# *Symposium: Newly Emerging Viral Diseases: What Role for Nutrition?*

## The Public Health Threat of Emerging Viral Disease[1,2]

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ABSTRACT ''Emerging diseases'' are those that either have newly appeared in the population or are rapidly increasing their incidence or expanding their geographic range. Emerging viruses usually have identifiable sources, often existing viruses of animals or humans that have been given opportunities to infect new host populations (''viral traffic''). Environmental and social changes, frequently the result of human activities, can accelerate viral traffic, with consequent increases in disease emergence. Host factors, including nutrition, have often received less attention in the past but are of considerable importance. These factors, combined with the ongoing evolution of viral and microbial variants, make it likely that emerging infections will continue to appear and probably increase, emphasizing the need for effective surveillance. J. Nutr. 127: 951S–957S, 1997.

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"Emerging infectious diseases" can be defined as infections that have newly appeared in the population or are rapidly increasing their incidence or geographic range. Among recent examples are HIV/AIDS, hantavirus pulmonary syndrome, Lyme disease and hemolytic uremic syndrome (a food-borne infection caused by certain strains of the common bacterium Escherichia coli) (Morse 1995a). One recent year alone, 1993, marked the 10th anniversary of the formal recognition of acquired immune deficiency syndrome (AIDS) and the first recognition of hantavirus pulmonary syndrome, as the result of an outbreak in the "Four Corners" area of the western United States that resulted in over 20 deaths (Centers for Disease Control and Prevention 1993). In the last decade, AIDS has risen to become a leading cause of death in young men (Centers for Disease Control and Prevention 1996). Influenza, one of our most familiar viruses, periodically causes massive epidemics (the most massive are called pandemics because the entire world is affected), and another influenza pandemic seems virtually inevitable. There have been four influenza pandemics (1918–1919, 1957, 1968 and 1977) in this century, the most severe being the notorious pandemic of 1918–1919, which resulted in some 25 million deaths worldwide (Crosby 1989). Lyme disease, a bacterial infection caused by Borrelia burgdorferi, has recently emerged to prominence in both the United States and Europe (Barbour and Fish 1993). More than two dozen infections, some very severe, have been first identified in the last 20 y (Centers for Disease Control and Prevention 1994, Satcher 1995).

Because of their great diversity and capacity for rapid evolution, and because therapeutic interventions are more limited, viruses have received the greatest share of attention, and this review will deal primarily with emerging viruses. However, many of the general principles discussed here are also applicable to other types of infectious agents, and a few are mentioned as appropriate. Some examples are given in **Table 1** (the list is merely illustrative and is not intended to be exhaustive; throughout this review, the emphasis will be on the factors underlying the appearance of new infections, rather than on the specific diseases).

Analyzing the various episodes, I suggest that viral emergence (or infectious disease emergence generally) can be viewed as a two-step process: *1*) introduction of the virus into a new host, followed by *2*) "Adoption" of the infectious agent by the new host species (establishment and dissemination within the new host population). Emphasis should therefore be placed on understanding the conditions that affect each of these steps. Depending on the virus and its evolutionary potential and on ecological conditions, step 2 may rapidly follow step 1, be separated by some period of time, or may never occur. In the transition to step 2, and within step 2 itself, rapid evolution may occur, including changes in virulence or tissue tropism. "Viral traffic" (or, more generally, "microbial traffic"), factors allowing the introduction of existing viruses into new settings, such as across species or into new host populations, can play a key role in both steps, by serving to introduce viruses into a human population from a zoonotic source or to spread a previously localized virus to new hosts (Morse 1991). Factors responsible for the emergence of infectious diseases can be identified (**Table 2**); in most cases, these factors operate by promoting introduction, dissemination, or both.

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## TABLE 1

*Some examples of recent emerging infections and probable factors in their emergence*[1]

| Infection or agent | Factor(s) making major contribution to emergence |
|---|---|
| **Viral** | |
| Argentine hemorrhagic fever (Junin virus) | Changes in agriculture favoring rodent host |
| Bolivian hemorrhagic fever (Machupo) | Changes in agriculture favoring rodent host, with exposure to rodent host in homes |
| Bovine spongiform encephalopathy (BSE) (cattle) | Changes in rendering process |
| Dengue, dengue hemorrhagic fever | Disseminated by transport, travel and migration; urbanization, water containers encouraging breeding of mosquito vector |
| Ebola, Marburg | Unknown (in Europe and United States, importation of monkeys) |
| Hantaviruses | Ecological or environmental changes favoring increased contact between humans and rodent host bearing given hantavirus (in some cases, secondary to increase in rodent population); Hantaan: rice agriculture (favoring increase in natural rodent host); ratborne hantaviruses: disseminated on ships as rats carried to ports worldwide; HPS (hantavirus pulmonary syndrome), 1993: environmental conditions (including unseasonably wet and warm winter and spring) favored increase in population of infected natural rodent host (*Peromyscus*) |
| Hepatitis B | Transfusions, organ transplants, contaminated hypodermic apparatus, sexual transmission, vertical spread from infected mother to child |
| Hepatitis C | Transfusions, organ transplants, contaminated hypodermic apparatus, probably sexual transmission, other (unknown) |
| HIV | Introduction and dissemination to new areas by migration to cities and travel; after introduction, disseminated and established in new area by sexual transmission, vertical spread from infected mother to child, contaminated hypodermic apparatus (including in intravenous drug use), transfusions, organ transplants |
| HTLV | Contaminated hypodermic apparatus, sexual transmission (HTLV-2 also apparently long widespread in some populations) |
| Human herpesviruses 6, 7 | Probably long widespread, now recognized |
| Influenza (pandemic) | (Pandemic: possibly pig-duck agriculture, facilitating reassortment of avian and mammalian influenza viruses)[2] |
| Lassa fever | Urbanization and other factors favoring rodent host, increasing exposure to rodent host (usually in homes) |
| Parvovirus B19 | Probably long widespread; increase possible through bone marrow transplants? |
| 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 then facilitated by reduced water chlorination; a new strain (type 0139) 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 (*E. coli* 0157:H7) | Mass food processing technology allowing contamination of meat |
| *Legionella* (Legionnaire's disease) | Cooling and plumbing systems of buildings (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, together with *Peromyscus* or other rodents as primary reservoir hosts) |
| *Mycobacterium* | Changes in host susceptibility (immunosuppressed, homeless), and environmental conditions (e.g., in homeless shelters, prisons, other high density population settings) favoring spread; for multidrug-resistant *M. tuberculosis,* incomplete antimicrobial treatment (selecting from resistance) |
| *Streptococcus,* group A (invasive, necrotizing) | Uncertain (some cases perhaps are reappearance of strains from past not recently prevalent, others possibly new strains; necrotizing fasciitis has been known for at least a decade, and it is not certain whether cases are actually increasing) |
| Toxic shock syndrome (*Staphylococcus aureus*) | Ultra-absorbency tampons, other factors (unknown) |
| **Parasitic** | |
| *Cryptosporidium,* other water-borne pathogens | Contaminated surface water, faulty water purification; possibly may be introduced into new areas by travel or from livestock; immunosuppressed populations, highly susceptible, are increasing in number |
| Malaria (in ''new'' areas) | May be introduced into new areas by travel or migration |
| Malaria, drug-resistant | Selective use of chloroquine in endemic areas |
| Schistosomiasis | Dam building |

[1] From Morse (1995a).

[2] 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).

**TABLE 2**

*Factors in infectious disease emergence*[1,2]

| 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 United States in 1993 (weather anomalies) |
| Human demographics, behavior | Societal events: population growth and migration (movement from rural areas to cities); war or civil conflict; economic impoverishment; urban decay; factors in human behavior such as: sexual behavior (including urban prostitution and ''sex-for-drugs''); intravenous drug use; diet; outdoor recreation; use of child care facilities (high density settings) | Introduction of HIV; spread of dengue; spread of HIV and other sexually transmitted diseases |
| International travel | Worldwide movement of goods and people; air travel | ''Airport'' malaria; dissemination of mosquito vectors such as *Aedes albopictus* (Asian tiger mosquito); dissemination of dengue; ratborne hantaviruses; introduction of cholera into South America; dissemination of 0139 (non-01) cholera organism |
| Technology and industry | Food production: globalization of food supplies; changes in food processing and packaging; health care: new medical devices; organ or tissue transplantation; drugs causing immunosuppression; widespread use of antibiotics | Food processing: hemolytic uremic syndrome (*E. coli*) contamination of hamburger meat), bovine spongiform encephalopathy; health care: 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 | Changes in virulence and toxin production; development of drug resistance (antimicrobial-resistant bacteria, chloroquine-resistant malaria); ''antigenic drift'' in influenza virus |
| Breakdown in public health measures | Curtailment or reduction in prevention programs; lack of, or inadequate, sanitation and vector control measures | Resurgence of tuberculosis in United States; cholera in refugee camps in Africa; resurgence of diphtheria in former Soviet republics |

[1] From Morse (1995a).

[2] Categories of factors (column 1) adapted from Institute of Medicine (1992); examples of specific factors (column 2) adapted from Centers for Disease Control and Prevention (1994). Categories are not mutually exclusive; several factors may contribute to emergence of a disease (see Table 1 for additional information).

## ECOLOGICAL SOURCES OF EMERGING VIRUSES AND THE ZOONOTIC POOL

In considering those viruses that have emerged to date, it is striking that many are viruses already existing in nature that simply gain access to new host populations, often as a result of changed ecological or environmental conditions (Table 1). Human pathogens, which may include agents currently in an isolated human population, are often best positioned to cause future epidemics; such pathogens bear careful scrutiny, especially if they are highly transmissible (Ewald 1993, Mims 1991), particularly by the respiratory route. But the numerous historical examples of infections originating as zoonoses (Fiennes 1978, McNeill 1976) suggest that the "zoonotic pool"—introductions of viruses from other species—is an important and potentially rich source of emerging diseases, some of which might become successful given the right conditions.

The human immunodeficiency virus (HIV) is a likely example of a zoonotic introduction meeting this criterion. The identification of numerous species-specific lentiviruses in a variety of primate populations (Allan et al. 1991, Myers et al. 1992) suggests a long coevolutionary history. The actual ancestor of the most prevalent HIV-1 strains remains to be found, and therefore the origin of HIV-1 is still uncertain. But with HIV-2 a plausible scenario is suggested by the identification of an infected man in a rural area of Liberia whose HIV-2 strain more closely resembled viruses from the sooty mangabey, a presumed reservoir of a virus closely ancestral to HIV-2, than it did HIV-2 strains circulating in the city (Gao et al. 1992). This suggests that zoonotic introductions of viruses such as HIV may well occur periodically in isolated populations but go unnoticed. The recent identification of a new subtype of HIV-1 from Africa (represented by strains Ant70 and MVP-5180), which seems to have branched off fairly early in the HIV lineage and is closely related to a virus isolated from chimpanzees, can be interpreted as evidence of a separate, possibly earlier, zoonotic introduction (Myers and Korber 1994). History may be a guide to the future. There is a large pool of simian immunodeficiency viruses (SIV) in African green monkey populations (Allan et al. 1991, Myers et al. 1992), including the probable ancestor of the sooty mangabey virus. Which among the other primate lentiviruses, including some not yet identified, might have the potential to enter the human population and emerge as yet another HIV? In the case of HIV-1, social changes that allowed the virus to reach a larger population after introduction (including movement of people to cities) and that allowed the transmission of the virus despite its relatively low natural transmissibility were instrumental in the success of the virus in its human host (the long period from infection to clinical disease, with long duration of infectivity, also allowed the virus many opportunities to be transmitted).

The zoonotic pool appears by no means exhausted. Periodic discoveries of "new" zoonoses suggest that the known viruses are only a fraction of the total number that exist in nature, and they are continually evolving. The identification of the virus responsible for the recent "Four Corners" disease in the western United States is another example (the disease is now called hantavirus pulmonary syndrome; the name "Sin Nombre" has been proposed for the original virus). Beginning in May 1993, patients were admitted to area hospitals with fever and acute respiratory distress; a number subsequently died from respiratory failure. Serology and detection of genetic sequences by polymerase chain reaction (PCR) provided evidence for a previously unrecognized hantavirus as the cause of the outbreak (Nichol et al. 1993) and identified a virus with the same genetic sequences in local rodents, primarily the common species Peromyscus maniculatus (deer mouse), which was also the rodent most frequently trapped near homes. Over 20% of captured Peromyscus were positive. It is likely that the virus had long been present in mouse populations (Tsai et al. 1985) but that unusual climatic conditions led to increased adult survival over the winter, increased rodent population in the spring and summer, and thus greater opportunities for people to come in contact with infected rodents (and hence with the virus). As might be expected for viruses that are newly recognized but have probably been widespread for a considerable time in their natural hosts, additional sporadic cases have since come to light in parts of the United States outside the original area (Centers for Disease Control and Prevention 1993), probably reflecting our new ability to recognize this longstanding occasional cause of death.

Thus, changing environmental conditions are often responsible for precipitating the emergence of new infections. Because people are major agents of ecological change, often these changes are brought about by human activities. Introduction of viruses into the human population can result from human activities, such as agriculture, that cause changes in natural environments, often by placing humans in contact with previously inaccessible viruses or natural hosts (Table 1). For example, Junin virus, the cause of Argentine hemorrhagic fever, is an arenavirus normally maintained in the rodent Calomys musculinus. Changes in land use favored this rodent, and human cases increased in proportion to the expansion of maize agriculture (de Villafañe et al. 1977, Johnson 1993). Hantaan (Korean hemorrhagic fever) is associated with Apodemus agrarius, for which ricefields are a favored habitat (Johnson 1993). The other arenaviruses and hantaviruses have similar life histories, and more are likely to appear as new areas become subject to conditions that allow increased density of a natural host. Viruses transmitted by mosquitoes, which include such important and widespread diseases as dengue (Gubler and Trent 1993), yellow fever and Rift Valley fever, are often stimulated by expansion of water supplies, because many of the mosquitoes that transmit these viruses breed in water. This expansion usually involves dams or water for irrigation, or stored drinking water in settings where there is insufficient infrastructure or where (as in rapidly expanding periurban areas) population growth outstrips the infrastructure. These events can be additive or synergistic with changes in climate, which can cause similar effects (Patz et al. 1996).

Ecological conditions, often influenced by human activities, can also transfer viruses between other species of animals or plants. Bovine spongiform encephalopathy (BSE) appeared in Britain within the last few years as a probable interspecies transfer of scrapie from sheep to cattle (Morse 1990a). Changes in rendering processes, allowing incomplete inactivation of scrapie agent in sheep byproducts fed to cattle, may have been responsible (Wilesmith et al. 1991). In any case, the use of such byproducts was clearly instrumental in amplifying the infection. Other viruses that have recently emerged in other species by cross-species transmission include seal plague, canine distemper in African lions, canine parvovirus, SIV in captive Asian macaques, and "callitrichid hepatitis," an introduction of lymphocytic choriomeningitis virus into captive monkeys fed infected mice.

Pandemic influenza, which is the result of gene reassortment between avian and mammalian influenza viruses, is also an interspecies transfer. Present evidence indicates that waterfowl, such as ducks, are the major natural hosts of influenza viruses and that pigs can serve as "mixing vessels" for new mammalian influenza strains containing avian influenza genes (Webster et al. 1992). Scholtissek and Naylor (1988) 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 close contact, providing a natural laboratory for making new influenza reassortments.

## ADOPTING A NEW VIRUS: FACTORS AFFECTING ESTABLISHMENT AND DISSEMINATION

However a new virus may have originated and been introduced, the next step depends on its establishing itself and spreading within the human population after introduction. A framework for analyzing this aspect was developed by Anderson and May (1979 and 1991), who, pointing out the parallels between the introduction and spread of infectious diseases and invasions of new species into an area, divided this process into three phases: initial establishment, persistence in the longer term, and spread to other host communities. They note that the basic reproductive rate (transmission potential) of the introduced pathogen is a key factor in all three phases, especially in establishment and spread, where high transmission potential greatly benefits the parasite. Transmission will, of course, be influenced by population factors (such as host density) and by host factors (such as immune response to the pathogen).

Many zoonotic introductions are highly virulent and not readily transmissible from person to person, preventing their establishment. As mentioned earlier, the evolutionary potential of the virus and chance will also play a role in whether the virus will be able to establish itself. Increases in effective host density can allow for greater spread; increasing the number of infected individuals might also increase the opportunity for a more readily transmissible variant to evolve. Analysis of the coevolution of virus and host following the introduction of myxoma to control the rabbit population in Australia (Fenner 1983) suggested a relationship between virulence and transmissibility (Ewald 1993, Levin and Pimentel 1981). It has been suggested as one consequence that more rapid transmission can select for greater virulence (Ewald 1993), a suggestion that has stimulated debate on how virulence evolves. In any case, it is clear, as will be discussed, that opportunities for increased transmission are expanding, because of such factors as population movements and high population density.

## ROLE OF HUMAN ACTIVITIES IN DISSEMINATION

Human intervention, in addition to providing opportunities for introduction of viruses, also provides increasing opportunities for dissemination of previously localized viruses, including viruses already present in a limited or isolated human popula-

tion (viral traffic again) (Morse 1991, Shope and Evans 1993). As with the spread of HIV, human activities can be especially important in disseminating newly introduced viruses that are not yet well adapted to the human host and therefore may not be efficiently transmitted from person to person, or in affording these viruses additional opportunities to adapt.

Human activities may also disseminate vectors or reservoir hosts. Even if a zoonotic agent is not able to spread readily from person to person and so establish itself, if the reservoir host or vector becomes more widely disseminated, then the microbe can appear in new places. This is essentially what happened in the 14th century as rats, which had been establishing themselves there following their introduction from Asia, spread the bubonic plague in Europe, and this scenario was probably repeated more recently with the ratborne hantaviruses.

Another factor in viral traffic is human traffic. Human migration from rural areas to cities, especially in areas with a high degree of biodiversity, can introduce remote viruses to a larger population. The United Nations (1991) has estimated that, largely as a result of continuing migration, by the year 2025, 65% of the world population expected to be larger in absolute numbers as well), including 61% of the population in developing regions, will live in cities. The human immunodeficiency virus has been (and, in Asia, is likely to become) the best known beneficiary of this recent movement to cities, but many other diseases stand to benefit, as mentioned already with dengue. It was suggested that mosquitoes carrying dengue viruses in Thailand may have been spread along railroads (Wellmer 1983). Highways, too, can be conduits for viral and microbial traffic. After its likely first move from a rural area into an initial city, HIV-1 spread along highways to other regional cities, then later by long-distance routes to progressively more distant places. Similar opportunities are afforded on a global scale by rapid air travel, as suggested by studies modeling the spread of influenza epidemics (Longini et al. 1986) and of HIV (Flahault and Valleron 1990 and 1992).

Viruses are not, of course, the only objects of microbial traffic. The emergence of Lyme disease in the United States and Europe was probably due largely to such environmental changes as increases in deer populations and the development of forested land near homes (Barbour and Fish 1993). 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, supporting the suggestion that the organism was introduced in contaminated bilge water from an Asian freighter (Glass et al. 1992, Wachsmuth et al. 1993). New bacterial strains, such as the recently identified cholera 0139 or an epidemic strain of Neisseria meningitidis (Moore 1992), can also disseminate rapidly along routes of trade and travel, as can antibiotic-resistant bacteria (Soares et al. 1993).

Re-emerging diseases are those that were previously decreasing but are now rapidly increasing again. Although important, 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. This should be a reminder that complacency is a potent ally of the infectious diseases. Human activities can also encourage the emergence of drug-resistant bacteria (by careless use of antimicrobials) and, in industrialized countries such as the United States, allow the spread of infections (e.g., tuberculosis) through conditions of high population density such as day care centers and prisons.

## VIRUSES MOST LIKELY TO EMERGE: ROLES OF VIRAL VARIATION AND EVOLUTION

Many emerging viruses contain RNA genomes. Domingo and Holland (Domingo 1997, Domingo and Holland 1994, Holland 1992) noted that because enzymes that copy RNA, such as viral RNA replicases, lack proofreading functions, RNA viruses have high mutation rates, with consequent potential for rapid evolution. This may account for the great number and diversity of RNA viruses, which represent the majority of known viruses, and for the relative ease with which RNA viruses may infect new species. Because the error rates in replication of RNA viruses can be high enough to yield one or more mutations in each progeny viral genome per round of virus replication, many viral stocks represent a population of genomes with a considerable range of variation centered around a "population mean" represented by an average, or consensus, set of gene sequences, in Manfred Eigen's analysis a "quasispecies" (Howard Temin called it a "swarm"). This allows plasticity within the viral population for adaptation to harsh new environments such as a new host and selective pressures of the host immune system or antiviral drugs.

Many viral variants and recombinants can be identified both in nature and in the laboratory (Domingo and Holland 1994, Holland 1992); for many viruses, it has also long been known that tropism and virulence can be altered by conditions of passage in tissue culture. In other cases, such as Venezuelan equine encephalomyelitis (Rico-Hesse et al. 1994) or influenza (Webster et al. 1992), a new epidemic variant may arise from a circulating pool. However, despite their high mutation rate, many viruses show remarkable apparent stability over relatively long periods of time, indicating that there are factors strongly stabilizing viral phenotype and even the viral genome, probably through natural selection (reviewed in Morse 1994). Influenza A is in evolutionary stasis in its presumed reservoir, waterfowl (Gammelin et al. 1990, Webster et al. 1992), as apparently are many other viruses, such as Eastern equine encephalomyelitis (Weaver et al. 1991). The quasispecies distribution is presumably stabilized by such factors as competition among the variants, with selection for variants relatively suited to that environment (discussed in Morse 1994), although chance will also play a role. It has been suggested that upon introduction into a new environment, such as a new host, certain variants will be selected from within the population and a new equilibrium eventually re-established. There is some recent evidence that can be interpreted as selection of specific variants from within a quasispecies, such as perhaps lymphocytic choriomeningitis virus (an arenavirus) in mice, in which a single amino acid change, frequently appearing as a favored mutation in the course of infection, seems sufficient to alter viral tropism (Ahmed et al. 1991, Salvato et al. 1991).

Competition in the viral population may therefore be an important stabilizing factor, as noted by Darwin for other organisms. The familiar "annual" influenza epidemics are due to "antigenic drift," the appearance of an influenza variant selected during the previous season's epidemic that escapes immediate recognition by antibodies. Typically a dominant variant replaces the previous one (Buonagurio et al. 1986, Fitch et al. 1991). In contrast, the variants of HIV form a broad or "bushy" phylogenetic tree. It has been suggested that this difference is due to intense intraspecific competition among the influenza variants, whereas HIV undergoes broad diversification within the largely unoccupied ecological niche represented by the host (Myers and Korber 1994). Some have argued for immune selection as a driving force (Fitch et al. 1991), a suggestion possibly supported by failure to identify an

accumulation of variants in an immunosuppressed child with chronic influenza infection (Rocha et al. 1991).

## ROLE OF NUTRITION

Host factors have generally received less attention, partly because they are harder to study, but are clearly of great importance. Nutrition, for both macro- and micronutrients, must be considered among the relevant host factors. Improved nutrition has been a key factor in improving health during the last century; conversely, poor nutrition can exacerbate disease. Diarrhea caused by rotavirus, for example, is far more severe and more likely to be fatal in poorly nourished infants than in those who are well nourished. Immunosuppression, which can be caused by some types of nutritional deficiencies, might allow newly introduced pathogens or classic agents to spread more rapidly within the compromised populations and possibly play an amplifying role, especially at high population density (an example is tuberculosis in homeless shelters in the United States). In some cases, poor nutrition can even allow unexpected disease manifestations (immunodeficiency and fulminant disease reported with measles in some African children may possibly be an example), which can also hinder recognition of the agent.

The study of possible interactions between nutrition and evolution of pathogens is still in its infancy. Some have suggested that immunocompromised or malnourished individuals might permit a relatively avirulent pathogen additional opportunities to infect and possibly evolve to greater virulence, although there is little evidence to date that this has actually occurred. More rarely, but significantly, a "new" variant, with altered biological properties, may appear. The intriguing and seminal, experiments of Beck and colleagues (Beck 1997, Beck et al. 1995) demonstrated that a virulent variant could arise during infection of selenium-deficient or vitamin E–deficient mice with a normally avirulent (mild) coxsackievirus B3 isolate. The exact mechanism is unknown. The virulent virus that appeared closely resembled other known virulent genotypes of the same virus. The genotype was stable, and it retained virulence upon infecting healthy mice. Although other examples of this remarkable phenomenon remain to be found, it would be surprising if this turned out to be an isolated case.

Nutrition, and nutritional practices, can also have indirect effects. Many important infectious diseases are food- or waterborne. As another indirect effect, as mentioned above, the use of animal feed supplements made from animal byproducts may have been responsible for the emergence of BSE in cattle in the 1980s.

## CAN DISEASE EMERGENCE BE PREDICTED AND CONTROLLED?

An integrated approach to ecology of disease, including consideration of social factors, is still necessary. Viral traffic, often facilitated by human actions, is a major factor in viral emergence. People are creating much of the viral and microbial traffic, albeit often inadvertently. This must be recognized so that we can learn how to become better "traffic engineers." Because ecological changes (including deforestation, dam building, changes in agricultural products or land use) and major demographic changes (such as population migrations) often precipitate emergence, these "signals" for viral traffic should be seen as warning signs. Consideration of biodiversity should include viruses and microbes, and environmental impact assessments in development planning should take health effects into account. In addition to paying attention to viral traffic signals, we can begin developing a more systematic understanding of viral traffic and strengthen predictive capabilities by effectively using molecular epidemiology (Myers and Korber 1994) and geographic methods and modeling systems to track disease and better anticipate its appearance and spread (Anderson and May 1991, Cliff and Haggett 1988, Flahault and Valleron 1990 and 1992).

If we are to protect ourselves against emerging diseases, the essential first step (of many) is effective global disease surveillance to give early warning of emerging infections (Henderson 1993, Institute of Medicine 1992, Morse 1990b). This must be tied to incentives such as national development and be backed by a system to provide an appropriate rapid response. World surveillance capabilities are critically deficient (Berkelman et al. 1994, Institute of Medicine 1992, Morse 1995b). As a result of financial constraints and diminished interest, surveillance capabilities are weaker today than they were in 1968, when the World Health Assembly held preliminary discussions on global surveillance. Efforts now underway in the United States (Centers for Disease Control and Prevention 1994) and internationally to remedy this situation deserve strong support. As well as political will, broad interdisciplinary contributions from both the biomedical and social sciences will be required. In addition, viral evolution is a continual process. Basic research, such as that described here, will continue to provide important insights and must be encouraged.

It is likely that the viruses of the future (as well as the ancestors of others that may yet evolve) are here now, in other species and in previously isolated human populations, awaiting their opportunities to emerge. This historical process has been going on for centuries (McNeill 1976), but the conditions of modern life provide rich new opportunities. The factors responsible for emerging infections are continuing and increasing, and the rapidity and extent of movement worldwide render all places increasingly vulnerable to new introductions. If we wish to prevent tragedies such as the AIDS pandemic from occurring, we must be prepared to find these infections and control them when they first appear.

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