Infectious Diseases: Considerations for the 21st Century

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The discipline of infectious diseases will assume added prominence in the 21st century in both developed and developing nations. To an unprecedented extent, issues related to infectious diseases in the context of global health are on the agendas of world leaders, health policymakers, and philanthropies. This attention has focused both on scientific challenges such as vaccine development and on the deleterious effects of infectious diseases on economic development and political stability. Interest in global health has led to increasing levels of financial support, which, combined with recent technological advances, provide extraordinary opportunities for infectious disease research in the 21st century. The sequencing of human and microbial genomes and advances in functional genomics will underpin significant progress in many areas, including understanding human predisposition and susceptibility to disease, microbial pathogenesis, and the development new diagnostics, vaccines, and therapies. Increasingly, infectious disease research will be linked to the development of the medical infrastructure and training needed in developing countries to translate scientific advances into operational reality.

The history of the medical discipline of infectious diseases is rich in extraordinary accomplishments that have had a major impact on humankind [1]. The successful diagnosis, prevention, and treatment of a wide array of infectious diseases has altered the very fabric of society, providing important social, economic and political benefits.

In considering the importance of infectious diseases globally as well as in the United States in these first years of the 21st century, I reflect back to December 1967, when then–Surgeon General William H. Stewart, contemplating the benefits realized from antibiotics and vaccines, declared victory against the threat of infectious diseases and suggested that our nation turn its attention and resources to the more important threat of chronic diseases [2]. At the time, I was completing my residency training in internal medicine at New York Hospital-Cornell Medical Center and anticipating my move to Bethesda, Maryland, to begin my infectious diseases fellowship at the National Institutes of Health. I became concerned that I was entering a subspecialty of clinical medicine and an area of biomedical research that was disappearing at the same time that I was training for it. However, the history of infectious diseases from that time in my training until the present day has proven quite the opposite. At the dawn of the 21st century, the future of infectious diseases and its impact on societies throughout the world is strikingly apparent. It is this future that I will address herein.

THE SCOPE OF THE PROBLEM

Infectious diseases are the second leading cause of death and the leading cause of disability-adjusted life years worldwide (1 disability-adjusted life year is 1 lost year of healthy life) and the third leading cause of death in the United States [3, 4]. Among these infectious diseases causing death worldwide, acute lower respiratory tract infections, HIV/AIDS, diarrheal diseases, tuberculosis, and malaria predominate (table 1). Clearly, despite earlier predictions to the contrary [2], infectious diseases remain a dominant feature of domestic and international public health considerations for the 21st century. In fact, the continual evolution of emerging and reemerging diseases, particularly the acceleration of the HIV/AIDS pandemic in developing countries, will heighten the global impact of infectious diseases in this century.

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Table 1. Leading infectious causes of death worldwide, 1999.

Cause	Rank	Estimated no. of deaths
Acute lower respiratory infections	1	3,963,000
HIV/AIDS	2	2,673,000
Diarrheal diseases	3	2,213,000
Tuberculosis	4	1,669,000
Malaria	5	1,086,000
Measles	6	875,000
Tetanus	7	377,000
Pertussis	8	295,000
Sexually transmitted diseases (excluding HIV)	9	178,000
Meningitis	10	171,000

NOTE. Adapted from [3].

EMERGING AND REEMERGING INFECTIONS

The extent of the global burden of infectious diseases depends on the already established incidences and prevalences of known infections together with the constant, but uneven, flow of emerging and reemerging infections [5–8]. Emerging infections are those that have not been previously recognized. The AIDS pandemic is a prototypical example of a truly new and emerging infectious disease whose public health impact had not been previously experienced. Reemerging infections have been experienced previously but have reappeared in a more virulent form or in a new epidemiological setting. The influenza A pandemics of 1918, 1957, and 1968 are prototypical examples of reemerging infections [9].

HIV/AIDS. Despite the fact that the HIV/AIDS pandemic exacted a terrible toll in deaths and human suffering in the last 2 decades of the 20th century, the full impact of this disease will be realized in the 21st century. As of the end of 2000, there were 36 million people worldwide living with HIV infection; >90% of them live in developing countries, and 70% live in southern Africa [6]. There have been ~22 million cumulative deaths due to AIDS. In certain countries in Africa, such as Botswana, Zimbabwe, and Swaziland, 25%–35% of the adult population (ages 15–49 years) are infected with HIV [10]. In South Africa, it is estimated that there are >4 million people infected with HIV, ~10% of the entire population and 20% of the adult population. The life expectancy in several southern African countries has decreased dramatically because of the HIV/AIDS pandemic, negating the impressive gains that had been made over the previous few decades.

India and other southern and southeastern Asian countries will be the next epicenters of the HIV/AIDS pandemic; the cultural and socioeconomic conditions in those countries are unfortunately well-suited to explosive spread of this infection [10]. Indeed, it is estimated that ~4 million people in India are already infected with HIV. The potential for catastrophic spread in this country of >1 billion people is enormous, as it is for China, the most populous nation in the world. Aggressive and sustained AIDS prevention programs are critical to contain the epidemic in these Asian countries.

The continual evolution of infectious diseases. In addition to HIV/AIDS and pandemic influenza [10], which have had an extraordinary impact on global health, there is a continual evolution of a wide range of emerging and reemerging infectious diseases with varying potentials for global spread. Figure 1 illustrates some salient examples of emerging and reemerging infections throughout the world in recent years. Some, such as Ebola virus and Nipah virus, have been highly virulent but have involved relatively small numbers of people, have remained tightly restricted in their spread, and so have been more medical curiosities than global public health threats. Others, such as multidrug-resistant malaria, have involved large numbers of people but have, because of the demography of the infection, remained for the most part geographically restricted. This has resulted in a serious situation in the region involved but not a global public health threat. Multidrug-resistant tuberculosis and vancomycin-resistant *Staphylococcus aureus* and enterococci are examples of emerging infections that do not immediately involve large numbers of persons but that will ultimately have a serious impact on public health throughout the world [8].

Two examples of recently reemerging infections that are currently causing considerable concern in the United States are dengue and West Nile fever. Dengue has posed an extraordinary problem in Brazil, with >530,000 cases reported in 1998 [11]. In addition, other nations in South and Central America and the Caribbean have varying degrees of problems with dengue. Dengue has appeared infrequently in the United States since the 1940s. However, it remains a threat because the mosquito vectors for dengue are widely dispersed in the United States, particularly in the states bordering the Gulf of Mexico. Indeed, in 1999, 17 locally acquired cases of dengue were reported in Texas (Gubler D, Centers for Disease Control and Prevention, personal communication). In contrast, West Nile fever had never been seen in the United States before 1999, when there were 62 cases and 7 deaths identified in the New York City area [12]. West Nile fever is caused by a flavivirus that is transmitted by mosquitoes, with a variety of birds serving as intermediate hosts. It is indigenous to the region of the West Nile River (hence its name) and is seen commonly in Middle Eastern countries such as Israel. The virus survived the winter of 1999–2000 in the United States; in 2000, 18 human cases (including 1 death) and numerous infections in various avian and

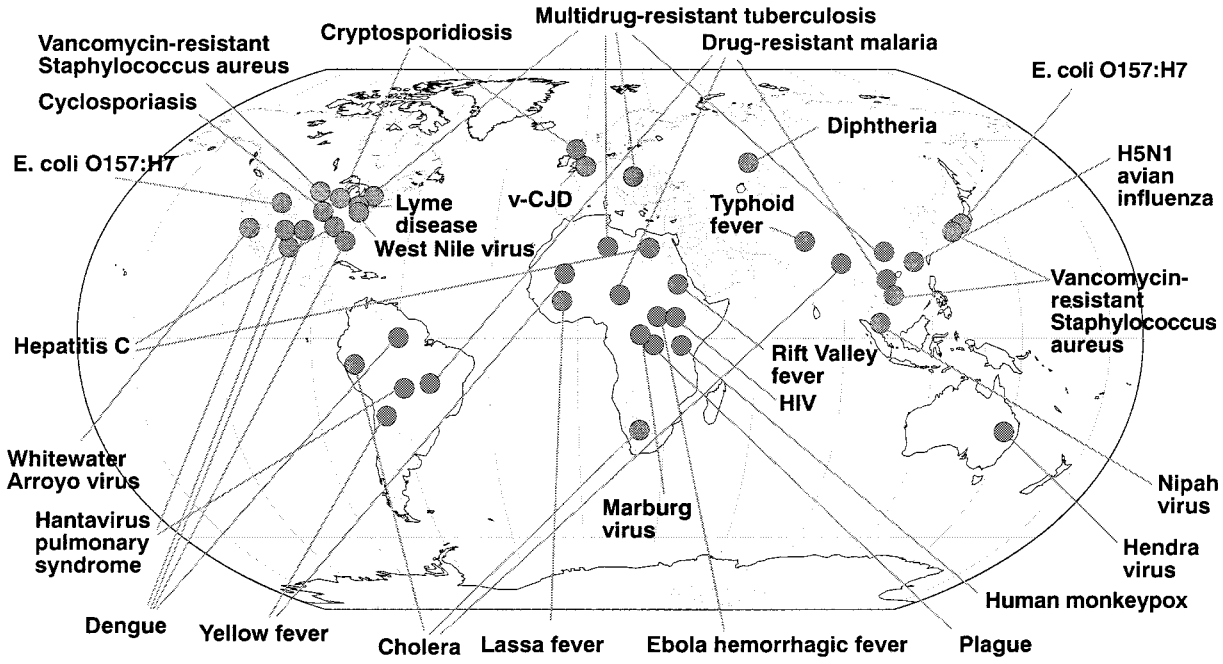

Figure 1. Range and recognized site(s) of origin of variety of emerging and reemerging infections. v-CJD, variant Creutzfeldt-Jakob disease; E. coli, *Escherichia coli.*

mammalian species were reported in the summer and early fall. Infected birds were identified along the eastern seaboard as far south as North Carolina [13]. Here again, the major vector for this virus (the *Culex pipiens* mosquito) is widely dispersed throughout the eastern part of the country. It is unclear how serious West Nile fever will turn out to be in the United States; however, it is clearly a new infectious diseases problem that must be dealt with, and it illustrates the constant threat of reemergence of old diseases in new epidemiological settings.

No discussion of the threat of reemerging infectious diseases in the 21st century would be complete without mention of the threat of yet another catastrophic influenza A epidemic. In an average year, influenza A is responsible for ~20,000 excess deaths in the United States [14]. During the influenza A pandemic of 1918, there were at least 20 million deaths worldwide and >500,000 deaths in the United States. In 1957, the second most deadly influenza A epidemic occurred, accounting for ~70,000 deaths in the United States. In 1968, the third most important influenza epidemic occurred, accounting for ~35,000–40,000 deaths. Thus, serious influenza epidemics occur about every 20–40 years. The appearance of bird-to-human transmission of H5N1 influenza A virus in Hong Kong in the winter of 1997–1998 [15] was a cogent reminder of the ever-present threat of a new strain of influenza A virus entering a population that is relatively naïve for the microbe in question. Most public heath experts agree that it is only a matter of time before another catastrophic influenza epidemic occurs, and it certainly will occur in the 21st century.

Antimicrobial resistance. The development of resistance of microbes to antimicrobial drugs has been a problem in medicine since the use of the very first antimicrobial agents. Unfortunately, this problem has worsened, in part because of the widespread and often inappropriate use of antimicrobials [16]. In this first decade of the 21st century, we are faced with this continuing threat on a wider scale than ever before, with the emergence of resistant strains of a number of important microbes, including pneumococci, enterococci, staphylococci, *Plasmodium falciparum,* and *Mycobacterium tuberculosis.* Furthermore, despite the extraordinary success of antiretroviral drugs in the treatment of HIV/AIDS, the development of viral resistance is a major problem in the management of HIV-infected persons. Strategies to contain antimicrobial resistance in these early years of the 21st century should include heightened surveillance; appropriate infection control programs, particularly in hospitals; promotion of the rational use of antimicrobials; and accelerated basic and applied research in the areas of microbial pathogenesis, improved diagnostics, and vaccine and drug development. The recent sequencing of the genomes of important pathogens (see below, "The pathogens") will provide novel opportunities to delineate more precisely the genetic basis for resistance, as has been accomplished with *P. falciparum* and chloroquine resistance [17]. Such information

will greatly facilitate the development of alternative therapies against resistant strains of microbes.

INFECTIOUS CAUSES OF CHRONIC DISEASES

During the second half of the 20th century, a number of chronic diseases not thought to be associated with microbial infections were shown to be directly caused by or indirectly resulting from infectious microbes [18–20]. Table 2 provides a partial list of chronic diseases whose etiologies have proven to be infectious. Perhaps the most dramatic example has been the recent proof that *Helicobacter pylori* is directly responsible for most peptic ulcer disease as well as gastric carcinoma. Also of considerable interest and importance is the relationship between hepatitis B and/or C virus and hepatocellular carcinoma, as well as the strong association of certain strains of human papillomavirus with cervical, vulvar, and anal carcinoma. These associations have potentially important implications for the use of vaccination to prevent microbe-associated cancers. In this regard, the successful use of hepatitis B vaccine has already resulted in a decrease in the incidence of hepatic cancers in certain populations [21]. Indeed, the association of infectious diseases with cancer is striking; it is estimated that ~16% of all cancers are directly or indirectly associated with a microbial agent (figure 2) [22].

BIOTERRORISM

A bioterrorism attack against the civilian population in the United States is inevitable in the 21st century [23, 24]. The only question is which agent(s) will be used and under what circumstances will the attack(s) occur.

The threat of bioterrorism underscores the importance of pathogen genome sequencing projects, because rapid diagnostics will be critical to an adequate response to an attack. The availability of genomic sequences of microbes likely to be used in a bioterrorism attack will allow for the development of gene chips for sensitive, rapid, and accurate diagnosis [24, 25]. In addition, it is likely that microbes used for bioterrorism will be genetically modified for antimicrobial resistance. Understanding the genetic basis of resistance will greatly facilitate the development of alternative antimicrobials. Depending on the microorganism used in the bioterrorism attack, vaccines may be effective in protecting substantial numbers of the population after initiation of the attack, as would be the case with an agent such as smallpox. Hence, the development of new and improved vaccines against smallpox and similar agents, as well as the stockpiling of antimicrobials against such agents, will be important components of the effort against bioterrorism in the coming decades.

Table 2. Examples of chronic diseases that have infectious etiologies.

Microbe	Disease
Helicobacter pylori	Peptic ulcers, gastric carcinoma
Human papillomavirus	Cervical, anal, vulvar carcinoma
Hepatitis B/C viruses	Hepatocellular carcinoma
Epstein-Barr virus	Burkitt's lymphoma, nasopharyngeal carcinoma
Human T lymphotropic virus type I	Adult T cell leukemia
Human herpesvirus 8	Kaposi's sarcoma
Borrelia burgdorferi	Lyme arthritis
Tropheryma whippelii	Whipple's disease

NOTE. Based on data from [18–20].

THE SCIENCE BASE FOR INFECTIOUS DISEASES IN THE 21ST CENTURY

Critical to our ability to meet the challenges of infectious diseases in the 21st century is the continual and rapid evolution of the scientific and technological advances that serve as the foundation for the response of the public health enterprise to established, emerging, and reemerging diseases (table 3) [26]. For the discipline of infectious diseases, the application of functional genomics and proteomics will be a critical component of this science base and will draw from the sequencing not only of the human genome but also of a wide array of microbial pathogens. The areas of synthetic chemistry and robotics will greatly facilitate drug design and high-throughput screening of potential antimicrobial candidates. Computer and mathematical modeling likewise will prove useful in drug design and will also provide predictive models of microbial transmission. The field of molecular epidemiology will allow more precise delineation of microbial transmission and virulence patterns. Genetic epidemiology will lead to greater insights into host susceptibility at the individual and population levels. Finally, the rapidly advancing field of information technology will have a great impact on the field of infectious diseases in the 21st century, because rapid access and exchange of information among developed and developing nations will be critical to the overall success of any global health program.

The pathogens. Although we have entered the 21st century armed with an ever-expanding array of technological advances to meet the current and future challenges of microbial pathogens, the microbial world is extraordinarily diverse and possesses an adaptive capacity that in many respects matches our technological capabilities [5–8, 27–29]. Microbes are an important part of the external and internal environment of the human species. Indeed, microbial species constitute ~60% of the Earth's biomass, but <0.5% of the estimated 2–3 billion microbial species have been identified [27–29]. Microbes pre-

ceded animals and plants on Earth by >3 billion years, and although only a minute fraction of all microbial species are real or potential pathogens for the human host, these pathogens continue to emerge and reemerge.

One of the most important recent technological advances in infectious diseases research has been the ability to rapidly sequence the entire genome of microbial pathogens [29]. This capability will be a critical component of 21st century strategies for the development of diagnostics, therapeutics, and vaccines against currently recognized as well as emerging pathogens. Indeed, the microbial genome sequencing project will likely have as great an impact on the field of infectious diseases as the human genome project will on the entire field of medicine, including infectious diseases.

The first sequence of a human pathogen was obtained for *Haemophilus influenzae* in 1995 [30]. Subsequently, the pace of microbial genome sequencing has been extraordinary. As of January 2001, the sequencing of ~50 microbial genomes had been completed [31]. It is projected that within 2–4 years, the complete sequencing of an additional 100 microbial species will be available. Table 4 provides a partial list of some of the important human pathogenic microbial species for which genomic sequences have been published. The ability to sequence and perform sequence analysis rapidly on microbial species has resulted from the development and application of novel sequencing and computational techniques. The bold and successful application of the whole-genome "shotgun" sequencing technique used to determine the complete genome sequence of *H. influenzae* has revolutionized the field of genome sequencing (figure 3) [29].

The real and potential advantages of a microbial genomics approach to diagnostics, therapeutics, and vaccines are already being realized despite the fact that only ~50% of the genes of already sequenced microbes have tentatively assigned functions

Table 3. Science base for infectious diseases research in 21st century.

Field	Research applications
Genomics and proteomics	Host immunity
	Diagnostics
	New drug targets
	Vaccines
	Drug resistance
	Pathogenesis
Synthetic chemistry/robotics	Drug design
	High-throughput screening
Computer/mathematical modeling	Drug design
	Predictive models of transmission
Molecular epidemiology	Pathogen virulence
	Transmission patterns
Genetic epidemiology	Host susceptibility
Information technology	All encompassing

[29]. When the functions of the remaining 50% of genes of these microbes become known, it is likely that some proportion of these will provide medically applicable insights. Determination of the function of these genes should assume a high priority in the post-sequencing, functional genomics era of the first decade of the 21st century.

The host: the human genome project and infectious diseases. The discipline of infectious diseases is centered around the study of the microbes, the host, or the interaction between the two. The completion of a working draft of the sequence of the entire human genome [32, 33] and the subsequent assignment of function to the 30,000–40,000 human genes, which is projected to occur over a period of several years, will have an enormous impact on the entire field of medicine [34]. This

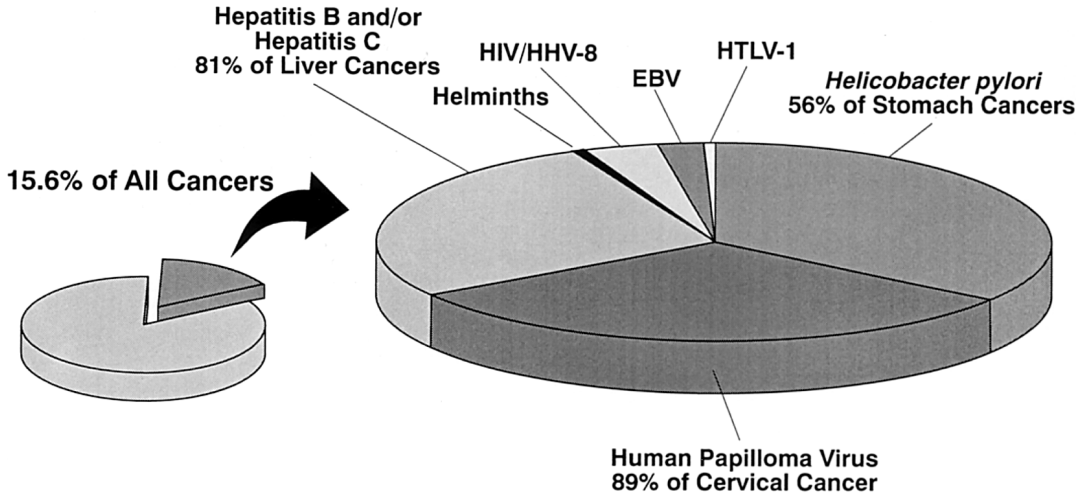

Figure 2. Infectious causes of cancer, based on data from [22]. EBV, Epstein-Barr virus; HHV, human herpesvirus; HTLV, human T lymphotropic virus.

Table 4. Examples of important human pathogens for which complete genomic sequences have been published.

Pathogen	Sequence, year(s) published
Haemophilus influenzae	1995
Mycoplasma species	1995, 1996
Helicobacter pylori	1997, 1999
Borrelia burgdorferi	1997, 2000
Treponema pallidum	1998
Chlamydia trachomatis	1998
Mycobacterium tuberculosis	1998
Plasmodium falciparum (Chr2, Chr3)	1998, 1999
Leishmania major (Chr1)	1999
Chlamydia pneumoniae	1999, 2000
Campylobacter jejuni	2000
Neisseria meningitidis	2000
Vibrio cholerae	2000
Pseudomonas aeruginosa	2000

NOTE. Data are from [31]; Chr, chromosome.

will clearly be the case in the discipline of infectious diseases, as well as that of immunology, a large component of which represents the host response to invading microbes. The ability to examine across the entire human genome the expression of the full menu of host factors involved in the response to a microbial pathogen will provide unprecedented opportunities to understand disease pathogenesis. The cascade of gene expressions involved in the response of the innate immune system and the adaptive immune system [35] to an invading microbe will clarify the important relationship between these two essential components of host defenses. The feasibility of identifying and assigning function to the entire array of soluble factors (cytokines) and their receptors, together with the relevant signal transduction pathways associated with the host response to pathogens, will truly revolutionize the field of host defense mechanisms.

Before the availability of the sequence of the human genome and the continuing assignment of specific functions to all genes, the recognition of the association of identifiable phenotypes with genetic polymorphisms was often a chance event and was relatively restricted in its scope. In the future, the study of gene polymorphisms and their role in host-microbe interactions will assume a new dimension in the era of human genomics. Polymorphisms are variations in DNA sequence, and most are single-nucleotide polymorphisms [36]. Certainly, only a small fraction of single-nucleotide polymorphisms might be relevant to host defenses; however, this small degree of difference would still play a potential role in the susceptibility to certain infectious agents at the individual and population levels. In addition, genetic polymorphisms will be identified that determine responses to certain drugs, including antibiotics [36]. The availability of gene chips or microarrays will enable us to scan the entire human genome for relevant polymorphisms.

The availability of sequences of the entire genomes of nonhuman species that have a considerable degree of homology with humans will greatly facilitate the task of assigning function to the human genes as they are identified. Species such as the mouse, rat, zebrafish, *Caenorhabditis elegans, Drosophila melanogaster,* and *Saccharomyces cerevisiae,* among others, whose genomes have and will be sequenced will serve as invaluable tools for experimentation on the function of a wide array of genes [37, 38]. Among these will surely be a variety of genes whose expression is directly or indirectly involved in host defense mechanisms against pathogenic microbes. Thus, the era of genomics will affect the study of infectious diseases from a number of standpoints, including the availability of the genomic sequences of the microbes in question, the human host species, and a variety of animal species that will serve as models for experimentation and delineation of pathogenic processes associated with infection by microbial pathogens.

VACCINOLOGY IN THE 21ST CENTURY

The impact of vaccinology on the public health in the 20th century has been enormous. Without question, vaccines have been our most powerful tools for preventing disease, disability, and death and controlling health care costs [39–42]. The evolution of the field of vaccinology has been driven by the development of enabling technologies, such as detoxification methodologies, the use of a variety of tissue culture systems to propagate microbes, and the new biotechnology of the last quarter of the 20th century, particularly that of recombinant DNA. The use of the currently available and future technologies in the 21st century promises to provide a renaissance in an already vital field. As mentioned above, the availability of the annotated sequences of the entire genomes of virtually all of the microbial pathogens will allow for the identification of a wide array of new antigens for vaccine targets. In the 21st century, vaccines derived from microbial genome–based expression of candidate antigens will be widely used. In addition to the traditional live attenuated and whole killed vaccines, concepts that are currently being actively pursued are recombinant proteins, conjugated vaccines, pseudovirions, replicons, vectored vaccines, "naked" DNA vaccines, microencapsulated vaccines, and edible vaccines [43].

One of the important challenges for the 21st century is the development of safe and effective vaccines for the 3 greatest microbial killers worldwide: HIV/AIDS, malaria, and tuberculosis. These 3 diseases account for one-third to one-half of healthy years lost in less developed countries [3]. They have become the target of a proposed Millennium Vaccine Initiative [44] and were addressed in the communiqué from a summit

of 8 major industrialized nations (G8) held in Okinawa in July 2000, which stated the goal of substantially reducing the burden of these 3 diseases by the year 2010 [45] (see below).

Despite the enormous successes of vaccines in decreasing the burden of morbidity and mortality caused by a variety of pathogens worldwide, continual frustration has resulted from the fact there are still millions of deaths from vaccine-preventable diseases worldwide (table 5) [46]. This is largely caused by the failure to implement vaccine delivery programs in a number of developing countries. As advanced technologies allow for the development of new vaccines against microbes for which no vaccines currently exist and improved vaccines against microbes for which a vaccine currently does exist, it is imperative that a vigorous effort is mounted to assure the delivery of such vaccines for the populations at risk.

Table 5. Global mortality from major vaccine-preventable diseases.

Disease	Estimated no. of deaths annually
Polio	720
Diphtheria	5000
Pertussis	346,000
Measles	888,000
Tetanus	410,000[a]
Haemophilus influenzae type b	400,000
Hepatitis B	900,000
Yellow fever	30,000
Total	2,979,720

NOTE. From [46].

[a] Including 215,000 neonatal tetanus.

GLOBAL HEALTH

Global health has long been a subject of intense interest and an area of commitment for a relatively small proportion of the biomedical research and public health communities in the United States. Over the past decade, this interest has become more universal and will become even more intensified in the 21st century. Although humanitarian concerns alone should have spurred such an interest, it was other factors that precipitated an acceleration of involvement in global health issues.

The globalization of our economy has led to an unprecedented dependence on the economic and political stability of our trading partners [47, 48]. The economic and political stability of a nation is heavily influenced by the general health of that nation. The AIDS epidemic in less developed countries, particularly in sub-Saharan Africa, is a cogent example of this tenet; the same can be said for countries with a high prevalence of endemic malaria, tuberculosis, diarrheal diseases, and a wide range of parasitic diseases [47, 48].

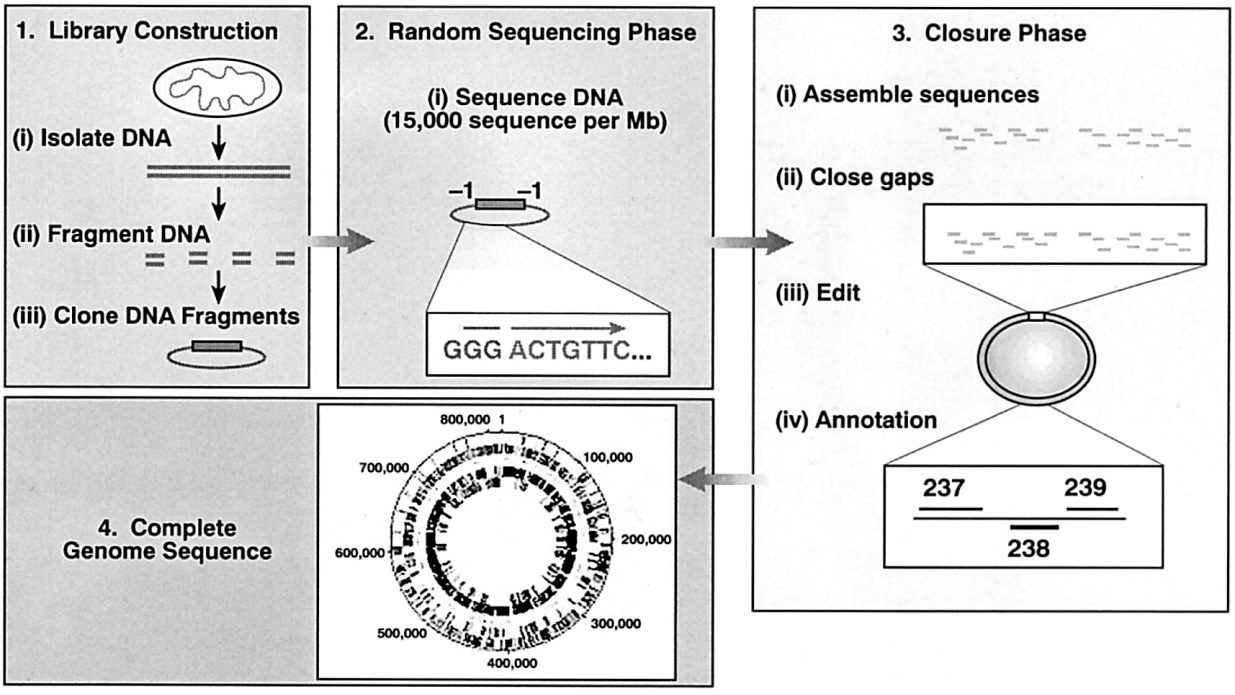

Figure 3. Steps in a whole-genome sequencing project. A "shotgun" sequencing strategy for whole-genome analysis is based on construction of a random cloned DNA library from the microbe in question, followed by sequencing of DNA clones, followed by the assembly of sequences, closing of gaps, editing of sequences, and finally annotation or assignment of function. Adapted from [29] (with permission).

The globalization of health problems and their relevance to the United States have been brought emphatically to the attention of the American public with the HIV/AIDS epidemic. Although first recognized in the United States, HIV/AIDS is now predominantly a disease of developing countries [9]. The scientific and public health response to HIV/AIDS in the United Sates, to which I will refer as "the AIDS model," provides important scientific and policy lessons that should be considered in our approach to other diseases of high global health impact.

The AIDS model. There have been >750,000 reported cases of AIDS in the United States and >430,000 deaths [49]. Despite dramatic decreases in the infection rate, the number of new infections has plateaued at an unacceptably high level of 40,000 per year since the early 1990s [50]. Nonetheless, the importance and speed of research advances that have been made since the disease was first recognized in the summer of 1981 have been breathtaking and unprecedented [51]. Within 3 years of recognition of this new disease, the etiologic agent was identified and causality proven. A simple and accurate diagnostic test was available for screening blood donors and populations in general. Pathogenic mechanisms of HIV disease have been extensively delineated. There are currently 17 antiretroviral drugs available for the treatment of HIV disease, and these together with earlier and better treatment and prophylaxis of opportunistic diseases has led to a striking decrease in the AIDS-related death rate over the past 5 years [52, 53] (figure 4). Many of these drugs were approved by the US Food and Drug Administration with unprecedented speed. Furthermore, a number of vaccine candidates are in various stages of clinical trials [54]. Government and private organizations mobilized quickly and effectively for the care of HIV-infected persons. Education and behavioral modification efforts have contributed to considerable progress in the prevention of HIV infection, although continued and heightened vigilance is essential, because the successes with therapy have led to an unfortunate increase in risky behavior among certain groups, such as young men who have sex with men [55].

These striking advances would not have occurred without the extraordinary investment in resources for biomedical research at the National Institutes of Health (figure 5). In addition, major investments have been made in the public health arenas of education, behavioral modification, prevention measures, and care of HIV-infected persons. In fiscal year 2000, US Department of Health and Human Services funding for AIDS research and services exceeded $8.5 billion [56]. These investments were made possible only by the consistent bipartisan commitment of several administrations and congresses to support such endeavors. The paradigm was highly successful: a major domestic public health problem was met with a major investment of public resources, and the results in the United States and other industrialized nations were striking. However, in the last few years of the 20th century, it became apparent that the toll in suffering and death from HIV/AIDS in developing nations was enormous and dwarfed that in the United States. HIV/AIDS had evolved into a true global health catastrophe. Furthermore, the global impact of AIDS began to call greater attention to the fact that other diseases, such as malaria and tuberculosis (table 6), had been having a similar impact in developing nations for centuries. Indeed, in certain countries in sub-Saharan Africa, the "big three" of HIV/AIDS, malaria, and tuberculosis account for ⩾50% of all deaths [3]. Compared

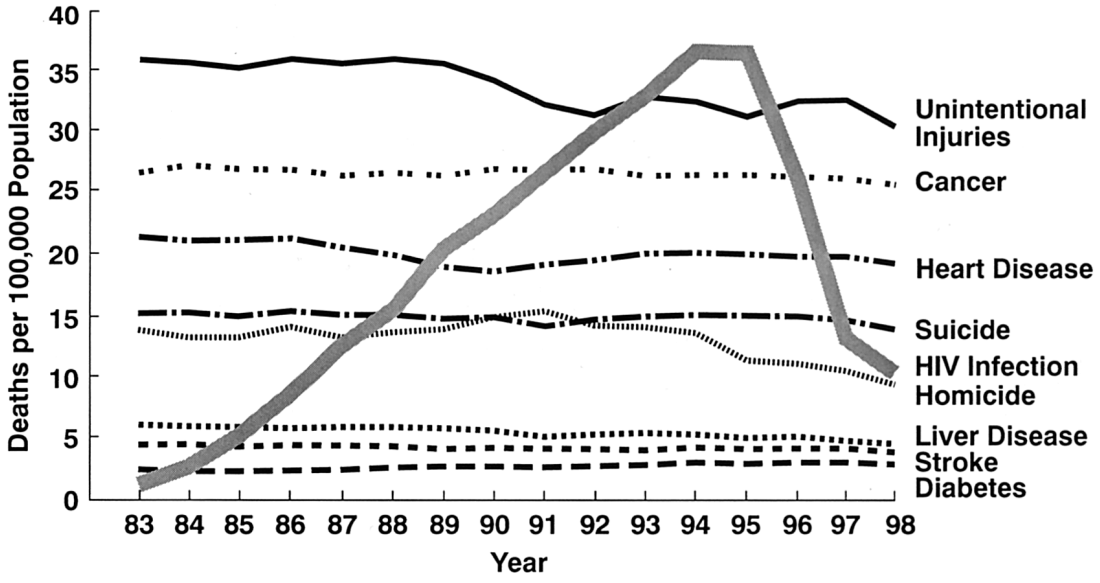

Figure 4. Death rates from leading causes of death in persons aged 25–44 years, United States, 1983–1998 [53]

with HIV/AIDS, relatively few research and public health resources were committed to these latter diseases by the United States and other developed nations. The question arises whether we can accomplish in malaria and tuberculosis research what has been accomplished in AIDS research. Almost certainly an infusion of dollars into malaria and tuberculosis research, analogous to the "AIDS model," would yield advances similar to those associated with HIV/AIDS research. Obviously, effective vaccines for all 3 of these diseases would be the ultimate accomplishment of a heightened research effort and would have an enormous impact on global health. However, implementation of such advances would be extremely problematic in many developing nations under the current economic conditions and with the lack of adequate health care infrastructure. In a different era, this would have been seen as an insurmountable problem, or at least someone else's problem. Today, however, global health problems, particularly those related to infectious diseases, are beginning to be perceived by political leaders in the United States and in other nations as a threat to destabilize the world [57].

Global health as a foreign policy issue. For the first time in the history of the United States, global infectious diseases are being viewed in the context of foreign policy. In January 2000, HIV/AIDS was discussed by the Security Council of the United Nations [57], and in April 2000, the White House formally designated HIV/AIDS as a threat to the national security of the United States in that it could potentially contribute to the fall of foreign governments, touch off ethnic wars, and undo decades of work in building free-market democracies abroad [58]. As noted above, a Millennium Vaccine Initiative targeting HIV/AIDS, malaria, and tuberculosis for vaccine development and delivery has been proposed [44]. In addition, a number of legislative proposals have been put forth in the US Congress relating to varying forms of assistance in the development and delivery of vaccines and therapeutics that would benefit developing nations [57]. Other developed nations are also expressing renewed awareness of the implication of global health issues. At a meeting of the G8 nations in Okinawa in July 2000, a communiqué was issued stating that "infectious and parasitic diseases, most notably HIV/AIDS, tuberculosis, and malaria, as well as childhood diseases and common infections, threaten to reverse decades of development and to rob an entire generation of hope for a better future." It also established goals to reduce the number of infections and deaths caused by HIV/AIDS, malaria, and tuberculosis by 25%–50% by the year 2010 [45].

Table 6. Global burden of 3 diseases.

Disease	Estimated no. of deaths worldwide, 1999	NIH funding in fiscal year 2001 (estimate), US$
HIV/AIDS	2.7 million	2.2 billion
Malaria	1.1 million	55.1 million
Tuberculosis	1.7 million	86.8 million

NOTE. From [3] (Budget data from Office of Financial Management, National Institutes of Health [NIH], personal communication).

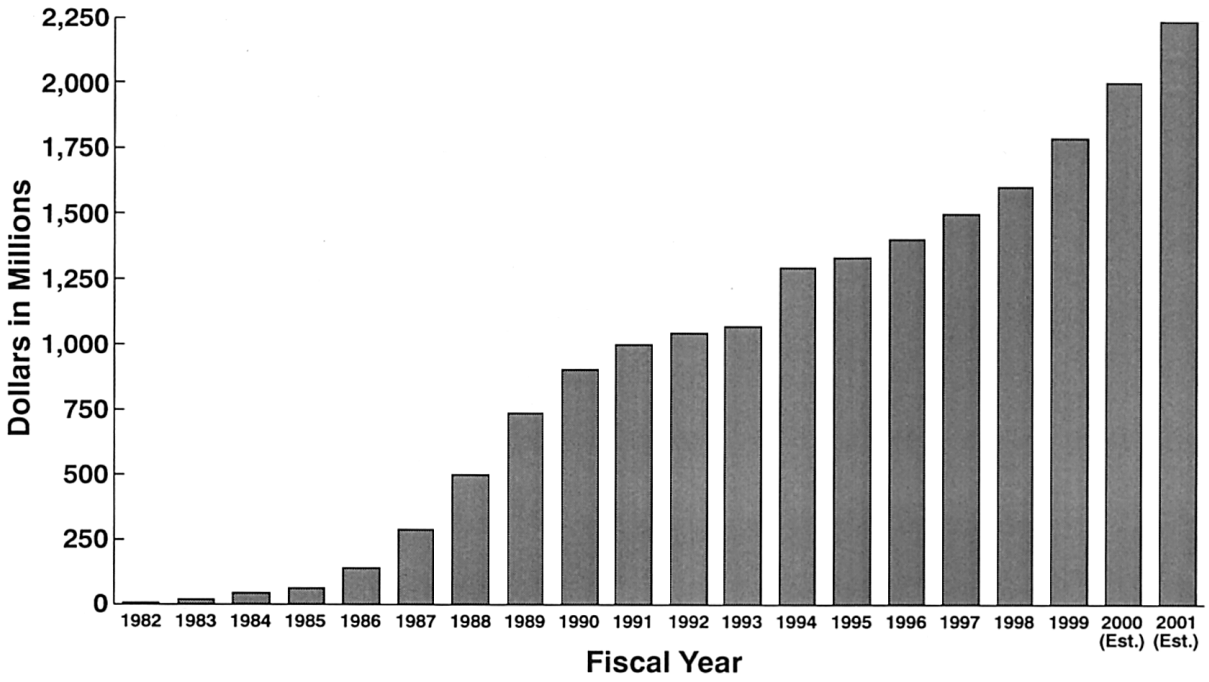

Figure 5. Funding at National Institutes of Health for HIV/AIDS research. Est., estimated (Office of Financial Management, National Institutes of Health, personal communication).

Philanthropic organizations are investing billions of dollars to assist developing countries in the promotion of health [59].

It is noteworthy that the area of science that contributed most obviously to foreign policy in the 20th century was the physical sciences related to nuclear weapons, the cold war, and the race for space exploration [60]. It appears that the growing forces of globalization together with the fact that the health of nations is critical for economic and political stability will lead to an increasing appreciation in the 21st century of the role of biological sciences and global health, particularly with regard to infectious diseases, in the development and execution of foreign policy.

CONCLUSION

The 21st century will see an ever-increasing emphasis on infectious diseases, both because of the certainty that emerging and reemerging diseases will continue to challenge us and because globalization has led to an increased awareness of and commitment to addressing the terrible burden of infectious diseases in developing nations. Indeed, global health with an emphasis on infectious diseases is gradually assuming an important role in the foreign policy agenda of the United States and other developed nations. Clearly, the anxiety that I felt in 1968 as I traveled to the NIH for my infectious diseases fellowship because of the proclamation by the then–Surgeon General of the United States, that infectious diseases were no longer a problem, has been replaced by a realization of the enormity of the infectious diseases challenges that lie ahead in the 21st century and beyond.

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