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EMERGING AND RE-EMERGING INFECTIOUS DISEASES: The Third Epidemiologic Transition

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ABSTRACT

We use an expanded framework of multiple epidemiologic transitions to review the issues of re/emerging infection. The first epidemiologic transition was associated with a rise in infectious diseases that accompanied the Neolithic Revolution. The second epidemiologic transition involved the shift from infectious to chronic disease mortality associated with industrialization. The recent resurgence of infectious disease mortality marks a third epidemiologic transition characterized by newly emerging, re-emerging, and antibiotic resistant pathogens in the context of an accelerated globalization of human disease ecologies. These transitions illustrate recurring sociohistorical and ecological themes in human–disease relationships from the Paleolithic Age to the present day.

INTRODUCTION

The problem of emerging infectious disease has recently captured the public's imagination and the attention of the scientific community. Popular books (e.g. Preston 1994) and movies (e.g. *Outbreak*, released in 1995) tell grisly tales of hapless victims bleeding from all orifices, prey to mutating microbes that chal-

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lenge the supremacy of Western biomedical progress. A number of books aimed at an educated general audience chronicle the scientific research effort to understand these deadly pathogens (Garrett 1994; Rhodes 1997; Ryan 1993; Ryan 1997). Recent academic conferences (Lederberg et al 1992; Morse 1994) have brought together researchers in microbiology, public health, and biomedicine to survey the seriousness of the problem; they report an ominous resurgence of morbidity and mortality from new and old infectious diseases. These reports warn of the eroding efficacy of antimicrobial therapies in the face of growing multidrug resistance (Lewis 1994; Swartz 1994; Vareldzis et al 1994). They note the first rise in infectious disease deaths in affluent postindustrial nations since the Industrial Revolution: In the US, age-adjusted mortality from infectious disease has increased by 40% from 1980 to 1992 (Pinner et al 1996). For its part, the US Centers for Disease Control and Prevention (CDC) has compiled a list of 29 pathogens that have emerged since 1973 (Satcher 1995), and has initiated an online journal—*Emerging Infectious Diseases*—to address this growing problem.[1]

The current spate of attention belies the fact that emerging infections are not a recent phenomenon but have always played a major role throughout human history (Armelagos & McArdle 1975; Boyden 1970; Cockburn 1971; Fenner 1970; Lambrecht 1985; Polgar 1964). We seek to contextualize these recent emerging infectious disease trends within an evolutionary and historical perspective, using an expanded framework of epidemiologic transition theory. By tracing the emergence of disease in the Paleolithic Age, the Neolithic Age, the Industrial Revolution, and contemporary global society, we argue for the existence of three distinct epidemiologic transitions, each defined by a unique pattern of disease that is intimately related to modes of subsistence and social structure. We suggest that current trends—the re/emergence of infectious disease in the industrialized world and an increasingly globalized disease ecology (Colwell 1996; Elliot 1993; Gubler 1996; Patz et al 1996)—herald the arrival of a qualitatively distinct third epidemiologic transition in human health.

Recognizing the complexity of the diverse sociocultural processes involved in the re/emergence of infectious disease, many researchers in biology, medicine, and public health are calling for input from the social and behavioral sciences (Sommerfeld 1995). With its integrative approach to complex biocultural issues, anthropology is well positioned to make significant theoretical and practical contributions.

In the sections that follow, we provide a brief overview of epidemiologic transition theory and propose an expanded framework to consider the recurring social, political, and ecological factors implicated in emerging disease

[1]Full text articles from CDC's *Emerging Infectious Diseases* and *Morbidity and Mortality Weekly Report* can be accessed electronically using the CDC's Web site at http://www.cdc.gov.

patterns from the late Paleolithic era to the Industrial Revolution. We apply this broader framework to explain the most recent pattern of emerging disease as part of a third, qualitatively distinct, epidemiologic transition.

AN OVERVIEW OF EPIDEMIOLOGIC TRANSITIONS

The concept of the epidemiologic transition was first formulated by Omran as a model for integrating epidemiology with demographic changes in human populations (Omran 1971). Omran stated that this model "focuses on the complex change in patterns of health and disease and on the interactions between these patterns and the demographic, economic, and sociological determinants and consequences." Omran described the epidemiologic transition as occurring in three successive stages, or "ages": 1. of pestilence and famine; 2. of receding pandemics; and 3. of degenerative and man-made diseases. The third age described the shift in age-specific disease mortality from infectious diseases to chronic degenerative diseases in England and Wales following the Industrial Revolution. Classically associated with the concept of the epidemiologic transition as a whole, this particular sequence of events represented an important tradeoff between mortality and morbidity as a result of the interaction between epidemiological and demographic processes. On one hand, decreased child and maternal mortality resulting from declining infectious diseases resulted in an overall increase in population size. On the other hand, a subsequent increase in life expectancy entailed an aging population with increasing mortality because of chronic degenerative diseases associated with the latter years of life.

Important criticisms have been made concerning this initial framing of the epidemiologic transition. Akin to assumptions of unilinear evolutionary progress in early models of cultural evolution, this framework implies that each stage of the transition is more advanced and desirable than previous stages. Because epidemiologic transition theory focuses solely upon trends in mortality, debates surrounding the ramifications of increased longevity for quality of life and well-being are not addressed by the model. It has been argued that the increase in life expectancy associated with the shift from acute infectious to chronic disease may be gained at the expense of increased total suffering and ill-health (Johansson 1992; Riley 1992; Riley & Alter 1989). However, others contend that populations undergoing the epidemiologic transition may eventually experience a delay in the age of onset of chronic disabilities and disease (Fries 1980; Olshansky & Ault 1986).

Second, although this framework emphasizes socioeconomic and ecological factors as chief determinants in disease mortality transition, the use of whole nations as units of analysis has been criticized for burying the differential experience of these events according to race, gender, and class within

population statistics (Gaylin & Kates 1997). A parallel criticism has been made of "emerging infectious diseases," a classification which may not signify the emergence of new pathogens as much as a re-emerging awareness among affluent societies of old problems that never went away (Farmer 1996). These critiques underscore the need to expand this model to account for the heterogeneity of disease experience within populations undergoing epidemiologic transitions.

While Omran accounted for accelerated, delayed, and transitional variants of his "classical" model of epidemiologic transition in Europe and North America (Omran 1971, 1983), more recent modifications have improved its applicability to a broader array of contexts and issues. Bobadilla and colleagues adapted the model to fit observations in "middle income" nations such as Mexico, where trends in chronic disease have increased despite a persistence of infectious disease morbidity and mortality, resulting in what they describe as an overlap of eras (Bobadilla et al 1993). Popkin suggests that some chronic conditions have entered a refractory stage in populations such as in the United States, where individuals have changed their diet and lifestyle in an effort to prolong a healthy lifespan (Popkin 1994). This is akin to an additional stage of the epidemiologic transition proposed to explain the delayed onset of the symptoms and ill-health associated with chronic conditions in some industrial nations (Olshansky & Ault 1986).

Even with these modifications, however, the epidemiologic transition is restricted to a particular set of historical circumstances in the recent shift from infectious to chronic disease mortality. Yet, by further expanding this framework to include multiple transitions from the Paleolithic Age to the present day, we are able to illustrate how recurring sociohistorical and ecological themes have had an important influence on shifting disease patterns throughout modern human evolution. In this manner, we have reset the baseline for three distinct epidemiologic transitions to the conditions that existed just prior to the widespread changes that occurred with the adoption of agriculture in human populations.

EPIDEMIOLOGIC TRANSITIONS: FROM THE LATE PALEOLITHIC AGE TO THE INDUSTRIAL REVOLUTION

Paleolithic Age Baseline

During much of our evolutionary history, hominid ancestors of modern humans roamed the African savanna as small, nomadic bands of foragers. Early hominid populations likely were too small and dispersed to support many of the acute communicable pathogens common in densely populated sedentary communities (Burnet 1962), especially those for which human populations are the only disease pool (Cockburn 1971; Polgar 1964). Acute upper respiratory

infections decline soon after being introduced to isolated communities, suggesting that they would have been absent from the dispersed populations of the Paleolithic era (Popkin 1994). Similarly, pathogens such as smallpox, measles, and mumps were unlikely to afflict early hominid groups (Cockburn 1967a).

Hominid social organization and demographics would have presented less of a barrier to the transmission and perpetuation of pathogens with long periods of latency or low virulence. Viruses such as chickenpox and herpes simplex may survive in isolated family units, suggesting that they could have been sustained in early dispersed and nomadic population. The current distribution of parasite species common to human and nonhuman primates provides evidence for longstanding hominid-parasite relationships that predate the divergence of the hominid lineage (Cockburn 1967b; Kliks 1983). Sprent (1969b) coined the apt term "heirloom species" to describe such parasites, which he distinguished from the "souvenir" parasites contracted through chance encounters with infected nonhuman hosts or vectors.

Long-term coevolutionary relationships between hominids and a heirloom parasite imply a good match between the parasite's mode of transmission, virulence, and lifecycle, and the lifestyle and demographics of early foraging bands (Sprent 1962, 1969a). As one example, the gregarious behavior, nesting habits, and frequency of hand-to-mouth contact typical of hominoid primates likely favored the persistence of the pinworm *Enterobius vermicularis* in hominid evolution, which continues to inflict contemporary human populations (Kliks 1983). Similarly, ectoparasites such as head and body lice (*Pediculus humanus*) and enteric pathogens such as *Salmonella* would likely have infested early hominids (Cockburn 1971; Polgar 1964).

Hominids would have contracted novel, or souvenir, parasites in their daily rounds of collecting, preparing, and eating raw plants, insects, meat, and fish (Audy 1958; Bennett & Begon 1997). The distribution and characteristics of these pathogens would have placed constraints on the ecosystems open to hominid exploitation. Lambrecht contends that the trypanosomiasis parasite carried by the tsetse fly opened ecological niches for hominid exploitation by eliminating trypanosome-susceptible fauna (Lambrecht 1980). Because modern humans are trypanosome-susceptible and thus have not developed genetic resistance to the disease, Lambrecht argues that early hominids must have adapted culturally and behaviorally to tsetse by residing in fly-free areas, and perhaps through the advent and use of fire. Similarly, Kliks argues that particularly problematic and ubiquitous helminths, such as those associated with schistosomiasis and onchocerciasis, may have limited access to productive niches, much as they do throughout large tracts of Africa today (Kliks 1983).

The distinction between the heirloom and souvenir parasites afflicting early hominid bands underscores the antiquity of disease "emergence" in human populations, which is as old as the hominid lineage itself (Sprent 1969a,b).

Then as today, the environment provided the pool of potential emerging infections or parasites, and the social, demographic, and behavioral characteristics of hominid adaptation provided the opportunity for disease emergence. The rate of emergence may have increased as tool use allowed exploitation of novel ecological niches (Kliks 1983), and as ecological zones shifted with climate change during glacial and interglacial periods (Lambrecht 1980). The eventual movement of hominid populations out of Africa into Europe, Asia, and beyond would have exposed migrating bands to novel ecologies and parasites, increasing the rate of emergence at least temporarily in such groups. However, it is likely that disease ecologies in these new habitats would have remained qualitatively similar, owing to the continuation of a nomadic foraging adaptation and low population densities.

The First Epidemiologic Transition

Beginning about 10,000 years ago, a major shift occurred in most human populations, from a nomadic hunting and gathering lifestyle to sedentism and primary food production. This shift involved major changes in human social organization, diet, demographics, and behavior that created conditions favorable for zoonotic infections to make the transition to human hosts, and for preexisting human pathogens to evolve to more virulent forms. We describe the subsequent increase in infectious disease mortality that arose in the context of these changes as the first epidemiologic transition.

The shift to permanent settlements created larger aggregates of potential human hosts while increasing the frequency of interpersonal contact within and between communities, likely fostering the spread and evolution of more acute infections (Ewald 1994). In addition, accumulation of human waste would have created optimal conditions for dispersal of macroparasites and gastrointestinal infections. Skeletal remains from archaeological sequences spanning this cultural transition generally show an increase in the prevalence of infectious lesions as populations shifted from foraging to sedentism and food production (Cohen & Armelagos 1984), adding empirical support to these expectations.

The appearance of domesticated animals such as goats, sheep, cattle, pigs, and fowl provided a novel reservoir for zoonoses (Cockburn 1971). Tuberculosis, anthrax, Q fever, and brucellosis could have been readily transmitted through the products of domesticated animals such as milk, hair, and skin, as well as increased ambient dust (Polgar 1964). In these contexts, it should not be surprising that many contemporary human infections have their origins in the zoonoses of domesticated animals (Bennett & Begon 1997).

Agricultural practices increased contact with nonvector parasites such as schistosomal cercariae, contracted in irrigation work, and intestinal flukes,

which were acquired through use of feces as fertilizer (Cockburn 1971). With the advent of food storage, the threat of contamination and wide-scale outbreaks of food poisoning increased (Brothwell 1972). Breaking the sod during cultivation may expose workers to insect bites and diseases such as scrub typhus (Audy 1961). Other vectors developed dependent relationships with human habitats, as in the case of the yellow and dengue fever-carrying mosquito, *Aedes aegypti*, which breeds preferentially in artificial containers (Thompson & O'Leary 1997; Whiteford 1997).

Reliance upon staple crops and a decline in dietary diversity may have predisposed Neolithic populations to nutritional problems similar to those experienced by subsistence-level agrarian communities in developing nations today (Harrison & Waterlow 1990). Most staple crops are efficient producers of calories capable of supporting more dense populations yet often lack critical micro- or macronutrients. Nutrient deficiencies are thus common in agrarian societies and are often exacerbated during periods of seasonal hunger or periodic droughts (Chambers et al 1981). Skeletal evidence suggests that such nutritional problems were typical in early agrarian communities and increased with agricultural intensification in some areas (Cohen & Armelagos 1984), and may have contributed to a more vulnerable host population.

Skeletal analyses demonstrate that women, children, and—with development of stratified societies—the lower classes suffered disproportionately from the first epidemiologic transition. Female remains among Neolithic populations indicate higher frequencies of bone loss and nutritional anemia (Martin & Armelagos 1979). Comparisons between agricultural populations and their foraging predecessors show greater mortality, dental defects, and impaired bone growth among infants and young children for populations in transition (Cohen & Armelagos 1984). Artifacts indicating social status differences correlate positively with nutrition and bone-growth among Lower Illinois Valley males during the Middle Woodland Period, emphasizing the role of early social stratification in the differential experience of disease (Buikstra 1984). Related issues of political organization also had health implications, as in the case of Nubian populations during the Neolithic period, in which life expectancies were inversely related to the degree of political centralization (VanGerven et al 1990).

The severity of disease outbreaks during the first epidemiologic transition intensified as regional populations increased and aggregated into urban centers. The crowded, unsanitary living conditions and poor nutrition characteristic of life in these early cities fostered rapid and devastating regional epidemics (Flinn 1974; McNeill 1976; McNeill 1978). The establishment of large cities increased problems of supplying clean water and removing human waste, while facilitating spread of more virulent pathogens in enclosed and densely crowded habitations (McNeill 1976; Risse 1988). Cholera contaminated water

supplies, epidemics of vector-borne disease such as plague and typhus devastated populations, and outbreaks of measles, mumps, smallpox, and other viral infections were increasingly common (Knapp 1989). Unlike the infectious disease mortality common in early Neolithic populations, adults were frequently the target of epidemic outbreaks, paralyzing societies economically in their wake. As a dramatic example, tuberculosis routinely killed one third of all adults in many European communities, and by the end of the nineteenth century had claimed an estimated 350 million lives (Knapp 1989). Similarly, the Black Death of the 1300s is estimated to have eliminated at least a quarter of the European population in a decade (Laird 1989).

McNeill (1976) also discusses two important historical trends that initiated the global spread of pathogens across previously intractable geographic boundaries. First, increasing migration and trade between state-level societies in Eurasia led to the convergence of regional infectious disease pools beginning in the fifth century CE. Second, expansion of these networks into the New World through exploration and conquest brought European populations with acquired immunity to childhood infections into contact with Native Americans with no history of exposure to these pathogens (Black 1990). This contact resulted in massive pandemics of smallpox and typhoid that killed millions of people and facilitated the colonial domination of two continents (McNeill 1976, Dobyns 1993). It also probably resulted in the introduction of treponemal infections to Europe (Baker & Armelagos 1988), where sexual promiscuity in crowded urban centers may have favored a venereal mode of transmission in the form of syphilis (Hudson 1965). These historical events illustrate how the globalization of state-level societies has provided opportunities for pathogens to cross considerable social and geographic boundaries.

The Second Epidemiologic Transition

The second epidemiologic transition roughly coincided with the Industrial Revolution in mid-nineteenth century Europe and North America. It is distinguished by a marked decline in infectious disease mortality within developed countries. This decline is the major focus of the second proposition in Omran's model of epidemiologic transition: "a long-term shift in mortality and disease patterns whereby pandemics of infection are gradually displaced by degenerative and manmade disease as the chief form of morbidity and primary cause of death"(Omran 1971:516).

The decline of infectious diseases in the nineteenth and twentieth centuries has often been cited as an objective landmark in the progress of modern civilization—a product of developments in medical science and technology in the industrialized world that would eventually diffuse to less-developed societies. Garrett shows how early successes in the eradication of polio and smallpox influenced western medical establishments in their confident forecast for the

eminent demise of infectious diseases before the end of this century (Garrett 1994). However, these projections did not consider that the larger secular trend of declining infectious disease mortality was already well under way before the advent and application of antimicrobial technologies (McKeown 1976).

Based largely upon data from Scandinavia, Germany, France, Italy, and England, Schofield & Reher roughly estimated the decline in European infectious disease mortality to have occurred in three major phases beginning in the late seventeenth century (Schofield & Reher 1991). The first phase, lasting from the late seventeenth century to the beginning of the nineteenth century, is characterized by a flattening of crisis mortality peaks owing to sporadic epidemics of diseases such as plague, smallpox, and typhus. Beginning in the mid-nineteenth century, the second phase was characterized by an overall secular decline in mortality that, although subject to significant regional variation, contributed to an increased life expectancy by more than three decades, resulting in a major overall population increase despite concurrent fertility declines. The third phase began with the advent of antimicrobial therapies in the 1940s, representing a more modest decline in infectious disease mortality in more affluent nations that continued until the early 1980s.

McKeown argued for the primacy of nutritional factors in declining European mortality (McKeown 1976). However, McKeown has been criticized for weighing nutritional inferences beyond the resolution of available data (Schofield & Reher 1991; Johansson 1992). While evidence suggests that the creation of an international grain market may have spurred improved agricultural yields and distribution networks, the relative importance of other factors such as pasteurization, public hygiene, and home-based primary health care deserve further evaluation (Kunitz 1991; Woods 1991). Moreover, there is little disagreement that certain biomedical innovations such as the worldwide vaccination campaigns against smallpox played a significant role in mortality decline.

The decrease in infectious disease in industrialized nations and the subsequent reduction in infant mortality has had unforeseen consequences for human health. Namely, the subsequent extension of life expectancy has also brought increased morbidity from chronic diseases (Riley & Alter 1989). These so-called "diseases of civilization" include cancer, diabetes, coronary artery disease, and the chronic obstructive pulmonary diseases (Kaplan & Keil 1993). Other health tradeoffs of the second transition concern the role of industrial technology in the creation of artificial environments that have influenced the appearance of chronic diseases. Particularly in urban environments, increasing water and air pollution subsequent to industrialization has been linked to significantly higher rates of cancer (Anwar 1994; Dietz et al 1995), allergies (Barnes et al 1998), birth defects (Palmer 1994), and impeded mental development (Perrera 1993). These issues are compounded by the psychoso-

matic effects of urbanization, which is correlated with increased levels and incidences of hypertension (Grossman & Rosenthal 1993), as well as depression and anxiety (Harpham 1994).

As in the cases of the Paleolithic-era baseline and the first epidemiologic transition, social inequalities account for many of the differences in the way the second transition has been experienced within and between populations. Within more industrialized societies, socioeconomic, ethnic, and gender differences are strongly associated with differences in morbidity and mortality for both chronic and infectious diseases (Arriaga 1989; Blair 1993; Dressler 1993). Buried within national statistics, and temporarily masked by antibiotics, the conditions selected for the first transition persisted among the poorest people of the richest nations in the second.

Following the Second World War, the second epidemiologic transition made a more modest appearance in many less-developed nations and was marked by improvements in child survival and life expectancy at birth (World Bank 1993). Unlike the epidemiologic transitions experienced in the United States and Europe, which largely proceeded the advent of modern biomedical innovation, biomedical fixes such as oral rehydration therapy, immunizations, and antibiotics played a pivotal role in the initial successes in mortality reduction in these societies (Gwatkin 1980; Hill & Pebley 1989; Ruzicka & Kane 1990). While variability of these declines between countries and their possible deceleration since the 1960s has been a source of controversy (Gwatkin 1980; United Nations 1982), there is little doubt that the second transition has fallen short of optimistic projections for the developing world (Gobalet 1989). Rapid urbanization combined with marked social inequalities and a continued lack of public health infrastructure have led to communicable diseases among the urban poor, with chronic degenerative diseases among the affluent and slowly emerging middle classes (Muktatkar 1995). In middle-income countries such as Mexico and Brazil, socioeconomic status now relates inversely to important chronic disease risk markers like obesity and hypertension (Popkin 1994), akin to similar associations in the United States, the United Kingdom, and other affluent nations (Kaplan & Keil 1993).

THE THIRD EPIDEMIOLOGIC TRANSITION

The current phenomenon of emerging infectious diseases indicates a third epidemiologic transition characterized by three major trends. First, an unprecedented number of new diseases have been detected over the last 25 years that are becoming significant contributors to adult mortality. Second, there is an increased incidence and prevalence of preexisting infectious diseases that were previously thought to have been under better control. Third, many of these reemerging pathogens are generating antimicrobial-resistant strains at a faster

rate than safe new drugs can be developed. These three trends are occurring within the broader context of an increasing globalization, involving not only international trade, migration, and information networks, but also the convergence of human disease ecologies.

Recently Emerging Infections

The Centers for Disease Control and Prevention (CDC) has compiled a list of 29 newly emerging pathogens since 1973 (Satcher 1995). It is possible that the overall size of this list is more a function of increased detection than the actual emergence of new pathogens in human populations. Such is the case of the *Legionella* bacterium responsible for the high-mortality pneumonia known as Legionnaire's Disease. Following its initial detection during a 1976 outbreak in a convention of American World War II veterans (Fraser et al 1977), environmental and retrospective patient cultures subsequently indicated that *Legionellae* had long been responsible for 2000 to 6000 deaths previously diagnosed as pneumonias of unknown etiology (McDade et al 1977), many of which were attributed to the exposure of susceptible elderly hosts to contaminated large-scale air conditioning units (Miller 1979; Morris et al 1979; Saravolatz et al 1979).

Despite possible increases in detection rates, it cannot be denied that at least some of these new diseases are making unprecedented contributions to adult mortality. The most dramatic example of this is the Human Immunodeficiency Virus (HIV). Although retrospective studies have detected cases in Europe and Africa going back as far as 1959 (Huminer et al 1987; Nahmias et al 1986), HIV has more recently become the second leading cause of death among adult males aged 25–40 years of age in the United States, and the chief contributor to a 40% increase in infectious disease mortality over the past 15 years (Pinner et al 1996). With the exception of the flu pandemic of 1918, this trend marks the first of such increases in affluent societies since the Industrial Revolution.

Phylogenetic analyses of HIV and related retroviruses indicate a recent evolution from a simian virus of Central African origin (Essex & Kanki 1988). Yet biological evolution alone does not account for the rampant spread of this disease, nor its unequal distribution within and between populations (Ewald 1994; Feldman 1990; MacQueen 1994). Throughout Asia, Africa, and the Americas, high HIV and sexually transmitted disease (STD) prevalence rates have been indices of deeper sociohistorical issues such as neocolonialism (Alubo 1990), the disintegration of poor families because of seasonal labor migrations (Hunt 1995), sexual decision-making strategies (Bolton 1992; Waddell 1996), and the gendered experience of poverty (Connors 1996; Daily et al 1996; Farmer et al 1993; MacQueen et al 1996; McCoy et al 1996). Yet, neither is this simply a case of the poor transmitting their problems to the affluent. For example, contrary to the myth of Haitian origin following the initial dis-

covery of AIDS, evidence suggests an earlier transmission to urban Haiti by more affluent Westerners engaging in sex tourism (Farmer 1992).

The social history of AIDS provides a prototype for similar issues surrounding the transmission of other infectious diseases. Outbreaks of Ebola hemorrhagic fever have received much attention in the popular press, which has mainly focused on the gory aspects of its clinical manifestations, high mortality rates, and fears of airborne transmission accentuated with images of "virus hunters" running around in spacesuits (Preston 1994). Contrary to these dramatized accounts, however, the instances of possible airborne transmission was restricted to very close contact between unprotected healthcare workers and patients in the late stages of this disease (Garrett 1994). The Ebola outbreaks along Kinshasa Highway of Central and Eastern Africa in the 1970s mainly involved transmission via the commercial sex trade and the reuse of dirty syringes by untrained Western missionaries and underequipped healthcare workers (Garrett 1994). Regarding fears of transmission across national borders, the appearance of the closely related filoviruses detected in Reston, Virginia, and Marburg, Germany, were caused by the importation of primates for drug research, which ironically included the development of vaccines for other viruses (Bonin 1971; Morse 1993, 1995).

Ebola and Marburg are but two examples of a much larger set of recently discovered hemorrhagic diseases. Recent outbreaks of these diseases in the New World have been linked to climatic fluctuations and ecological disruption. In 1993, a sudden outbreak of a virulent hemorrhagic fever in the Four Corners region of the American Southwest was quickly identified as a novel strain of hantavirus spread through the excreta of the deer mouse, *Peromyscus maniculatus*, but not before infecting 98 individuals in 21 states and claiming 51 lives (Weigler 1995). The 1993 outbreak was associated with abnormal weather patterns (Epstein 1995), and oral histories of local American Indian healers describe three clusters of similar outbreaks that coincide with identifiable ecological markers (Chapman & Khabbaz 1994), supporting the idea that this disease has long coexisted with and periodically afflicted human populations across the United States without detection by the medical community (Weigler 1995). The initial outbreaks of Argentinian hemorrhagic fever, or Junin, were traced to ecological disruption associated with the spread of maize agriculture and increasing rodent vector habitats (Benenson 1995).

First identified in the mid 1970s, tick-borne Lyme disease has since surfaced in all 50 states as well as overseas (Jaenson 1991), and has rapidly become the most often reported anthropod-born disease in the United States (Oliver 1996). Regrowth of Eastern forests felled in the eighteenth and nineteenth centuries to make way for agricultural fields has greatly expanded the habitat of deer, mice, and their *Ixodes* tick parasites, which carry the disease-causing *Borrelia* spirochete (Walker et al 1996). Residential housing has expanded

into forested areas, bringing populations into contact with the ticks and their wild-animal reservoirs. As exemplified by diseases as distinct as HIV, Ebola virus, and Lyme disease, pathogens are often provided the opportunity to jump the "species barrier" (Lappe 1994) by a combination of ecological disruption or change, and increased contact between humans and wild reservoir species. The size and mobility of human populations increases the potential for the pathogen to escape its geographic barrier (Armelagos 1998).

RE-EMERGING INFECTIONS Ecological disruption has also been cited as a major factor in re-emerging infectious diseases as well. Warmer climates have led to increased coastal blooms of algae, creating favorable environments for the proliferation of *Vibrio cholerae*, and inland changes in temperature and humidity are increasing the reproduction of malaria vectors (Martens et al 1995; Patz et al 1996). In addition, climactic fluctuations such as El Niño are thought to have significant effects on pathogen and disease vector environments (Bouma & Dye 1997; Colwell 1996).

While acts of nature may account for changing disease patterns, most of these ecological changes have anthropogenic origins (Brown 1996; Coluzzi 1994; de Zulueta 1994). In the last 15 years, dengue fever has shown a dramatic resurgence in Asia and Latin America, where poorly developed urban environments have led to the proliferation of the *Aedes egypti* mosquito vectors in open water pools (Chinery 1995; Whiteford 1997), contributing as well to sporadic outbreaks in the Southwestern United States (Gubler & Clark 1995). The practice of combined swine-duck agriculture in Southern China as well as commercial swine and turkey farming in the United States is thought to contribute to the genetic adaptability of flu viruses (Shortridge 1992; Shu et al 1994; Wright et al 1992). Bradley critically reviewed the practice of "third-world dumping" by multinational corporations, in which industrial production facilities are "outsourced" into developing countries with cheap labor pools and greatly relaxed environmental regulations, resulting in localized climate changes (Bradley 1993a,b). Increases in mosquito populations have compounded the problem of malaria and dengue in places where poor living conditions and the unequal distribution of health resources have already contributed to higher levels of preventable mortality (Brown et al 1996; Gubler & Clark 1995).

Among the re-emerging infectious diseases, tuberculosis (TB) is the greatest contributor to human mortality, and it is estimated that nearly a third of the world's population has been latently infected with the mycobacterium (Malin et al 1995). After more than a century of steady decline, the incidence of reported TB cases in the United States increased by more than 20% from 1985 to 1992. This trend is particularly unsettling given that the previous decline of TB was the single largest contributor to North American and European declines in

infectious disease mortality during the middle stages of the second epidemiologic transition (Caselli 1991; Puranen 1991).

The resurgence of tuberculosis in affluent nations was preceded by decreased public health expenditures, becoming a forgotten disease in the context of overly optimistic predictions for its continued decline (Ryan 1993). Yet TB has remained the leading cause of infectious disease mortality in developing countries, where 95% of all cases occur (Raviglione et al 1995). Notoriously endemic to populations living under conditions of malnutrition, poor sanitation, and inadequate housing, tuberculosis has long been considered to be the classic disease of poverty (Darbyshire 1996). While HIV comorbidity is implicated in the most recent first world resurgence of TB, especially among young adults, higher rates of both diseases among the urban homeless indicate that socioeconomic issues play much the same etiological role in the re/emergence of infectious diseases today as they have in centuries past (Barclay et al 1995; Barnes et al 1996; Farmer 1997; Zolopa 1994).

ANTIMICROBIAL RESISTANCE The history of antimicrobial resistance is almost as long—or rather, as short—as the widespread use of the drugs themselves. The first recorded instance of drug resistance occurred in 1917 during the initial trials of Optochine in the treatment of pneumococcal pneumonia (Moellering 1995; Moore 1917). Three years after the 1941 introduction of penicillin for clinical use against gram-positive "staph" infections,[2] new strains of *Staphylococcus aureus* began to emerge with penicillin-destroying beta lactamase enzymes (Neu 1992). The lessons of emerging resistance were well known even before the DDT fumigation campaigns to eradicate malaria-carrying *Anopheles* mosquitoes, in which warnings of impending insecticide susceptibility accompanied strong recommendations for a single major international campaign (Brown 1996; Olliaro et al 1996; Roberts & Andre 1994). These unheeded warnings would prove correct, not only for the vectors, but for the quinine and chloroquine-resistant plasmodium parasite itself (de Zulueta 1994; Longworth 1995; Roberts & Andre 1994).

At present, more than 95% of *S. aureus* strains are resistant to most forms of penicillin, and strains resistant to methycilline (MRSA) have become endemic to US nursing homes and acute-care settings around the world (Jacoby 1996). Last year, the first strains of *S. aureus* possessing intermediate resistance to vancomycin were identified in Japan and the United States (Centers for Disease Control 1997), joining the ranks of already emerging *Enteroccoci* with full resistance to this antibiotic (Nicoletti & Stefani 1995; Rice & Shlaes 1995;

[2]Although Alexander Fleming first identified a staphylocidal substance in *Penicillium notatum* molds in 1928, the actual development and distribution of penicillin for clinical use took another 13 years.

Swartz 1994). In many cases, vancomycin represents the last in the line of "magic bullet" defenses against these kinds of pathogens (Gruneberg & Wilson 1994; Nicoletti & Stefani 1995; Rice & Shlaes 1995). As such, the emergence of vancomycin-resistant pathogens hails the beginning of what has been called "The Post-Antimicrobial Era" (Cohen 1992).

In many ways, biological evolution provides the ultimate critique of biomedicine by demonstrating the inevitability of genetic adaptations of microorganisms to the selective conditions posed by human technology and behaviors (Lederberg 1997). Beyond this, however, predictions of specific resistance patterns have been problematic. *Streptococcus pneumoniae* provides a good example of this problem. Long since ranked among the pneumonias known as "the old man's friend" in affluent nations (Garrett 1994), *S. pneumoniae* has also been the microbial source of more than 1,000,000 annual deaths of children under five years of age (Obaro et al 1996). In the last five years, drug-resistant strains of this bacteria have emerged worldwide (Gerber 1995; Goldstein & Garau 1994; Jernigan et al 1996), with reported frequencies as high as 50% among clinical isolates (Obaro et al 1996). Yet there is no theoretical explanation for why it took more than 40 years for this organism to develop antibiotic resistance, while other drug-resistant species emerged in less than a decade (Bartlett & Froggatt 1995).

Bartlett & Froggatt outline three general themes in the emergence of antimicrobial resistance: 1. that high-grade resistant organisms are typically foreshadowed by low-grade resistant intermediates; 2. that resistant strains are typically resistant to more than one antibiotic; and not surprisingly, 3. that resistance develops under conditions of extensive antibiotic use (Bartlett & Froggatt 1995). The overuse of antibiotics by both trained and untrained health providers throughout the world is a major factor in the evolution of antimicrobial-resistant pathogens (Kollef 1994; Kunin 1993; Kunin et al 1987).

Besides the practices of health providers, the patients themselves have created selective conditions for antimicrobial resistance by early termination of prescribed courses of antibiotics, providing additional generation time for partly reduced organism populations within the host (Appelbaum 1994). This is especially problematic for diseases such as tuberculosis, which requires up to a year of medication adherence in the absence of detectable symptoms to completely eliminate the mycobacterium (Barnes & Barrows 1993). Acquired resistance owing to incomplete adherence to TB regimens is partly responsible for the emergence of multi-drug–resistant tuberculosis (MDRTB) (Jacobs 1994; Nunn & Felten 1994)—a situation compounded by issues of access and conflicting explanatory models between patients and healthcare providers (Dedeoglu 1990; Menegoni 1996; Rubel & Garro 1992; Sumartojo 1993; Vecchiato 1997).

Host susceptibility is another major factor in the evolution of antimicrobial-resistant pathogens (Morris & Potter 1997). The large majority of MDRTB outbreaks in the United States occurred in the context of comorbidity among HIV-infected patients (Crawford 1994; Zolopa 1994). Multi-drug resistant nosocomial infections are predominantly found among elderly and immunocompromised patients in long-term and acute-care hospital settings (Hayden & Hay 1992; Koll & Brown 1993; Kollef 1994; Rho & Yoshikawa 1995; Schentag 1995; Toltzis & Blumer 1995). The emergence of the eighth cholera pandemic, involving the drug-resistant 0139 Bengal strain, has been found among populations of refugees and the poorest inhabitants of the fourth world already susceptible to the effects of unsanitary water sources (Martin et al 1994; Siddique et al 1995; Islam et al 1995; Toole 1995; Weber et al 1994).

The overuse of antiobiotics in industrial animal husbandry also contributes to the rise of multi-drug resistant strains of food-borne pathogens (Tauxe 1997). Nontyphoid strains of *Salmonella* have been on the rise in the United States since the Second World War, where it is currently the most common food-borne infection. Overuse of antibiotics in chickens has contributed to the emergence of *Salmonella* strains resistant to all known drug therapies. These were recently identified in British travelers returning from the Indian subcontinent (Rowe et al 1997). In Europe, the emergence of strains of *Campylobacter* resistant to enrofloxacin increased in parallel to the use of this antibiotic among poultry (Endtz et al 1991). Similarly, the use of avoparicin as a growth-promoter in European livestock is believed to have created selective conditions for the emergence of vancomycin-resistant enterococci (VRE), which are transmitted to human hosts through fecal-contaminated animal products (McDonald et al 1997).

While antibiotics have played a relatively minor role in the latter stage of the second epidemiologic transition, the erosion of these human cultural adaptations in the face of more rapid genetic adaptations of microorganisms forces us to confront major issues without the aid of technological crutches. We will discover to what degree these magic bullets may have subsequently obscured the relative efficacy of primary prevention in both affluent and underdeveloped societies.

INFLUENZA AND THE GLOBALIZATION OF HUMAN DISEASE ECOLOGIES Had the historical precedents of influenza been given closer consideration, previous projections for the continued decline in infectious diseases might not have been so optimistic. With an estimated worldwide mortality of over 20,000,000, the Spanish influenza pandemic of 1918–1919 killed more human beings than any previous war or epidemic in recorded history (Crosby 1989). This was followed by the less-virulent pandemics of 1957, 1968, and 1977

(Wiselka 1994), each bringing the millenialist promise of another major outbreak at some unknown year to come (Glezen 1996; Webster et al 1993).

Noting the rapidity with which the Spanish Flu spread throughout the world in the days of steamships and isolationism, Garrett grimly suggested how such an outbreak could spread in the present age of international economics and jet travel (Garrett 1994), a timely subject given the recent appearance of a potentially lethal influenza strain in Hong Kong poultry markets with H5 antigens, to which humans have no known history of previous exposure (Cohen 1997; Shortridge 1995). With revolutionary changes in transportation technology (Reid & Cossar 1993; Wilson 1996), worldwide urbanization (Muktatkar 1995; Phillips 1993), and the increasing permeability of geopolitical boundaries (Farmer 1996), human populations are rapidly converging into a single global disease ecology (McNeill 1976).

McNeill (1976) cites the early effects of transnationalism on the transmission of infectious diseases with the establishment of extensive Eurasian trade networks in the fifth century CE. Intercontinental shipping routes provided for the transport of pathogens as well as trade goods and organized violence. The European conquests of the new World presented a dramatic example of this trend, in which adult carriers of childhood diseases endemic to post-first transition populations suddenly infected unexposed Native American populations, resulting in massive pandemics of smallpox and typhus. Neither was this a one-way trade, as returning sailors brought syphilis and tobacco back to the European continent with them.

The current trend of accelerated globalization challenges us to consider the health implications not just of converging microbial ecologies, but also of the international flow of ideologies, behavior patterns, and commodities that underlie human disease patterns. This broader picture of globalization, involving the international exchange of *memes* (units of cultural information) as well as microbes, entails a convergence of both chronic and infectious disease patterns. This is evidenced in the many developing societies that are suffering what has been called the "worst of both worlds"—the postwar rise in chronic degenerative diseases among the poor without significant declines in infectious disease mortality (Bradley 1993a), while these infections re-emerge in post-second transition societies (Armelagos et al 1996).

CONCLUSION

Buoyed by early successes in the control of scourges such as polio and smallpox in the 1950s and 1960s, the Western medical establishment claimed that it was time to close the book on infectious diseases and focus research attention on the growing problem of chronic degenerative disease (Garrett 1993). Un-

fortunately, the book on infectious disease remains very much open, and new chapters continue to be added at an alarming pace. We address this issue from an evolutionary perspective, using the concept of epidemiologic transition theory as an organizing framework. Our discussion of epidemiologic transitions during the course of human evolution reveals that disease "emergence" is not new but has been a dynamic feature of the interrelationships between humans and their sociocultural and ecological environments since the Paleolithic period.

The initial formulations of the epidemiologic transition provided a useful interdisciplinary framework for macrolevel analyses of demographic changes associated with major declines in infectious disease mortality in Europe and North America in the wake of the Industrial Revolution (Omran 1971). Despite later modifications, however, interpretations of this framework still remained largely restricted to a single set of events at a particular period of human history (Omran 1983). The subsequent particularism of this transition fueled notions of unilinear progress, resulting in falsely optimistic projections for the continued decline and eventual elimination of infectious disease in human populations (Garrett 1994). Our expanded framework of multiple epidemiological transitions avoids these pitfalls by providing a broader historical and evolutionary perspective that highlights common themes that pervade changing human-disease relationships throughout modern human evolution.

In our review of epidemiologic transitions, we have highlighted the socioecological, technological, and political factors involved in human disease dynamics. The US Institute of Medicine has identified six principal factors contributing to the current problem of re/emerging infectious diseases: 1. ecological changes; 2. human demographics and behavior; 3. international travel and commerce; 4. technology and industry; 5. microbial adaptation and change; and 6. breakdown in public health measures (Lederberg et al 1992; Morse 1995). The degree to which these factors are fundamentally anthropogenic cannot be overstated, nor can the influence of socioeconomic inequalities across these factors.

Recognizing the complexity of these sociobehavioral dynamics, many researchers in biology, medicine, and public health are calling for greater involvement of social and behavioral scientists in addressing infectious disease issues (Morse 1995; Satcher 1995; Sommerfeld 1995). By taking a holistic approach to these important human issues, anthropologists are well positioned to make significant theoretical and practical contributions within interdisciplinary research settings. For example, 40 years ago, Livingstone described the emergence of malaria following the introduction of agriculture in sub-Saharan Africa in what has become a classic example of the ability of humans to shape their physical environments—with unforeseen health consequences (Livingstone 1958).

Anthropologists have explored the health implications of (*a*) sexual behaviors (Lindenbaum 1991; MacQueen et al 1996; Waddell 1996); (*b*) funerary practices (Lindenbaum 1990); (*c*) ethnic conflict and genocide (Tambiah 1989); and (*d*) population displacement (Bisharat 1995; Malkki 1995; Toole 1995). Recent work in transnationalism identifies the political, economic, and social trends that are increasingly integrating the world's diverse populations (Kearney 1995). The emerging paradigm of evolutionary medicine demonstrates the applicability of evolutionary principles to contemporary health issues (Armelagos 1997), and emphasizes the ability of humans to shape their environment through pathogen selection (Lederberg 1997). Finally, anthropologists have critiqued the political-economic constraints that limit access to health care and basic public-health needs (Farmer 1996; Inhorn & Brown 1990; Risse 1988). Given this range of issues impacting human-disease relationships, even anthropologists not directly concerned with infection can make significant contributions to an improved understanding of disease emergence.

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