can co-circulate. Both viruses were isolated from different mosquitoes of the same species collected in the same trap on several occasions.

A further six cases of BF virus disease were reported after record wet season rains in the Kimberley region in early 1993. The cases occurred just after mosquitoes in the Kimberley region had been collected by personnel from this laboratory. These collections yielded 12 isolates of BF virus. Eleven of these were from *Ae. vigilax* and *Cx. annulirostris* mosquitoes trapped less than 2 weeks after the first heavy wet season rains near the West Kimberley towns of Broome and Fitzroy Crossing and the East Kimberley town of Halls Creek (see Figure 1 for locations, Table 1 for isolation details). A twelfth isolate was obtained from *Ae. normanensis* collected 5 weeks after the first rains at Willare in the West Kimberley. The timing of the collections was such that all three mosquito species could have transmitted BF virus to the infected persons in the region. Vector competence studies are required to determine if one or more species were likely to have been the main vectors.

A single case was reported from the metropolitan area of Perth, the state's capital, in August 1992. This was the first evidence of BF virus activity in the temperate and populous southwestern region of Western Australia. However, the travel history of the patient was not obtained. Then, in early January

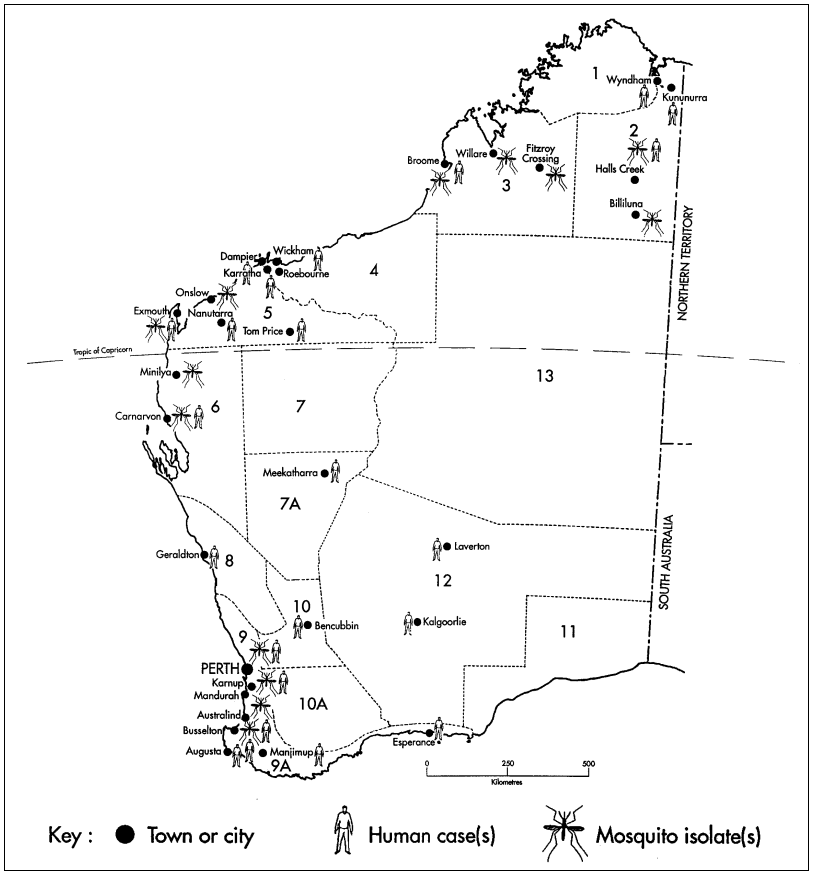

Figure 1. Meteorological regions and towns in Western Australia where human cases of Barmah Forest virus disease were reported and Barmah Forest virus was isolated from mosquitoes, 1989–1994. Meteorologic regions: 1. North Kimberley; 2. East Kimberley; 3. West Kimberley; 4. Pilbara (De Grey); 5. Pilbara (Fortescue); 6. West Gascoyne; 7. East Gascoyne; 7A. Murchison; 8. North Coastal; 9. Central Coastal; 9A. South Coastal; 10. North Central; 10A. South Central; 11. Eucla; 12. Southeast (Goldfields); and 13. Northeast (Interior).

1993, this laboratory isolated BF virus from *Cx. annulirostris* and *Coquillettidia* species near *linealis*[2] mosquitoes collected at Karnup, south of Perth (Table 1). A week later a single human case was reported from an address near the site at which the mosquitoes were trapped. BF virus was also isolated from *Cx. annulirostris* mosquitoes trapped in the southern suburbs of Perth in early January 1993, providing evidence that the virus may be transmitted to humans in the metropolitan area. Two further cases were reported from the Perth metropolitan area, one in February and one in May 1993. Again, no travel histories were available for these patients, but it appears that the virus remained and was actively transmitted in the southwest during the autumn and winter of 1993, as it was isolated from *Ae. camptorhynchus* mosquitoes trapped in July and August (Table 1).

A larger outbreak of BF virus disease occurred in the southwest region between September 1993 and March 1994. This has been described in detail elsewhere (2). Twenty-eight serologically confirmed cases were reported from the southwest region during that period. Of these, more than half (17 cases) were in or near the small coastal towns of Mandurah (Peel) and Busselton during spring (September-November) of 1993. BF virus was isolated on 20 occasions from pools of *Ae. camptorhynchus* mosquitoes collected in the Mandurah and Busselton regions before and during the outbreak (Table 1), thereby implicating that species, along with *Cx. annulirostris* and *Cq*. species near *linealis*, as an important vector in the southwest. *Ae. camptorhynchus* breeds in salt marshes and brackish wetlands during all but the hottest months of the year in the southwest and is the main vector of Ross River virus in the region (3, 11). The ratio of the carriage rate of BF virus in *Ae. camptorhynchus* during the outbreak to the number of human cases was very high compared with the rate observed for Ross River virus in *Ae. camptorhynchus* in the same regions during previous Ross River virus outbreaks (M.D. Lindsay, C.A. Johansen, and J.S. Mackenzie, unpublished observations). This suggests that the ratio of subclinical (therefore unreported) to clinical cases may be much larger with BF virus than with Ross River virus or that fewer humans were infected, possibly because *Ae. camptorhynchus* may not transmit BF virus to humans as efficiently as it does Ross River virus. Seven cases were reported between November 1993 and March 1994 in small towns in the inland southwest region in a later cycle of virus activity. Unfortunately, no collections of mosquitoes were carried out in the region during that time. Small clusters of cases or individual cases were also reported from several other regions of Western Australia during this time, including three additional cases from Broome in the West Kimberley region, presumably associated with the 1993-94 wet season.

BF virus disease was made a notifiable disease in Western Australia in June 1994 as a direct result of

[2] This species is similar to, but distinct from *Coquillettidia linealis*, according to E.N. Marks, the leading Culicid taxonomist in Australia.

the 1993-94 southwest outbreak (Health [Infectious Diseases] Amendment Order 1994, Government Gazette, Western Australia, 24 June 1994). The outbreak was also the first report of a substantial number of cases in the absence of Ross River virus activity anywhere in Australia. Ross River virus is endemic in the Mandurah (Peel) region but only one case of Ross River virus disease was reported from the area during spring-summer (September-February) 1993-94. This is the lowest recorded number of cases for that period in the region since record keeping began in 1984. Environmental conditions and vector mosquito populations in the southwest were unfavorable for Ross River virus transmission during the BF outbreak. In particular, populations of *Ae. camptorhynchus* from October onwards were much smaller than in years when larger numbers of cases of Ross River virus disease were reported (M.D. Lindsay, C.A. Johansen, J.S. Mackenzie, unpublished observations). It is not known whether the BF virus outbreak occurred because BF virus can circulate under conditions that are not suitable for Ross River virus activity or whether extremely low levels of immunity in "virgin" vertebrate host and human populations in the southwest may have enhanced transmission cycles.

Surveillance and epidemiologic studies carried out by this laboratory in the north of Western Australia since 1972 and in the southwest since 1987 have found no convincing evidence of BF virus activity in these regions prior to the events described in this report. No BF virus was isolated from the north of Western Australia before 1989, despite large-scale processing of field-caught mosquitoes over a 17-year period that yielded hundreds of isolates of other arboviruses. Similarly, no BF virus isolate was obtained from more than 400,000 mosquitoes collected throughout the southwest between 1987 and 1992 and processed for virus isolation. Furthermore, an ongoing serosurvey has found no evidence of infection with BF virus in more than 1,000 individuals of 18 vertebrate species collected in the southwest before 1992 (C.A. Johansen, unpublished results). This suggests that the virus responsible for the recent outbreaks was recently introduced to Western Australia. The means of introduction, initially to the northwest and more recently to the southwest of Western Australia, is not known. In view of the activity at Nhulunbuy in the Northern Territory, before the first Western Australia cases in 1992, it is possible that the virus may have been introduced from that region in a viremic human or in livestock. However, little is known about the duration and height of viremia in infected humans or other animals, and it is not known whether person-to-person vector-mediated transmission of Barmah Forest virus can occur. Our laboratory has begun a study to investigate the molecular epidemiology of BF virus, particularly whether the strain of virus responsible for the Western Australia outbreaks was introduced from Eastern Australia or was a local, hitherto undetected, strain.

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An Outbreak of *Shigella sonnei* Infection Associated with Consumption of Iceberg Lettuce

To the Editor: *Shigella sonnei* outbreaks in England and Wales are typically associated with primary schools and nurseries. The mode of transmission is usually from person to person by the fecal-oral route (1). In a June 1994 outbreak of *Sh. sonnei* food poisoning among adults in several countries in North West Europe, the vehicle of infection appeared to be iceberg lettuce (2).

In early June, the Communicable Disease Surveillance Centre (CDSC), Public Health Laboratory Service, received a report of an increase in domestic cases of *Sh. sonnei* infections in Sweden from the Salmnet network—a European international laboratory-based reporting system for human salmonella infections that provides a timely on-line database. In this instance the network was used for shigellosis. Of 100 reported cases of *Sh. sonnei* infection in Sweden, 52 occurred in two outbreaks in mid-May. Many cases seemed to be due to foodborne infection, and iceberg lettuce and peeled frozen prawns were implicated as vehicles of infection. *Sh. sonnei* phage types 2 and 3 alpha were associated with the outbreaks, and phage types 2 and 65 had been isolated from sporadic cases.

A message was sent throughout England and Wales on Epinet (a system for rapid electronic data transfer to all Consultants in Communicable Disease Control [CsCDC] in each District Health Authority, Public Health Laboratories [PHLs] and other agencies involved in infectious disease control) asking for information on possible foodborne *Sh. sonnei* infection to be sent to CDSC and for isolates to be referred to the Laboratory of Enteric Pathogens (LEP) for phage typing.

Epidemiologic studies

Laboratory reports of *Sh. sonnei* infection received through the routine reporting system at CDSC were scrutinized to determine the age group and sex distributions during weeks 21 to 24.

After the Epinet message, CsCDC and laboratory directors who reported clinical cases for which *Sh. sonnei* was isolated were asked to administer trawling questionnaires to apparently sporadic cases among adults with no recent history of overseas travel. Personal details and history of illness and exposure to particular foods were sought.

Several small outbreaks and clusters were reported during June. CsCDC was asked for results of any analytical epidemiologic studies to CDSC. The results of the national laboratory reporting system are shown in Table 1. Although there were fewer reports in the first 20 weeks of 1994 than in a similar period in 1993, there were more reports in the weeks 21 to 24 and many more reports among adults. The proportion of total reports constituted by those from adults was 66% in weeks 21 to 24 of 1994 compared with 44% with the same period in 1993. The proportion in women in the 2 periods was 42% in 1994 compared with 26% in 1993.

Forty trawling questionnaires were distributed. Almost all case patients (38/40) had eaten various salad items of which the common food was iceberg lettuce. The lettuce had been consumed in restaurants, pubs, and in the homes of the case-patients. The lettuce was purchased from supermarkets, greengrocers' shops, and street markets. In one outbreak in Northampton, 21 (52%) of guests at a party became ill with diarrhea. *Sh. sonnei* was isolated from fecal specimens. Illness was significantly associated with consumption of iceberg lettuce (relative risk 3.68, confidence intervals 1.34 - 10.11, p = 0.0004).

The hypothesis that consumption of iceberg lettuce was associated with apparently sporadic *Sh. sonnei* infection in adults was tested by a case-con-

Table 1. *Shigella sonnei* in England and Wales—Laboratory reports to CDSC

Year	Number of reports (%)				
	Week 1–20	Weeks 21–24			Weeks 1–24
	Total	Total	Adults	Women	Total
1993	3190	480 (100)	211 (44)	127 (26)	3670
1994	1557	505 (100)	333 (66)	214 (42)	2062

trol study. A case was defined as a person aged 14 or more years who became ill after May 1, 1994, and had microbiologic evidence (fecal isolation) of *Sh. sonnei* infection, no recent history of overseas travel, and no identifiable contact with other case-patients in the 3 days before onset. Controls were nominated by case-patients and matched by sex, age (within a 10-year age band), and area of residence (within a 10-mile radius of the case). For each case three matched controls were sought. A questionnaire was administered by telephone by three interviewers from CDSC. Clinical and demographic details and details of exposure to food items, including iceberg lettuce, mentioned in trawling questionnaires were sought.

Twenty-eight case-patients and 49 matched controls were interviewed and, after excluding those who had recently traveled abroad and controls who had been ill, results from 27 cases and 44 controls were analyzed. The median age of case-patients was 47 years, and the range was 19 to 79 years. Eight cases were among men and 19 among women. All case-patients had diarrhea (i.e., three or more loose stools in a 24-hour period), although only four of the 27 reported blood in the stools, 25 of the 27 had abdominal pain, and 11 reported vomiting. The median duration of symptoms was 9 days, and the range was 4 to 25 days. Taking into account the matching inherent in the study design, a matched analysis was performed. In any analysis 27 matched sets were possible. For 13 sets there was one control per case, for 11 sets there were 2 per case, and for 3 sets there were 3 controls per case. Single variable analysis of the different foods consumed revealed the possible risk factors ($p < 0.2$) (Table 2). A multivariable model was fitted with all those variables included. This procedure was repeated, removing nonsignificant items at each stage. In the third model, the only remaining significant item was iceberg lettuce ($p = 0.0172$). The estimated odds ratio for iceberg lettuce was 13.8 (95% confidence interval 1.26 to 150.5).

In sporadic cases associated with consumption of lettuce from particular restaurants or public houses, it was possible to compare the date of onset with the date of delivery of iceberg lettuce by the wholesalers. The distribution chain was traced back through importers supplying wholesale markets in England. The wholesalers were supplied by packers in Spain. This was consistent with the findings of the investigators in the Norwegian outbreak. Iceberg lettuce investigated by the Public Health Laboratory service during the second week of June 1994 did not grow *Sh. sonnei*. However, the iceberg lettuce season in Spain, which began in October, ended early in June, and the source of lettuce available for testing could not be traced.

Laboratory studies

All *Sh. sonnei* isolates referred to LEP after the Epinet message were phage typed by using the scheme described by Hammerstrom (3) and Kallings and Sjoberg (4), according to a protocol supplied by Dr. R. Wollin, Swedish Institute of Infectious Disease Control, Sweden. Isolates were also tested for resistance to a range of antibiotics by an agar dilution technique (5).

A total of 495 isolates were referred to LEP between June 14 and July 31, from 51 laboratories in England and Wales. Most isolates were from sporadic infections, but in a number of local outbreaks, there was a strong epidemiologic association between illness and consumption of iceberg lettuce. Two phage types predominated among the 19 types identified during this period, PT 2 (42.6% of isolates) and a variant of PT65 provisionally designated PT L (15.9%). In contrast, although a small number of isolates of PT 65 and PT L were identified among strains of *Sh. sonnei* isolated in England and Wales in 1991 and 1992, no isolates of PT 2 were seen before May 1994. Towards the end of the outbreak PT 3 and PT 6 were becoming reestablished in England and Wales as the predominant types, as they had been in previous years.

An exception to the recent pattern was an outbreak in North Wales, involving several children and adults, in which infection was associated either with eating ice cream at a particular establishment or having contact with children who had done so. All 73 of the isolates of PT 62 were associated with this outbreak.

A total of 357 *Sh. sonnei* isolated during this period (72.1%) were fully sensitive to all drugs

Table 2. *Sh. sonnei* case control study—Single variable matched analysis

	Case (n=27)			Control (n=44)				
Food	Ate	Did not eat	% ate	Ate	Did not eat	% ate	No. of sets	p-value
Prawns	4	22	15	7	37	15	(26s)	0.9388
Shrimps	0	27	0	1	43	2	(27s)	0.3070
Steak	7	19	27	6	37	14	(26s)	0.0139
Burgers	5	22	19	12	32	27	(27s)	0.2045
Salad	25	2	93	34	10	77	(27s)	0.0081
Cold meats	15	10	60	29	13	69	(23s)	0.7708
Tomatoes	22	4	85	33	11	75	(26s)	0.1039
Spring onions	5	21	19	9	35	21	(26s)	0.7556
Celery	5	22	19	5	39	11	(27s)	0.2956
Cucumber	16	11	59	31	13	71	(27s)	0.3798
Other salads	16	10	62	26	18	59	(26s)	1.0000
Lettuce	25	2	93	31	13	71	(27s)	0.0007
Cos lettuce	2	20	9	3	25	11	(17s)	1.0000
Webb's lettuce	5	18	22	4	34	11	(21s)	0.2632
Lamb's lettuce	2	17	11	6	36	14	(19s)	0.1002
Raddicio lettuce	4	20	17	7	34	17	(23s)	0.8720
Iceberg lettuce	17	8	68	19	23	45	(25s)	0.0023
Frisee lettuce	5	18	22	4	37	10	(22s)	0.2582
Home	15	8	65	27	16	63	(23s)	0.8494
Restaurant	6	16	27	5	33	13	(21s)	0.1546
Pub	4	18	18	2	34	6	(20s)	0.0795
Other outlet	10	14	42	7	31	18	(22s)	0.0012

tested. Phage types 2 (87% fully sensitive) and PT L (99%) were predominantly sensitive, as were all isolates of PT 62; usually one would expect more than 70% of *Sh. sonnei* isolates to be resistant to one or more drugs. The use of the same phage-typing scheme across several European countries has facilitated cross-referencing between the British, German, and Swedish outbreaks. Phage types 2 and 65 (or the closely related variant PT L) were identified in several countries.

From the epidemiologic studies, it was concluded that the strong statistical evidence ($p = 0.0172$) that consumption of iceberg lettuce was associated with the risk of becoming ill together with reports from other European countries, including Scotland, Sweden, and Norway, and the temporal association of the outbreak with the iceberg lettuce season in Spain implicated iceberg lettuce as the vehicle of infection. This was corroborated by the laboratory studies, which showed a change in predominant phage types during the period of the outbreak. The predominance of the same phage types in lettuce-associated *Sh. sonnei* infections in a number of countries added further weight to this conclusion.

In England, there were several anecdotal accounts of dual infection with salmonellae and viruses as well as *Sh. sonnei*. This was also true of infections in Norway and Sweden (6). A plausible explanation would be that fecally contaminated water was used to irrigate the lettuce or to cool it after packing. If iceberg lettuce is not washed thoroughly before consumption, contamination could be retained in the leaves.

This study demonstrates both the importance of coordinating laboratory results and epidemiologic investigations and the value of rapid communications and common typing techniques in various European countries.

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?Lyme Disease in Australia— Still To Be Proven!

To the Editor: The first case of a syndrome consistent with Lyme disease was reported from the Hunter Valley region of New South Wales (NSW) in southeastern Australia in 1982, but there was no confirming serology. More clinical cases, again without serologic confirmation, were reported in 1986, two from the south coast and one from the central coast of NSW. The Queensland State Health Laboratories reported that 186 (14.9%) of 1,247 sera taken from patients between 1986-1989 showed antibody response to *Borrelia burgdorferi* of ≥ 64 by indirect fluorescence antibody test (IFAT), but none of these results were confirmed by immunoblotting.

In 1988, a multidisciplinary investigation of putative Lyme disease began, encompassing clinical, serologic, vector, and reservoir host studies, and results from these studies have been published (1). What follows herein is derived from the accumulated published and unpublished data of the research team, the members of which are credited in the acknowledgments.

Over the past 6 years, principally because of local publicity, there has been an increase in serologic testing for Lyme disease in Australia, particularly in southeastern Australia. Testing has often been initiated by patients with undiagnosed health problems. Thus, most Lyme disease patients seen by infectious disease specialists are self selected and are referred for assessment on the basis of tick exposure and reported positive serologic test results for Lyme disease.

Patients with positive serologic test results frequently have long-standing symptoms for which no other diagnosis has been established. The most common symptoms are musculoskeletal, including myalgias and arthralgias without objective evidence of joint swelling, and syndromes involving fatigue and loss of energy resembling chronic fatigue syndrome. Some patients fulfill diagnostic criteria for fibromyalgia. The next most common symptoms are neurological, and include frequent headaches, inability to concentrate, and memory loss. The most common dermatologic manifestation of chronic Lyme disease, acrodermatitis chronica atrophicans, seen occasionally in Europe and rarely in the United States, has not been reported from Australia.

A few cases of *erythema migrans*, the characteristic dermatologic manifestation of acute Lyme disease, have been reported from southeastern Australia, but clinical diagnosis can be confounded by hypersensitivity reactions to tick bite; a spectacular erythematous reaction is often associated with the bite of *Ixodes holocyclus*, the most common tick biting humans in NSW. Only eight specimens submitted to our laboratory included skin biopsies done to isolate spirochetes. *B. burgdorferi* s.l. was isolated from one patient returning from Europe, but no spirochetes were isolated from local patients.

In our serologic diagnostic service, an enzyme-linked immunosorbent assay (ELISA) for IgG and an IFAT for IgG and IgM have been used with antigens derived from North American *B. burgdorferi* strain B31 (2). From 1988 to April 1994, 78 (1.8%) of 4,372 local patients were positive for IgG by both methods. All 78 patients were tested by IgG Western blot for confirmation by using the virulent North American *B. burgdorferi* strain 297 and a German strain designated B7: with *B. burgdorferi* strain 297, 46 patient samples showed as many as four indicative bands; with the European strain B7, 22 patient samples showed as many as three indicative bands; bands used were 18, 21, 28, 30, 31, 34, 39, 41, 45, 58, 66, 83, and 93 kDa, modified from Dressler et al (3). Twenty-four other patients with various bacterial, viral, or autoimmune syndromes not relating to Lyme disease were tested as controls: with strain 297, 11 control samples showed as many as two indicative bands, and with strain B7, 10 control samples showed as many as two indicative bands.

A high degree of cross-reactivity was demonstrated with the controls, particularly with respect to the 31, 41, 58, and 66 kDa bands for both the European and the American antigen. As none of the 78 patients, including putative late-stage patients positive by ELISA and IFAT, showed more than four

specific bands to either antigen, they would be considered negative by the criteria of Dressler et al (3). Fewer than 1% of all referred patients conformed with the national surveillance case definition used in the United States by the Centers for Disease Control and Prevention. Problems of specificity and sensitivity associated with serologic testing for Lyme disease are well recognized, particularly in Australia where no local spirochete has been isolated for use as a reference antigen.

Seroprevalence rates for *B. burgdorferi* infection in humans have been compared between 200 high (rural residents) and 200 low (urban residents) tick exposure groups in coastal NSW, by using the IgG ELISA. No significant difference was found between the two groups, and the overall seropositivity rate was 2.2% (9/400). A parallel survey of dogs in NSW has shown a similar result with an overall seropositivity rate of 2.5% (6/239). These results contrast with those reported from known endemic-disease areas outside Australia that have rural populations with considerably higher seropositive rates. The low rate found by our surveys is similar to that found by other studies undertaken in areas where Lyme disease is not endemic, and humans have 1%-3% positive serologic results cause by cross-reacting antibodies (4).

From January 1990 to December 1992, ticks were collected in areas associated with putative Lyme disease cases and were examined for spirochetes to detect a possible causative agent in potential vectors. Ticks were collected along the east coast of Australia, from southern Queensland through NSW into northern Victoria, by flagging in natural habitats, and from domestic and other native animals. Detection of spirochetes was attempted by dark-field microscopy and culturing of gut contents and by direct testing of ticks using polymerase chain reaction (PCR) to detect the *Borrelia*-specific flagellin gene (5).

In total, more than 12,000 (>1,000 by PCR) ticks were processed, including 7,922 *I. holocyclus* (1). No spirochetes were detected by dark-field microscopy or by PCR. Spirochete-like objects (SLOs), were observed in 94 cultures from bloodfed ticks and only in cultures with bacterial contaminants, presumably from the bloodmeal. Some SLOs yielded positive fluorescence results when tested with *Borrelia*-specific polyclonal antibodies, but tests with monoclonal antibodies (anti-flagellin H9724, anti-OspA H5332, anti-OspB H6831) were negative. Electron micrographs showed that the SLOs were not typical of *Borrelia*, were composed of fibers, and probably were not spirochetes. The electron micrographs were similar to micrographs of SLOs recovered from contaminated cultures from ticks in the United States and Europe and thought to be composed of aggregations of bacterial flagella, probably from the contaminants. Molecular characterization indicated that the SLOs were not related to *B. burgdorferi*.

A small number of native vertebrate animals (13 native rats *Rattus fuscipes*, 3 bandicoots *Perameles nasuta*, and 1 marsupial mouse *Antechinus stuartii*) trapped on the south coast of NSW were sampled by ear-punch biopsy (6) for culture and PCR investigation, but no evidence of borreliae was found. The animal sample was clearly inadequate, and the PCR primers used for the tick and animal studies may have been inappropriate and unable to identify native Australian spirochetes; however the extensive investigations of tick gut contents by culturing and dark field microscopy were also negative for borreliae.

There are some major differences between Australia and the Lyme-disease-endemic areas of the Northern Hemisphere with respect to the natural history of borreliosis. No ticks of the *I. persulcatus* complex, the principal vectors to humans in the northern hemisphere, occur in Australia. In eastern Australia, the logical candidate vector would be *I. holocyclus*, which has a wide host range and is the most common tick biting humans. *I. holocyclus* cannot transmit a North American strain of *B. burgdorferi* (7) but the association with any possible Australian spirochetes remains unresolved. Likewise, none of the mammal species identified as reservoir hosts in the Northern Hemisphere are present in Australia. There are reports of spirochetes in Australian native animals, and a local mammal could be a reservoir host for an indigenous spirochete that occasionally infects humans through a tick vector and produces a clinical syndrome similar to Lyme disease; however, no spirochete was detected in the ticks or animals studied.

The diagnosis of Lyme disease outside known disease-endemic areas should not be based solely on serology because unrelated syndromes, such as autoimmune diseases and cross reactions with other bacteria, can produce false-positive results. Likewise, a definitive diagnosis on clinical grounds alone in a nonendemic-disease area is difficult to justify without adequate scientific support based on isolation of the causative agent from the patient or from another patient or known vector from the region. In Australia, disagreement as to what constitutes a positive serologic result has additionally contributed to overdiagnosis of Lyme disease. Until an organism is isolated from a local patient and is characterized, the presence of Lyme disease in Australia will remain controversial.

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A Novel Morbillivirus Pneumonia of Horses and its Transmission to Humans

To the editor: On September 22 and 23, 1994, veterinary authorities in Queensland and at the CSIRO Australian Animal Health Laboratory were advised of an outbreak of acute respiratory disease in horses at a stable in the Brisbane suburb of Hendra. The trainer of the horses had been hospitalized for a respiratory disease and was in critical condition. At that time, the cause of the horses' illness was unclear and any link between equine and human disease was thought improbable. Poisoning, bacterial, viral, and exotic disease causes were investigated. The history of the horses on this property was considered important (Figure 1). Two weeks before the trainer's illness, on September 7, two horses had been moved to the Hendra stable from a spelling paddock in Cannon Hill (6 km). One of these, a pregnant mare, was sick and died within 2 days. The other horse was subsequently moved on and never became sick. By September 26, 13 horses had died: the mare; 10 other horses in the Hendra stable; one horse, which had very close contact with horses in the Hendra stable, on a neighboring property; and one which had been transported from the stable to another site (150 km). Four Hendra horses and three others (one in an adjacent stable, one moved to Kenilworth, and one to Samford) were later considered to have been exposed and recovered from the illness. Some of these horses were asymptomatic. Nine Hendra horses have remained unaffected. The sick horses were anorexic, depressed, usually febrile (temperature up to 41°C), showed elevated respiratory rates, and became ataxic. Head pressing was occasionally seen, and commonly, a frothy nasal discharge occurred before death.

On September 14, a stablehand at the Hendra stable developed an influenza-like illness characterized by fever and myalgia. The next day, the horse trainer also became ill with similar symptoms. Both had close contact with the dying mare, particularly the trainer who was exposed to nasal discharge while trying to feed her; he had abrasions on his hands and arms. The stablehand, a 40-year-old man, remained ill for 6 weeks and gradually recovered. Besides myalgia, he also had headaches, lethargy, and vertigo. The trainer, a 49-year-old man, was a heavy smoker and showed signs consistent with *Legionella* infection. He ultimately required ventilation for respiratory distress and died after 6 days (Selvey L, et al. A novel morbillivirus infection causing severe respiratory illness in humans and horses, submitted).

At the beginning of the diagnostic investigation in horses, African horse sickness, equine influenza, and hyperacute equine herpes virus were excluded as possible causes by antigen trapping enzyme-linked immunosorbent assay (ELISA), polymerase

	September 1994							
	7	**9**	**13**	**14**	**15**	**16**	**17**	**19-26**
Horses								
Cannon Hill (Paddock)	2 horses moved							
Hendra (Stables)		Mare died				2 horses moved		10 horses dead 4 recovered
Hendra (Neighboring property)		1 horse moved						1 horse dead 1 recovered
Kenilworth (150 km distant)								1 horse dead 1 recovered
Samford (Paddock)								1 recovered
			New South Wales					
Humans								
Stablehand				Becomes ill				Slow recovery
Trainer					Becomes ill		Hospitalized	Died

Figure 1. A chronology of the development of cases of acute equine respiratory disease and associated illness in humans.

chain reaction (PCR), or electronmicroscopy. Tests for *Pasteurella*, *Bacillus anthracis*, *Yersinia*, *Legionella*, *Pseudomonas*, and *Streptobacillus moniliformis* were negative, and poisons consistent with the clinical and gross pathology, such as paraquat, were excluded by specific testing.

However, within 3 days, a syncytial forming virus was detected in vero-cell cultures inoculated with diseased horse tissues and shortly thereafter was seen to grow in a wide range of cells. These included MDBK, BHK, and RK13 cells. Subsequently, a syncytial forming virus also was isolated in LLK-MK2 cells that had been inoculated with tissue from the deceased trainer's kidney. The isolation of these viruses and their preliminary characterization by electron microscopy, immunoelectromicroscopy, serology, and genetic analyses are described elsewhere (Murray PK, et al. A new morbillivirus which caused fatal disease in horses and man, submitted).

In summary, ultrastructural analysis showed that the virus is a member of the *Paramyxoviridae* family. It is enveloped, pleomorphic (varies in size from 38 nm to more than 600 nm), and is covered with 10 nm and 18 nm surface projections. It contains herringbone nucleocapsids that are 18 nm wide with a 5 nm periodicity. The presence of 'double-fringed' surface projections on this virus is considered unique. Immunoelectronmicroscopy showed that both the horse and the human virus react with convalescent-phase horse sera and with sera from the two human cases.

PCR primers were synthesized from consensus *Paramyxoviridae* matrix protein sequences and tested against the horse virus. Those specific for paramyxoviruses and pneumoviruses did not bind, but one pair of morbillivirus primers gave a 400 bp product. Determination of the sequence of this product enabled the synthesis of horse virus-specific primers. Phylogenetic analyses of the matrix protein sequence indicates that the virus is unique and distantly related to other known members of the group. A comparison of translated M protein sequence shows that it has a 50% homology with the morbillivirus group (80% if conservative amino acid substitutions are used). This distant relatedness is emphasized by our observations that neutralizing antisera to measles virus, canine distemper, and rinperest virus failed to neutralize the virus.

The viruses isolated from the horses and the trainer are ultrastructurally identical. Serum from the horses and the two human cases specifically cross-neutralize the virus, and the horse virus-specific PCR primers provide a positive reaction with the human virus isolate. Therefore, the horses and the trainer were infected with the same virus.

At the beginning of the diagnostic investigation, tissues from the lungs and spleens of diseased horses were injected into two recipient horses. After 6 and 10 days, the recipient horses became ill with high fever and severe respiratory signs, demonstrating that the disease was transmissible. Two days later the horses were destroyed. The equine morbillivirus

was isolated from tissues from both of these horses. To document that the isolated horse virus was pathogenic, experimental transmission tests were also conducted. Two additional horses received a total of 2×10^7 TCID50 of tissue culture virus by intravenous inoculation and by intranasal aerosol. Both horses became seriously ill, and after a short, severe clinical episode, were destroyed 4 and 5 days after exposure. At necropsy, they showed gross and histopathologic lesions that were primarily respiratory and consistent with the natural disease. Virus was reisolated from their lungs, liver, spleen, kidney, lymph nodes, and blood.

The pathology of this infection is interesting. In horses, the dominant gross pathology is lesions in the lungs. These are congested and edematous with prominent lymphatic dilation in the ventral margins. In natural cases, the airways were usually filled with thick, fine, stable foam which was occasionally blood-tinged; this was not seen in the experimental cases. Histologically, in horses, there is interstitial pneumonia, proteinaceous edema with pneumocyte, and capillary degeneration. Virus can be located in endothelial cells by immunofluorescence and syncytial cells also could be seen in blood vessel walls, confirming the vascular of trophism of this virus (Murray PK, et al, submitted). The trainer's post-mortem findings showed similarities to those of the horses (Selvey L, et al, submitted).

No further clinical cases of disease have been seen in horses or humans since this outbreak. Serologic surveillance of people who had close contact with the sick horses, mostly stable workers, veterinary pathologists, animal health field staff, or people who lived in the vicinity of the affected stables, was negative (Selvey L, et al, submitted).

Table 1. The premises and horses surveyed by serologic testing for equine morbillivirus, after the disease outbreak

	Premises	Horses
Quarantine Premises*	13	107
1 (within 100 m of Hendra stables)	7	54
2 (100 m to 200 m of Hendra stables)	21	122
3 (200 m to 1 km of Hendra stables)	93	730
4/5 (remainder of Queensland)	>500	963
Total	**>630**	**1,964**

*Quarantine premises included those with clinical cases, holding properties associated with the Hendra stables, and other premises where horses under investigation were kept.

Serologic testing of all horses on quarantined properties and within 1 km of the Hendra stable, and a sample of horses from the rest of Queensland was undertaken (Table 1). A total of 1,964 horses were tested from more than 630 premises. The negative results from this testing also indicate that the infection has not spread. In the entire horse survey, only seven horses, all from the Hendra property and the adjoining stables, were positive. Four of these animals had been clinically affected, but three were asymptomatic. Because of the potential risk and the difficulty in establishing freedom from infection, these seven recovered horses were later destroyed.

Although persistent virus excretion or carrier states are not known to occur in other morbillivirus infections, this equine virus is unique and it cannot be presumed to behave similarly. Australian veterinary authorities are now satisfied that the incident is over.

We have described a newly recorded disease of horses with an obvious zoonotic potential; moreover, the causative agent was previously unrecorded and is significantly different from other members of its genus, morbillivirus. Infection seems to have spread from the mare that first showed the now characteristic clinical signs, to other horses in the same stables, to a horse in close contact from an adjacent stable, and also to two human attendants. Clearly, this outbreak was not highly contagious and it rapidly resolved. However, the virus is highly pathogenic with 65% of naturally infected horses and all four experimental horses dying.

Further investigations of the virus and the disease are now warranted since it could reemerge in Australia or elsewhere. Investigations of its origin, its replication, its pathogenesis, and its possible occurrence elsewhere in connection with equine respiratory disease are merited.

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Electronic Communication and the Future of International Public Health Surveillance

Recent developments in electronic communication have enhanced national public health surveillance systems and facilitated progress in establishing surveillance that crosses national boundaries. The international foodborne outbreak of *Shigella sonnei* described by Frost and colleagues was first reported through Salmnet (1), a laboratory-based surveillance system designed to include an on-line network database. Salmnet was established in 1994 to improve the prevention and control of human salmonellosis and other foodborne infections in the countries of the European Union and the European Cooperation in Science and Technology.

Epidemiologists who have national surveillance responsibilities and heads of reference laboratories in 13 countries currently collaborate in the Salmnet project under the joint leadership of the Directors of the Laboratory of Enteric Pathogens and the Communicable Disease Surveillance Centre (CDSC) at the Public Health Laboratory Service campus at Colindale, London. During the course of two workshops, the collaborators agreed to a) develop and apply standardized phage typing for the most common salmonella serotypes within Europe, b) introduce an international quality assurance scheme for laboratory performance of *Salmonella* phage typing, c) establish a core set of data on each laboratory-confirmed and typed human salmonella isolate for rapid transfer into a shared nonaggregated dataset, and d) develop statistical analysis programs to facilitate the early recognition of international outbreaks. The collaborators also agreed to rapidly report any clusters detected and to exchange information concerning other infections, including those caused by *Shigella*, *Listeria*, and vero-cytotoxin-producing strains of *Escherichia coli*.

Currently six countries share data through the Internet, while the other seven countries rely on faxing material or sending diskettes through the mail. All collaborating countries plan to join the on-line network by the end of 1995. The opportunities offered by electronic communication have encouraged a remarkable degree of international cooperation in surveillance, as is evident in the far reaching objectives agreed upon for Salmnet.

The Salmnet collaboration was already in place when the *S. sonnei* outbreak in Sweden was reported to Colindale. CDSC responded by sending an electronic message throughout England and Wales by Epinet, an electronic system for the rapid transfer of vital public health information developed by the CDSC Welsh Unit in Cardiff (2). The message was sent to consultants in communicable disease control in each district health authority, to the 53 public health laboratories, and to other agencies in England and Wales involved in infectious disease control. Further information from Norway, Scotland, and Sweden reinforced and stimulated the ongoing investigation in England and Wales. Since its inception, Salmnet has also contributed information with potential international implications concerning several *Salmonella* serotypes (3,4).

The signing of the Treaty of Maastricht (1992) was an important milestone for international cooperation in public health surveillance. The treaty established a basis for European Community action in the field of public health and enjoined cooperation between member states, third countries, and international public health organizations to protect human health. Sufficient evidence has accrued on the added value of international surveillance of infectious diseases, and it is generally accepted that the potential for major public health hazards is amplified as a consequence of the increasing volume of international travel and the global extension of food distribution networks (5). Surveillance systems such as Salmnet and the European Surveillance of Travel-Associated Legionnaires' Disease (6) will pave the way for international surveillance by providing a communications network that will facilitate the rapid collection and analysis of data using standard case definitions, transmission of information for the prevention of communicable diseases, and the promotion of effective public health practice.

Parallel electronic surveillance systems in the United States offer equal opportunity for international collaboration. For example, since 1985, data on notifiable diseases have been transmitted electronically each week to the Centers for Disease Control and Prevention (CDC) from state health departments by the National Electronic Telecommunications System for Surveillance (NETSS) (7). NETSS was developed by CDC and the Council of State and Territorial Epidemiologists for electronically collecting, transmitting, analyzing, and publishing weekly reports of notifiable diseases and injuries from 50 states, New York City, the District of Columbia, Puerto Rico, the Virgin Islands, Guam, American Samoa, and the Commonwealth of the Northern Mariana Islands (8). The operation of NETSS is based on agreements on reporting conditions, standard case definitions, and protocols for formatting and transmitting data, rather than prescribed software or systems.

A second CDC electronic reporting system, the Public Health Laboratory Information System (PHLIS), is used by public health department laboratories in all states, New York City, the District of Columbia, and Guam to report laboratory isolate-based surveillance data to CDC. The PC-based system was developed jointly by the National Center for

Infectious Diseases, CDC, and the Association of State and Territorial Public Health Laboratory Directors to maintain a fast and direct link between public health laboratories in the United States and CDC. PHLIS is used to gather, analyze and transmit data (e.g., laboratory testing results, epidemiologic information, findings from special studies and surveys) among multiple sources of public health laboratory information (e.g., hospitals, laboratories, or public health departments), and it provides an automated program in its longitudinal databases to detect outbreaks (9).

European and U.S. surveillance databases and information systems should be linked to share public health information of international concern. To that end, CDSC and CDC are developing a cooperative communications information system that will use the Internet to mirror vital public health documents (e.g., CDSC's *Communicable Disease Report* [*CDR*], CDC's *Morbidity and Mortality Weekly Report* [*MMWR*], and selected surveillance data sets). This network is the beginning of a larger international network that will share data, exchange information, and improve public health. This larger network could link such systems as Salmnet, NETSS, and PHLIS to create a virtual on-line library of international surveillance data and information for public health.

With the diffusion of technology, internationally networked electronic public health surveillance systems are gaining in importance. Their existence clearly facilitates the rapid collection, analysis, and dissemination of vital public health information and promotes the establishment of effective international public health policies.

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Communicable Diseases Intelligence

Communicable Diseases Intelligence (CDI) is a fortnightly publication of the Australian Department of Human Services and Health and the Communicable Diseases Network of Australia and New Zealand. The Network comprises representatives of the Australian Department of Human Services and Health, the State and Territory health authorities, and other organizations involved in communicable disease surveillance and control from throughout the country. In addition, there is a representative from New Zealand. It has fortnightly teleconferences and other meetings to exchange information on emerging communicable disease activity and to coordinate surveillance and control activities.

Each issue of CDI incorporates reports from Australia's national communicable diseases surveillance systems, including the National Notifiable Diseases Surveillance System, the CDI Laboratory Reporting Schemes, and the Australian Sentinel General Practitioner Surveillance Network. Reports from the National Salmonella Surveillance Scheme, the Australian Gonococcal Surveillance Programme and the National HIV, AIDS, and Tuberculosis Reporting Systems are also regularly included.

CDI also publishes timely reports of communicable disease outbreaks and other articles dealing with a wide range of subjects relevant to the surveillance and control of communicable diseases in Australia. Recently published items have reported, for example, the first identification of endemically acquired hepatitis E in the Northern Territory of Australia, an outbreak of influenza in a nursing home, the epidemiology of hepatitis A in South Australia, the epidemiology of Barmah Forest virus disease in Western Australia, and the outbreak of respiratory disease in humans and horses due to a previously unrecognized paramyxovirus.

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DxMONITOR: Compiling Veterinary Diagnostic Laboratory Results

The DxMONITOR is a collaborative effort between the U.S. Department of Agriculture, Animal and Plant Health Inspection Service's Veterinary Services (USDA:APHIS:VS), the American Association of Veterinary Laboratory Diagnosticians, and the United States Animal Health Association. This quarterly animal health report presents compiled data from national animal disease control and eradication programs (bovine and porcine brucellosis, bovine tuberculosis, porcine pseudorabies and equine infectious anemia); patterns of selected diseases based on veterinary diagnostic laboratory data (bovine leukosis; bovine bluetongue; bovine, ovine and caprine paratuberculosis; equine arboviral encephalitis; equine viral arteritis; porcine reproductive and respiratory syndrome); data on selected etiologic agents associated with specific animal health events such as bovine abortion; global disease distribution (bovine spongiform encephalopathy); and notes from veterinary diagnostic laboratories about unusual laboratory findings or new diagnostic procedures.

The DxMONITOR has contributed to a greater awareness of animal diseases in the United States. Global trade agreements, the worldwide information explosion, and increasing public concern over the safety and quality of food have focused attention on animal health. Compilation of veterinary diagnostic laboratory data is one component of the USDA: APHIS efforts to respond to these increased demands for animal health information through an integrated and coordinated monitoring and surveillance system. Animal-health monitoring and disease surveillance concern not only animal health per se, but also interactions with the environment, animal welfare, production practices and product wholesomeness which impact animal health. The DxMONITOR is mailed to all interested parties without charge and is increasingly available through electronic dissemination channels. For more information or subscription, contact DxMonitor Animal Health Report, c/o Centers for Epidemiology and Animal Health, USDA:APHIS:VS, 555 S. Howes, Suite 200, Ft. Collins, CO 80521-2586; telephone 303-490-7800; e-mail DXMONITOR@aphis.ag.gov.

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WHO Scientific Working Group on Monitoring and Management of Bacterial Resistance to Antimicrobial Agents

Antibacterial resistance is a global clinical and public health problem that has emerged with alarming rapidity in recent years and undoubtedly will increase in the near future. Resistant bacteria do not respect national borders, and developments in the remote locations can have an impact throughout the world. Resistance is a problem in the community as well as in health care settings, where transmission of bacteria is greatly amplified, in both developed and developing countries. Because multiple drug resistance is a growing problem, physicians are now confronted with infections for which there is no effective therapy. The morbidity, mortality, and financial costs of such infections pose an increasing burden for health care systems worldwide, but especially in countries with limited resources.

The Division of Communicable Diseases at the World Health Organization, Geneva, Switzerland, recently convened a Scientific Working Group to address the problem of drug-resistant bacterial infections. From November 29 to December 2, 1994, participants from 23 countries reviewed and discussed scientific data on the nature and costs of drug resistance; recent national and global trends; approaches to limiting the emergence and spread of resistance in community and institutional settings; and strategies to strengthen local, national, and global surveillance. Participants included representatives from clinical medicine, public health, the clinical laboratory, and the biomedical research arenas and from the pharmaceutical industry.

The Working Group formulated a series of recommendations to address these issues at local, national, and international levels. The recommendations placed emphasis on enhanced surveillance of drug resistance through usage of WHONET software, increased monitoring and improved usage of antimicrobial drugs in human, veterinary, and animal husbandry settings, improved laboratory diagnostic capacity, standardization and quality control of laboratory methodology, professional and public education, development of new drugs and assessment of alternative therapeutic modalities, assessment of vaccine development and delivery priorities related to antimicrobial resistance, better implementation of infection control measures, and evaluation of prevention strategies.

The Working Group plans to release its final report in the spring.

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