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GLOBAL CHANGE AND HUMAN SUSCEPTIBILITY TO DISEASE

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ABSTRACT

Although the loss of good health is inherently unpredictable, human behavior at the individual and societal levels profoundly influences the incidence and evolution of disease. In this review, we define the human epidemiological environment and describe key biophysical, economic, sociocultural, and political factors that shape it. The potential impact upon the epidemiological environment of biophysical aspects of global change—changes in the size, mobility, and geographic distribution of the human population; land conversion; agricultural intensification; and climate change—is then examined. Human vulnerability to disease is strongly and deleteriously influenced by many of these ongoing, intensifying alterations. We then examine threats to human defenses against disease, including immune suppression, loss of biodiversity and indigenous knowledge, and the evolution of antibiotic resistance. Effective responses will require greatly enhanced attention by and collaboration among experts in diverse academic disciplines, in the private sector, and in government worldwide.

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INTRODUCTION

Recent and projected anthropogenic changes pose a serious threat to world health security (1, 2). After World War II, many believed that the coevolutionary battle between *Homo sapiens* and its disease parasites was ending in victory for humanity through the use of sanitation, water purification, vaccination, antibiotics, and pesticides. In 1969, US Surgeon General William H Stewart told the Congress that the time had come to "close the book on infectious disease" (3). In the wake of that optimism, the world today is beset with formidable health problems: ancient scourges such as malaria (see e.g. 4), tuberculosis (5, 6), and cholera (7) are resurgent; an important new epidemic disease, AIDS, is proving exceedingly difficult to contain; some strains of old bacterial enemies may be becoming more deadly (8); antibiotics and antimalarial drugs are losing their ability to control pathogens; and a variety of lethal viruses such as Ebola pose serious threats (see e.g. 9, 10, 11). Malaria eradication was once thought possible (12), yet now there are between 300 and 500 million cases annually, with the death toll estimated to be nearly three million (13). Here we review the paramount biophysical forces reshaping the epidemiological environment. The review is structured around 1. aspects of global change, broadly defined to include demographic change as well as changes in land use and atmospheric composition, and 2. threats to human defenses against disease, including immune suppression, the loss of biodiversity and indigenous knowledge, and the evolution of antibiotic resistance. Although our focus is restricted to biophysical forces, the social, economic, and political forces influencing the epidemiological environment are at least as powerful and difficult to manipulate.

THE EPIDEMIOLOGICAL ENVIRONMENT

The epidemiological environment consists of the conditions and processes, both biophysical and social, that influence the interaction between human beings and disease agents. This environment encompasses a complex of interrelated factors, including:

1. the parasites that are actually or potentially pathogenic to *Homo sapiens*, defined broadly to include subcellular, unicellular, and multicellular organisms such as prions, viruses, bacteria, fungi, protozoa, helminths, and arthropods;

2. biophysical determinants of the reproductive success of such parasites, including conditions such as temperature and moisture, availability of and transmittancy to vectors and hosts, the evolution of virulence, and coevolution of human immunity and parasites' resistance to the immune system and other human defensive measures;

3. social determinants of the spread of parasites, including the frequency and nature of interpersonal contact, travel and migration patterns, sanitation, access to health care and information, pharmaceutical markets, urbanization, poverty, public health policy, medical training, funding of medical research, and political leadership.

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In part because the pathogenic actors are largely invisible, the epidemiological environment is rarely appreciated**.** Anthropogenic impacts on this environment have been little examined as a whole and do not fit into the framework within which other aspects of the relationship of human beings to their environment have been explored (14–16). As the human population has grown to unprecedented size, it has unwittingly but dramatically changed the nature of its war with pathogens, in some instances to its great advantage, but now increasingly to its detriment.

IMPACTS ON HUMAN EXPOSURE TO DISEASE

Population Growth

A parasite must achieve a basic reproductive rate greater than one if it is to successfully establish itself in a host population (17, 18). In general, this means that each infected host, on average, infects more than one other host. Thus, a threshold population size is necessary for the perpetuation of most epidemic diseases. The precise threshold for disease establishment is determined by complex characteristics of both the parasite and the host. These characteristics include whether transmission is direct or by a vector, and whether animal reservoirs are involved; whether transmission is seasonal; the incubation, latent, and infectious periods of vectors and hosts; the existence and duration of acquired host immunity; reproductive requirements of the parasite; and so on (18). Human demographic factors are key variables in epidemiology, influencing the rate at which a population is invaded by new parasites, their chances of becoming established, the rate of their spread, the evolution of their virulence, and the capacity of human social structures (and other cultural traits) to coevolve in defense.

Paleolithic groups were probably relatively free of virulent epidemic disease (19, 20). Not until a critical community size was reached in early agricultural

societies were parasites previously confined to nonhuman animals able to significantly affect populations of *Homo sapiens*. Examples of such diseases include smallpox, influenza, and measles, which are thought to have evolved from monkeypox, avian flu, and rinderpest or canine distemper, respectively (21). Measles apparently could not invade human populations until there were aggregations of about 200,000–500,000 people (22–24). Urbanization led not only to virulent epidemics, but also to concentrations of human and animal wastes in waterways ideal for the propagation of protozoan and helminth parasites (20).

The emergence of mega-cities is one of several changes in key aspects of the human population that pose unprecedented threats to human health (25). Another factor is simply that today's 5.8 billion people constitute the largest population the world has ever seen. For a parasite, evolving host specificity to humans (as opposed to any of the world's endangered species) would amount to winning a jackpot. How HIV-1 (the virus that causes the most serious form of AIDS) first entered the human population is not clear, but one possibility is that it was the result of a transfer by a vector (e.g. a mosquito or tick) from another primate. Although such "jumps" from other species are thought to occur very rarely (26), increased human numbers increase contact rates and make them more probable. If in a certain area, one mosquito in a million is carrying a certain rodent virus, the chance of an infected mosquito feeding on a human being is much smaller if that area is populated by a clan of 20 persons than by a city of 500,000 people.

Large families, associated with population growth, increase the vulnerability of populations by presenting arrays of immune-similar individuals. As viruses colonize individuals in such families sequentially, they may evolve greater virulence (27). Immune-similarity of individuals may have contributed to the near extinction over recent centuries of native Americans (28). Black (29, 30) has argued that the decimation of these populations by disease was due not only to a lack of immunological experience that made them highly susceptible, but also to a relative lack of genetic variability (compared to other groups of people) tracing back to their rapid expansion after the genetic bottleneck of the trans-Bering invasion.

Population Mobility

Merchants, explorers, and conquistadores left a legacy little appreciated by most historians (31). Smallpox, measles, and swine flu were transported to the western hemisphere by European sailors. The first recorded epidemics of leprosy in Europe followed the expansion of the Roman Empire. Bubonic plague, known in fourteenth-century Europe as the black death, probably made its way from central Asia via the Silk Road. Cholera was likely carried unwittingly by traders and armies into Europe from India in the early 1800s.

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High-speed modern transport systems may expedite the delivery of food, pharmaceuticals, and medical personnel to populations in need, but they also often facilitate the spread of epidemics. Steamships alone made it possible to transport bubonic plague to all major ports in the world at the end of the last century, something that could not have occurred earlier because all of the susceptible passengers on plague-infested, slow-moving sailing ships would generally have died before the ships reached port (31). People (or vectors) carrying dengue fever on airplanes have contributed to its recent spread (32), and indices of the amount of international travel are highly associated with the spread of AIDS (33). Rapid transportation also facilitates the spread of antibiotic-resistant strains of some bacterial pathogens (34). In addition, rapid transportation plays a role in facilitating the worldwide distribution of recreational drugs, and sharing of needles by addicts contributes significantly to the propagation of infectious diseases.

The movement of potential vectors, disease reservoirs, and other organisms that might be involved in human disease, is also greatly facilitated by modern transport. Perhaps the most spectacular recent case of the transfer of a dangerous vector was the moving from Asia to the United States of a mosquito (*Aedes albopictus*, the Asian tiger mosquito) capable of transmitting dengue (32, 35). Soon after its introduction, *Ae. albopictus* was found to be carrying another potentially dangerous virus, that of La Crosse encephalitis (36–37a). The usual vector of this disease is a woodland mosquito that relatively rarely bites human beings. The combination of that virus and the aggressive tiger mosquito is worrying (37). Dengue has returned to Mexico just south of the border of the United States (38), from where the tiger mosquito could move it north into areas in which its normal vector cannot survive the cold winters.

Population Distribution

Urbanization is one of the most profound of global changes (see e.g. 39). In 1950 only New York, London, and Shanghai had populations of over 10 million. By the start of the twenty-first century, 23 cities will have surpassed that number, and more than half of all human beings are projected to be city dwellers by shortly after the turn of the century (40). Urbanization can improve the epidemiological environment by several means. Death rates from many diseases were lowered dramatically in today's developed nations long before antibiotics or other effective medical interventions were available (41). This reduction was accomplished largely with improved nutrition, housing less vulnerable to vermin, and cleaner drinking water. The latter can be traced back to Dr. John Snow's (1855) work on cholera (42), improved isolation of food and water from human fecal contamination, and personal hygiene (e.g. 41, 43, 44).

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Although available data may overstate the quality of urban drinking water in developing nations (45), they suggest that urban residents have greater access to clean water. An estimated 855 million people lack access in rural areas of developing nations, but only a fifth as many do in urban areas, although 35% of the population of developing nations now lives in cities. Urban residents may also have better access to medical care.

Urbanization may exert serious negative effects on the epidemiological environment as well (see e.g. 46). Cities bring large numbers of people into intimate contact. They would greatly facilitate the spread of transmissible disease even if all urbanites were well fed and supplied with clean water, adequate shelter, and access to health care. But many urbanites are not (see e.g. 47), and providing such resources and services will be difficult given the tremendous rate of growth in demand.

In rich and poor nations alike, cities are afflicted by a lack of control over disease reservoirs (e.g. rodents) and vectors (e.g. mosquitos). For example, urbanization has contributed to the great spread of dengue fever (48) by bringing large numbers of people into close association with the household mosquito *Aedes aegypti*, the vector of the causative virus (32). *Ae. aegypti* breeds in standing water in containers, ranging from coke bottles to old tires.

Risky behavior (from a health perspective), which tends to be suppressed in small, sedentary communities, often occurs in connection with the anonymity afforded by large-scale movement and urbanization. In both rich and poor nations, urban conditions may promote drug use, prostitution, and greater sexual promiscuity in general [(49), although time-series data on this point are lacking]. Interestingly, for diseases transmitted sexually or through the sharing of needles, long-lasting infection and lack of acquired immunity in recovered hosts permits persistence in low-density populations. In such cases, a principal criterion for persistence is a threshold average number of partners, rather than a general threshold host density (18, 50).

Growth of the human population is accompanied by inevitable increases in population density. Higher density is now thought by some (51) to increase the virulence of certain parasites, such as those that cause dysenteries and influenza, which do not depend on vectors for transmission (and thus whose spread is slowed if hosts are immobilized by illness). Evidence for this controversial hypothesis comes from the record of the increased virulence of such diseases among troops crowded in wartime. It has been suggested that the mysterious increase in virulence that made the 1918–1919 flu epidemic the worst ever resulted from the hideous trench conditions on the western front (51).

Other features of urban (and suburban) areas that cause deterioration in the epidemiological environment are the increased air tightness of buildings

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(to enhance energy efficiency); air conditioning; and the reduced rate of airflow in the cabins of modern jet airliners, also in the name of energy efficiency. All three factors tend to keep people breathing the same recirculated air, facilitating the transmission of airborne pathogens (52, 53).

Conditions favorable to crime, war, and other forms of social disruption that degrade the epidemiological environment appear to be promoted by overpopulation and concomitant urban crowding, although the connections are complex and disputed (see e.g. 54, 54a). For instance, some claim that the economic and social deterioration in the former Soviet Union has led to a decline in nutrition, a shattering of the public health system, higher mortality rates (especially in males) and, among other things, epidemics of diptheria (55, 56). [Others, however, assert that many of the apparent recent changes are actually merely artifacts of making the statistical reporting of morbidity and mortality conform to Western conventions (N Vorontsov, personal communication, 1996)]. Globally, the development of urban infrastructure, including public heath facilities, is retarded by violence (39). In short, urban centers may be considered "ecosystem[s] that can amplify infectious diseases" (57) or, more bluntly, "graveyards of mankind" (12).

The epidemiological environment, especially in the United States, has also been greatly altered by suburbanization. This trend clearly helped improve the epidemiological environment for those who left the cities, while often worsening it for those forced to stay behind with a diminishing tax base and decaying health-care delivery system. The large-scale ecosystem alteration associated with suburbanization has, however, created new problems. The massive clearing of eastern forests, which included the removal of both large trees and top predators such as wolves and mountain lions, was followed eventually by reclamation by second growth which, in turn, was fragmented by suburbs. The result is a habitat matrix ideal for deer, which often are also protected from hunting, and some small rodents, especially the white-footed mouse. Deer and small mammals in turn support the tick, *Ixodes scapularis,* which transmits the spirochaete (*Borrelia burgdorferi*) that causes Lyme disease from its natural reservoir in the mouse to human beings (58, 59). Large concentrations of deer support dense adult tick populations (the deer do not serve as important reservoirs of the spirochaete), and young ticks acquire the spirochaetes from smaller animals. In the past 15 years, Lyme disease has become the most common arthropod-borne infection in the United States (60). Babesiosis, a sometimes-fatal disease similar to malaria, can be transmitted in the same manner as Lyme, and sometimes people are infected with both. An emerging, sometimes deadly tick-borne disease, ehrlichiosis, caused by the rickettsia *Ehrlichia chafeensis* can also be transmitted in the same manner as Lyme disease (61, 61a).

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Land Conversion and Agricultural Intensification

It is not only the recent dramatic increase in human numbers, but also mass migration (often government-induced) into areas only marginally suited, at best, to intensive agriculture and dense human habitation, that increases the threat of "emergent viruses." Larger and larger human populations, pushed into contact with animal reservoirs of diseases such as HIV, Ebola, Marburg virus, and Lassa fever, increase the odds that a pathogen will invade human populations and that the disease will become endemic. Population growth has been especially rapid in Africa, which had only about 275 million people in 1960, now has 720 million, and may double that population size by 2025. Africa is the homeland of humanity, and our closest living relatives, the old-world monkeys and apes, are abundant there. Evolutionarily, these are the animals most likely to be harboring parasites, such as Marburg virus, that are capable of infecting *Homo sapiens* (62, 63).

One of the most frequent land-use changes caused by humanity, forest clearance, may exert positive or negative effects on the epidemiological environment. In some instances, it can reduce contact of human populations with forest-dwelling disease vectors or reservoirs, or even drive vectors and reservoirs to extinction. These events are difficult to document. Striking changes in the other direction are less likely to go unnoticed, however. The *Haemogogus* mosquito that transmits yellow fever among animal reservoirs inhabits forest canopy; once an epidemic is triggered by transfer into the human population, the disease is propagated by the domestic mosquito vector, *Ae. aegypti* (64). In Brazil, the most effective Amazonian vector of malaria is *Anopheles darlingi*, a species of the forest and forest edge (47). Clearing primary forest in Tanzania has caused expansion of malaria by increasing temperatures and creating sunny breeding sites for the vector *Anopheles gambiae*. Forest clearance has led to increases in the populations of both the mammalian reservoirs and the sandfly vectors of leishmaniasis throughout Latin America (65).

The epidemiological environment has been altered in many ways by recent intensification of agriculture. Expansion of food supplies has had an enormous positive effect (even if temporary; 66), but there have been negative effects as well. Broadcast spraying of synthetic organic insecticides has induced resistance not only in their intended targets—crop pests—but also in vectors of disease. Agricultural spraying, especially on cotton and rice, has contributed greatly to the evolution of pesticide resistance in the *Anopheles* mosquitos that transmit malaria and thus to the worldwide resurgence of that disease (67–70).

The switch from subsistence agriculture to intensive cash-cropping of rice in Guyana has supplied ideal breeding grounds for *Anopheles* mosquitos, and mechanization has reduced local populations of domestic animals, the preferred

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source for the local *Anopheles'* blood meals. The vectors turn to *Homo sapiens* and malaria epidemics result (see e.g. 71). Similar changes in Honduras have led to the concentration of disease vectors and reservoirs in peri-urban "misery belts," where the incidence of malaria, leishmaniasis, dengue fever, and Chagas' disease has increased dramatically (72). Rodents, in particular, are important consumers of agricultural crops and players in the life cycle of many groups of diseases, including bacterial and viral haemorrhagic fevers, tick-borne encephalitides, Venezuelan equine encephalitis, the hantaviruses, typhus, and spirochaetal and parasitic diseases. Agricultural intensification typically promotes rodent populations through the removal of predators and other natural enemies, while supplementing their food supply (73).

Another case of deleterious change associated with agricultural intensification is the upsurge of schistosomiasis (bilharzia) associated with the introduction of irrigation following the construction of the Aswan and other dams (1, 47, 74). Perennial irrigation and large impoundment lakes have proven to be ideal breeding grounds for snails that serve as intermediate hosts for the blood flukes that cause bilharzia (75). Thus the incidence of bilharzia in the population along the Nile between Cairo and Aswan increased from an estimated 5% before the dam to 35% afterward (76). Similarly, the mosquito vector (*Aedes pseudoscutellaris*) of a virus that causes Rift Valley Fever built up huge population sizes in newly irrigated fields, resulting in a major epidemic in the Aswan area in 1977 (77, 78). Water management schemes can either encourage or discourage the simuliid (blackfly) vectors of onchocerciasis (river blindness). A dam may destroy the rapids required by blackfly larvae and substitute bilharzia (which is easier to treat) for onchocerciasis (47).

The introduction of herbicides to fight weeds that competed with maize production was a feature of agricultural intensification in the Pampas of Argentina after World War II. The resultant change in the grass flora favored a mouse, *Calomys musculinus*, that was the natural reservoir of the Junin virus, the cause of Argentine hemorrhagic fever. The disease was described in 1953 and is still expanding its range (79). Another viral disease, Oropouche fever, emerged following the agricultural colonization of the Amazon and the planting of cacao as a cash crop. The latter makes excellent breeding conditions for the vector *Culicoides paraensis*, a biting gnat (32). In contrast, a shift from cattle raising to subsistence agriculture encouraged another small mouse, *Calomys callosus*, that is the reservoir of the Machupo virus. The latter invaded the human population, causing Bolivian hemorraghic fever.

Major reservoirs of influenza viruses include ducks, other waterfowl, and shorebirds (80). Some flu pandemics are thought to have their origin in integrated pig-duck farming in China (81). Pigs can function as "mixing vessels"

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for new flu strains able to infect human beings; an agricultural system that puts the reservoir and the mixing vessels in intimate contact seems bound to degrade the epidemiological environment. The pig-duck system, in place in China for several centuries and now being intensified, constitutes a natural laboratory for generating new flu strains (82), because viruses move back and forth between human beings and swine and between swine and ducks (80). This system might have been responsible for the catastrophic 1918–1919 pandemic, possibly the worst single disease catastrophe ever to afflict humanity in terms of numbers of lives lost in a short period of time (83). Even though many strains of flu that infect birds are genetically attenuated in primate systems (see e.g. 84), another deadly pandemic is certainly possible (80).

Climate Change

Anthropogenic climatic warming appears increasingly likely, although its regional consequences are still impossible to predict in detail (85). Such change, however, will almost certainly alter the geographic distributions of pathogens, reservoirs, and vectors; the competitive and predator-prey interactions among them; and the probability of disease transmission (86–88).

Temperate zones, where the majority of human beings live, may be invaded by various tropical diseases that now kill millions of people annually (89), but whose distributions are now restricted by climate (65, 90–91a). Recent modeling efforts indicate, for instance, that malaria could extend its range by tens of millions of square km (4, 92). This prediction is supported by extensive empirical information on the coupling of malaria outbreaks and climatic fluctuations, particularly those associated with the El Niño–Southern oscillation (93). In addition, detailed analysis of the 1987 resurgence of malaria incidence in Rwanda revealed that temperature and rainfall explained 80% of the variance in monthly malaria incidence (94). Climate change also appears to have played a role in India's recent bout with what was diagnosed (perhaps incorrectly) as bubonic plague (see e.g. 95). Careful monitoring of climatic changes, especially at the latitudinal and altitudinal limits of diseases, is crucial to anticipating outbreaks (96, 97).

Any large-scale change in an ecosystem can greatly affect human health—either positively or negatively. This is a general lesson that can be drawn from analyses of the possible impacts of global change on the epidemiological environment. Drainage of swamps, screening of houses, and improvements in sanitation and nutrition had yellow fever and malaria on the retreat in the southern United States and had malaria receeding from southern Europe long before the etiologies of those diseases were understood. Exceptionally wet weather in the southwestern United States in 1992 caused superabundant production of pinyon-pine nuts, which in turn led to a superabundance of deer mice

(*Peromyscus maniculatus*). The mice carried a previously unidentified strain of hantavirus that caused an outbreak of often-fatal respiratory disease (98, 99).

Deleterious changes in the epidemiological environment can be triggered by alterations of marine ecosystems accompanying climatic change, but these too are difficult to predict (100, 101). For example, one can merely guess at the impact of warmer waters and rising sea level on the strains of *Vibrio cholerae* living in the bays and estuaries of the Gulf Coast of the United States that serve as a reservoir for cholera (91).

The most significant impact of climate change on the epidemiological environment may be its effects on the immune system, mediated through agricultural production. Rapid climate change poses a serious threat to nutritional security (66, 102), which is an important defense against disease.

THREATS TO HUMAN DEFENSES AGAINST DISEASE

Immune Suppression

A suite of factors may suppress the human immune system, the most important of which is undernutrition. It is well established that undernutrition and infection act synergistically (see e.g. 103–106). Infections increase the need for nutrients (by raising a person's metabolic rate through fever) while simultaneously diminishing their supply [through reduced appetite, lower absorption by the gastro-intestinal tract, loss through feces, and direct loss in the gut (104, 107)]. Young children illustrate this synergism especially dramatically: Both mortality and morbidity are determined by a child's nutritional status, as measured by a weight-for-height ratio (108). Interestingly, the synergism is not universal; in fact, mild undernourishment may actually confer a survival advantage in some circumstances [e.g. iron-deficiency may suppress the reproductive rate of a pathogen, although this possibility remains speculative (see 107)]. Overnutrition, epidemic in some developed countries, may impair immune function as well (see e.g. 109).

Even though undernutrition has declined globally over the past few decades, both relatively and absolutely, about 1 billion people still do not have diets adequate to support normal daily activity, and nearly 500 million are essentially slowly starving to death (summary of data in 110). Disease eventually intervenes as the proximate cause of mortality; approximately 10 million people have been dying of hunger-related disease annually for several decades (111–114). Whether a reversal of the cheering trend in nutritional status can be prevented remains an open question (66).

AIDS victims and, often, narcotic addicts are also seriously immune compromised. Another potentially important cause of immune suppression is the

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growing presence of pollutants in the environment (115–117). Ozone depletion may also directly suppress immune responses, and it may play an important indirect role in immune suppression through its deleterious effect on agricultural production (118–120).

Although the mechanisms whereby these factors compromise the immune system are complex and remain in some cases poorly understood, their consequences are potentially serious. The bodies of afflicted individuals constitute ideal environments for the multiplication of numerous pathogens (see e.g. 121, 122) and for the viruses, bacteria, and fungi that in the past were viewed as benign to evolve resistance to antibiotics and other defenses (see e.g. 123, 124).

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Loss of Biodiversity

The paramount direct cause of the ongoing mass extinction of populations and species of other organisms is land conversion for agricultural purposes. As a matter of convenience, biodiversity loss is usually quantified in terms of the rate of loss of species diversity. A conservative estimate of the global rate of species loss (considering eukaryotes only) is one extinction per hour (125), which exceeds by at least four orders of magnitude the rate of evolution of novel (eukaryotic) species (126). The benefits of biodiversity to humanity are delivered through populations of species, however, and they are disappearing much more rapidly than are species (127, 128; J Hughes, G Daily & P Ehrlich, unpublished analysis).

Human health depends in part on the diversity of populations. Different populations of the same species may produce different types or quantities of defensive chemicals [potential pharmaceutical or pesticide compounds; see e.g. (129)]. For example, the development of penicillin as a therapeutic antibiotic took a full 15 years after Alexander Fleming's famous discovery of it in common bread mold. This delay occurred because scientists had great difficulty producing, extracting, and purifying needed quantities of the antibiotic. One key to obtaining needed quantities was the discovery, after a worldwide search, of a variant of Fleming's mold that produced more penicillin than the original (130).

Little appreciated is the impact of destroying not only other life forms themselves, but also their interactions, which can be clues to the discovery of new pharmaceuticals. The discovery of penicillin by Fleming occurred largely by accident when, upon returning from a weekend vacation, he noticed that the mold that had contaminated one of his bacterial cultures was actually killing the bacteria (131). It is difficult to appraise a weapon of war, or even recognize its existence, without observing it in use. Fleming saw the aftermath of the war being waged on his laboratory plates. Only then did he realize that penicillin

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is a mold's antibacterial weapon and that human beings might be able to wield it to great advantage, too.

It is difficult to overstate the importance of the extinction problem. A recent study has shown that 118 out of 150 top prescription drugs are based on chemical compounds from other organisms, three quarters of them from plants. In the United States, 9 of the 10 top prescription drugs are based on natural plant compounds (132–134). Yet only slightly more than a thousand of the world's 365,000 plant species have even been preliminarily screened for medicinal compounds. It is impossible to know what opportunities for pharmaceutical discovery are forever lost with the destruction of biodiversity—but the loss is akin to emptying our armory.

Loss of Traditional Medical Systems

Under the impact of industrialization and urbanization, western medicine has displaced indigenous medical systems in many areas, in the process leaving many without any health care. Ratios of physicians to population as high as one to more than 10,000 or 15,000 in the world's poorest countries leave no doubt that most people do not get medical treatment from trained professionals (3). According to the World Health Organization, over 80% of people rely for their primary health care on traditional plant medicines (133). Traditional medicinal knowledge is rapidly disappearing, however, owing to cultural change and declining access—in both urban and rural areas—to sources of natural medicinal products. Most villages in the world are no longer surrounded by the natural habitat that formerly served as a medicine cupboard, and bodies of folk knowledge that have accumulated and been honed for thousands of years are disappearing at an alarming rate. In some cases this loss may actually confer net health benefits; but modern society will never know what effective medicinal treatments are being lost. It is estimated that, in the Amazon Basin alone, one indigenous culture becomes extinct annually (133).

In the absence of traditional medicine, the role of doctor in most developing nations is played either by the local pharmacist or by the sick individual and his or her relatives themselves. Antibiotics and other powerful drugs are readily available without proper diagnosis and prescription, through pharmacies and black markets (131). This tragic situation is made worse by its sinister consequence, accelerated microbial evolution of resistance to antibiotics.

Evolution of Antibiotic Resistance

Concern about antibiotic misuse dates back to Alexander Fleming himself (e.g. 131, 135–140). Bacteria had billions of years of experience using antibiotics to battle each other, fungi, and other microbes before *Homo sapiens* evolved (141). Bacteria have very rapid life cycles, intrinsic mechanisms of resistance

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(142, 143), and extraordinary abilities to exchange genetic material (see e.g. 144; see also 145 on the malarial parasite). Horizontal gene transfer, which enables resistance arising in one bacterium to be passed on to other species, is rampant. Some of the genes conferring resistance reside on small, extrachromosomal molecules of DNA called plasmids that can be passed to a recipient cell (e.g. another bacterium or a yeast or plant cell) through a process called conjugation. Harmless bacteria that normally inhabit human tissues may evolve resistance through incidental exposure to antibiotics; they can then pass along the genes conferring resistance to infectious bacteria that invade those tissues. Some bacteria now harbor as many as 12 different types of antibiotic and disinfectant resistance (146).

In contrast, human beings are condemned by long generation times (decades rather than hours as in microorganisms) to evolve genetic responses very slowly. Their capacity for cultural evolution represents the best means of staying even in the coevolutionary race (e.g. 20, 147). Regrettably, human behavior with respect to antibiotics has been maladaptive since the start of their use. In anticipation of, or in response to illness, people have used antibiotics routinely without assessing their potential effectiveness (3, 131, 136) and often without taking the full dosage, thereby killing off the most susceptible bacteria while promoting those that are resistant.

Widespread ignorance of evolutionary implications among medical professionals, aggressive marketing by drug companies, inner-city poverty, and the determination of misinformed patients to get antibiotics by any means necessary have played major roles in the rapid evolution of antibiotic resistance in developed nations. In developing nations, the principal factors promoting resistance include the inaccessibility of professional health care, inability to afford the necessary full course of antibiotic treatment, and the casual availability of antibiotics through pharmacies and black markets. Poor health policy, in general, is responsible in both regions of the world (3, 131, 136).

Multiply-resistant bacterial strains can often be passed on to other people in hospitals or otherwise spread rapidly. In 1950 few, if any, strains of staphylococci exhibited antibiotic resistance. Yet by 1960, about 80% of the strains of staph showed resistance to penicillin, tetracycline, and chloramphenicol. By 1980, penicillin was effective against only 10% of the varieties of staph it once controlled (136). A similar story has unfolded in the case of most pathogenic bacteria; the initial source of gonorrhea bacteria resistant to penicillin, now found worldwide, was brothels in Southeast Asia (131). Most recently, bacteria have evolved a complex strategy for protecting themselves from vancomycin—the "last resort" antibiotic for use against enterococci (148). The fear now is that staph will acquire the resistance via plasmid transfer from enterococci.

Similarly, in response to overuse of antimalarials, evolution has produced strains of the most lethal malaria species, *Plasmodium falciparum*, that are resistant to virtually all drugs (149–151). The schistosomes, the blood flukes that cause Bilharzia, are now showing signs of becoming resistant to praziquantel, the most important drug used to treat the disease, which afflicts approximately 200 million people and kills about 200,000 annually (152).

The massive use of antibiotics in farm animals has contributed significantly to the problem of resistance. More than half the antibiotics produced in the United States—in the vicinity of 8000 tons—are fed annually to livestock to enhance growth, mostly in subtherapeutic doses, which are ideal for the development of resistance (3, 131, 136, 153–155). Transmission of antibiotic-resistant bacteria from livestock to humans can occur through routes hardly imagined initially. In 1991 in Massachusetts an outbreak of a dangerous strain of *Escherichia coli* (0157:H7) was traced to contaminated apple cider; the cider was made from apples from trees that had been fertilized with livestock manure. Subsequently, this strain of *E. coli* has been blamed for 6000 food poisonings, sometimes lethal in small children, each year in the United States (12). Antibiotics are also given to honeybees, fish, family pets, small plants, and trees; streptomycin is one of the two most commonly used antibiotics on plants, and resistance to it is now extremely widespread (131).

POLICY IMPLICATIONS AND CONCLUSIONS

In few aspects of environmental degradation is the fate of the rich so plainly and inextricably tied to that of the poor as it is in the interplay of global change and disease. Unilateral health measures on the part of rich nations would have limited impact on health security; it is in the selfish best interest of all nations to cooperate in the implementation of policies aimed at disease prevention. Briefly, direct measures needed worldwide include the improvement of water supplies and sanitation; education of the medical community and general public about the evolutionary and ecological dimensions of disease; support of vaccination research and administration; implementation of comprehensive disease monitoring and reporting systems; and coordinated restrictions of the use of antibiotics and pesticides. Indirect measures include almost any effort to reduce the total scale of the human enterprise by humanely halting population growth, greatly reducing wasteful per-capita consumption, and employing more environmentally sensitive technologies and cultural practices (66). In general, development planners must consider explicitly the potential deleterious impacts on the hidden epidemiological environment and ways of mitigating them. Although these recommendations represent a tremendous challenge, no less than the future of humankind is at stake.

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