Milbank Memorial Fund

2005 Robert H. Ebert Memorial Lecture
Emerging and Re-emerging Infectious Diseases:
The Perpetual Challenge

by Anthony S. Fauci

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FOREWORD

The Milbank Memorial Fund and the Association of American Medical Colleges (AAMC) established the Robert H. Ebert Lecture on Academic Medicine and the Public Interest as a memorial to an exemplary physician, scientist, dean, and foundation executive. Ebert Lecturers are persons whose careers and character demonstrate broad and effective concern for medicine and the health of the public. They are chosen by a committee appointed jointly by the AAMC and the Fund. The lecture is delivered in odd-numbered years at the spring meeting of the Council of Deans of the AAMC.

Robert Ebert (1914–1996) was an intensely private public man. He linked the laboratory bench and the clinic, care of individual patients with concern for the health of populations, and excellence in research with innovation in the organization and financing of health services. Ebert served his country and his profession as a clinician, investigator, department chairman, dean, foundation executive, and leader of many boards, committees, and commissions. The institutions he enriched during his career include Oxford University, the University of Chicago, Case Western Reserve University, Harvard University, the Population Council, and the Milbank Memorial Fund.

Paying tribute to Ebert in a talk that preceded the first lecture in 1997 and subsequently published by the Fund, Eli Ginzberg concluded his remarks as follows:

> *Ebert valued peace over contention, consensus over authority. He had an instinctive sense of the way in which institutions become captives of their own history, and he spent considerable time and energy seeking solutions that produced change without upsetting large numbers of persons whose concerns could not, or should not, be ignored. He was a diplomat by instinct, who saw little point in wasting time and energy in conflict if compromise offered a satisfactory alternative.*
>
> *But this man of peace was also a man of thought, who had a deep appreciation of how things were changing, especially in his area of expertise, and he considered it his duty to figure out what to do about the changes that were underway and how to respond to them constructively. Further, he concluded that it was also his duty to initiate and carry through actions to establish a new, improved match between opportunity and results. Ebert always wanted to improve life, not for those who had power and money, but for the average man and woman who had to work long and hard to make ends meet. He directed most of his life to figuring out how he could use his time and energy to improve the access of this population to medical care services; to do so at a price that society could afford to pay; and, in the process, to train the next generation of physicians, equipping them to minister more efficiently and effectively to the critical health needs of the American people. That was the challenge that Ebert set himself, surely from the time that he became dean of the Harvard Medical School, and that remained his goal for the remaining years of his life. In meeting this challenge, he displayed a dedication that must inspire those who now take up his responsibilities and follow his lead into the new century.*

Ebert helped to guide the Milbank Memorial Fund for 30 years: as a member of its Technical Board, a director, and twice as president. Reflecting on his association with the Fund in 1995, he saw a

"significant congruence between the evolution of my own thinking and the Fund's long-standing interest in public health and health policy."

The Board of Directors of the Fund adopted a resolution honoring Ebert that reads, in part, "We cherish Robert H. Ebert, the private as well as the public man. We affirm the moral and intellectual standards he set for himself, for his friends, and for the Fund. We will miss him."

Samuel L. Milbank
Chairman

Daniel M. Fox
President

ACKNOWLEDGMENTS

Jordan J. Cohen, President and Chief Executive Officer of the Association of American Medical Colleges, collaborated with the Fund, in creating the Robert H. Ebert Lectures on Academic Medicine and the Public Interest. The members of the committee who selected the fifth lecturer were David Blumenthal, Director, Institute for Health Policy, Massachusetts General and Partners Health System; Jo Ivey Boufford, Professor, Robert F. Wagner Graduate School, New York University; Darrell G. Kirch, Senior Vice President for Health Affairs and Dean, College of Medicine, Pennsylvania State University; Deborah E. Powell (Selection Committee Chair), Dean and Assistant Vice President for Clinical Affairs, University of Minnesota Medical School; Paul B. Roth, Associate Vice President for Clinical Affairs and Dean, University of New Mexico School of Medicine; and John D. Stoeckle, Professor of Medicine, Emeritus, the Stoeckle Center for Primary Care, Massachusetts General Hospital.

Staff members of the Association of American Medical Colleges who helped to organize and administer the lecture and supervise its publication were Albert Bradford, Senior Deputy Editor, *Academic Medicine*; and Joseph A. Keyes, Jr., Senior Vice President and General Counsel.

This article also appeared in *Academic Medicine*, 80(12)1079–85, in December 2005.

INTRODUCTION

In 1963, the respected physician and anthropologist T. Aidan Cockburn, in a book called *The Evolution and Eradication of Infectious Diseases*, made this statement:

> *We can look forward with confidence to a considerable degree of freedom from infectious diseases at a time not too far in the future. Indeed . . . it seems reasonable to anticipate that within some measurable time . . . all the major infections will have disappeared.*[1]

Five years later the U.S. surgeon general noted that it might be possible with interventions such as antimicrobials and vaccines to "close the book" on infectious diseases and shift public health resources to chronic diseases.[2]

At the time, I was just finishing my medical residency at the New York Hospital — Cornell Medical Center and was on my way to the National Institutes of Health to begin, of all things, a fellowship in infectious diseases. You can imagine how I felt after several years of internal medicine residency preparing myself for a subspecialty in which public health leaders were telling me indirectly that I was wasting my time because there was little left to do.

However, even public health leaders can make mistakes. At about that time there were scattered reports about a very interesting wasting disease among Africans that was noticed by missionaries. We now realize that these were the earliest cases of a newly emerging infectious disease: HIV/AIDS. Today, HIV/AIDS and other infectious diseases continue to pose a substantial threat throughout the world.

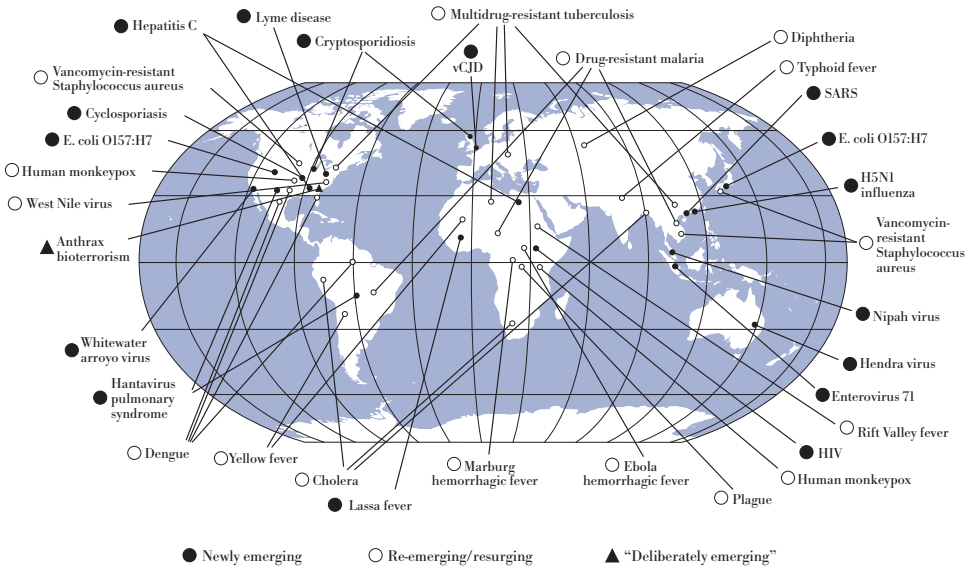
According to the World Health Organization's 2004 *World Health Report*, infectious diseases accounted for about 26 percent of the 57 million deaths worldwide in 2002.[3] Collectively, infectious diseases are the second leading cause of death globally, following cardiovascular disease, but among young people (those under the age of 50) infections are overwhelmingly the leading cause of death. In addition, infectious diseases account for nearly 30 percent of all disability-adjusted life years (DALYs), which reflect the number of healthy years lost to illness.[3]

Among the infectious diseases throughout the world there is the baseline matrix of infectious diseases that constitutes an ongoing threat. Then there are diseases that occur intermittently, some as little blips on the radar screen and some as major public health issues. At some point in time the matrix diseases have all been emerging diseases. But after a while they become so entrenched that they are considered part of the background matrix and not emerging or re-emerging diseases. So as we eradicate diseases such as polio and smallpox, something else emerges and takes their place. This is the nature of the perpetual challenge of infectious diseases, as stated in this article's title.

I now would like to discuss some of the lessons we have learned as we combat infectious diseases and how the next generation of physicians and researchers might build on our experience as they face the challenge of outwitting the microbes that will continue to plague mankind.

What do I mean by a newly emerging disease? A *newly emerging disease* is a disease that has never been recognized before. HIV/AIDS is a newly emerging disease, as is severe acute respiratory syndrome (SARS), Nipah virus encephalitis, and variant Creutzfeld-Jakob disease (vCJD) (see Figure 1).

FIGURE 1 EXAMPLES OF EMERGING AND RE-EMERGING INFECTIOUS DISEASES THROUGHOUT THE WORLD.



Adapted from Morens, D.M., et al. 2004. The Challenge of Emerging and Re-emerging Infectious Diseases. *Nature* 430:242–49.

Re-emerging, or *resurging*, *diseases* are those that have been around for decades or centuries, but have come back in a different form or a different location. Examples are West Nile virus in the Western hemisphere, monkeypox in the United States, and dengue rebounding in Brazil and other parts of South America and working its way into the Caribbean. *Deliberately emerging diseases* are those that are intentionally introduced. These are agents of bioterror, the most recent and important example of which is anthrax. Newly emerging, re-emerging, and deliberately emerging diseases are all treated much the same way from a public health and scientific standpoint.[4]

Multiple factors, including economic development and land use, human demographics and behavior, and international travel and commerce, contribute to the emergence and re-emergence of infectious diseases.[5] Almost all of these factors reflect in some measure the encroachment of human civilization on the environment and on the microbial species that inhabit our environment. The human species lives in a delicate balance with microbial species; there is an ever-present tension between the two. If we perturb this balance, microbes almost always figure out a way to counterbalance the effect. Lyme disease emerged as we developed land near forests; changes in social structure and human behavior contributed to the emergence of HIV/AIDS; and

monkeypox emerged in the United States when people started adopting exotic pets such as Gambian rats.

Approximately 75 percent of emerging pathogens are *zoonotic*,[6] that is, communicated by animals to humans. When humans encroach upon a rainforest, they become exposed to viruses and other microbes that they otherwise would not have encountered. HIV/AIDS, avian influenza, monkeypox, Nipah, SARS, and Ebola are all the result, to a greater or lesser extent, of interactions with animals that led to the emergence and re-emergence of deadly diseases.

Two fundamental characteristics of microbes allow them to circumvent our attempts to control them. Whereas human generations occur approximately every two decades, those of microbes occur in minutes, allowing them to rapidly replicate. Microbes also can mutate with each replication cycle. Their ability to replicate and mutate gives them the advantage of selectively circumventing human interventions, be they antimicrobials, vaccines, or public health measures.

In our battle with microbes, we have a number of factors in our armamentarium. First of all, we have an intellect and a will. We use these to implement public health measures, biomedical research, and technological advances. In essence the human species uses its intellect and will to contain, or at least strike a balance with, microbial species that rely on genes, replication, and mutation.

BASIC RESEARCH

Fundamental research underlies almost everything we do in studying and responding to infectious diseases. From understanding pathogenesis, virulence factors, patterns of transmission, and host susceptibility to developing new technologies and countermeasures such as vaccines, therapeutics, and diagnostics, basic research is an essential component of the enterprise.

In particular, advances in genomics and proteomics have helped us better understand mechanisms of pathogenesis, host immunity, and drug resistance and are helping us identify new drug targets and develop new vaccines and diagnostics. Progress in synthetic chemistry, robotics, and computer modeling are leading to advances in drug design, high-throughput screening, and predictive models of disease transmission. Developments in molecular and genetic epidemiology are helping us understand pathogen virulence, transmission patterns, and host susceptibility. This is particularly important in HIV/AIDS and avian influenza because we can trace the evolution of different viral subtypes across continents. Finally, information technology makes an important contribution to all aspects of basic and applied research.[7]

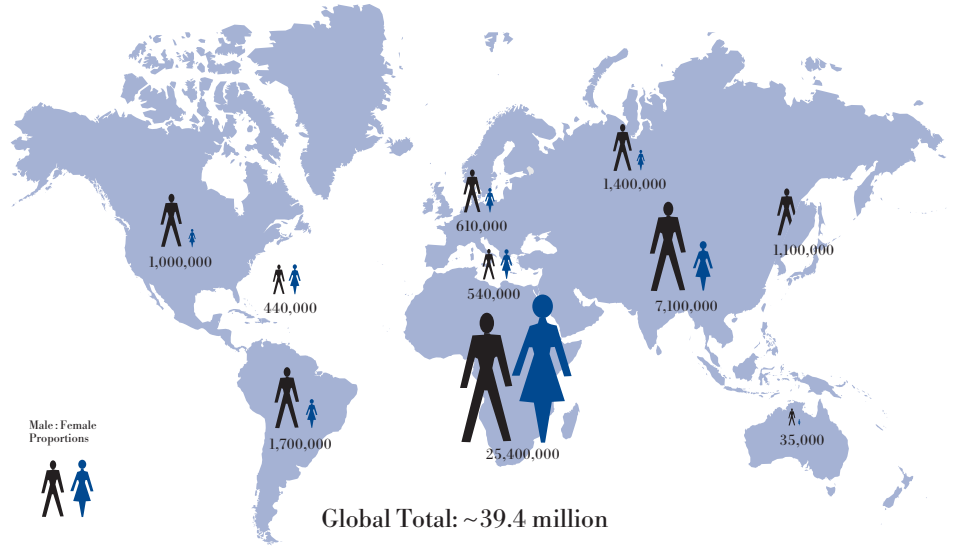
Genomics and proteomics have played a pivotal role in basic research in infectious diseases. Today, an unknown microbe can often be identified and sequenced within days.[8] This rapid sequencing capability helps to illuminate virulence factors and pathogenic mechanisms, as well as immune-evasion factors, receptors, and the immunodominant antigens to develop vaccines. The ability to sequence and annotate microbes now has taken its place at the forefront of how we deal with emerging and re-emerging infections. I would like to now examine a few of these diseases.

IMPORTANT EMERGING AND RE-EMERGING DISEASES

HIV/AIDS

HIV/AIDS was first described in the scientific literature in June 1981.[9,10] Because the AIDS pandemic is now more than 20 years old, it will soon be considered one of the fundamental matrix diseases. However, in 1981, it was truly an emerging disease. As illustrated in Figure 2, nearly 40 million people throughout the world are currently infected with HIV, two thirds of whom live in sub-Saharan Africa.[11]

FIGURE 2 GLOBAL GEOGRAPHIC DISTRIBUTION OF PEOPLE LIVING WITH HIV/AIDS, DECEMBER 2004.



Source: UNAIDS. 2004. AIDS Epidemic Update, December 2004 http://www.unaids.org/wad2004/EPI_1204_pdf_en/EpiUpdate04_en.pdf.

In 2004, three million people died from AIDS and nearly five million adults and children became infected with HIV; 90 percent of new infections occur in the developing world.[11]

When HIV/AIDS first emerged, there were many misunderstandings. Initially we measured the time from infection to disease manifestations in months or very few years. It now appears that without therapy there is a median 10-year time period before advanced HIV disease or AIDS develops. So those patients who were first identified in 1981 had likely been infected with HIV for many years before developing symptoms of the advanced disease.

Despite the current concentration of disease burden in sub-Saharan Africa, Asia likely will be the next epicenter of this disease. Currently about five million people in India are infected with HIV, but

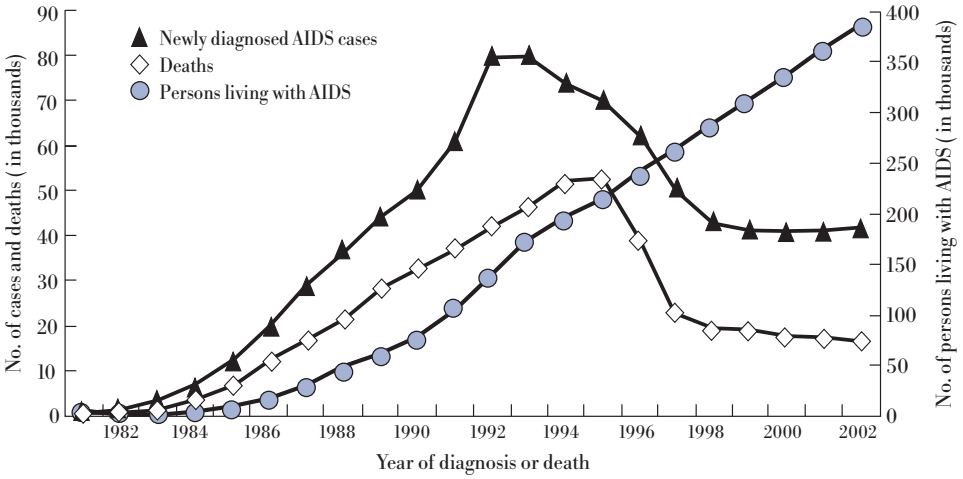
that is less than 1 percent of the adult population. In Botswana, 37 percent of the adult population is infected, but the population is only 1.6 million.[12,13] If the prevalence rate in India, which has a total population of more than a billion, were to approach what we are seeing in Africa, the impact would be enormous.

In our own country, we have become somewhat numbed to the HIV/AIDS pandemic. I gave a lecture recently to some students at a college in Washington, D.C., and realized that almost no one else in the room had been born when HIV emerged. To them, HIV/AIDS has just become part of the landscape. In the United States, cumulatively, we have had almost one million AIDS diagnoses, 525,000 deaths, and about a million people living with HIV infection, half of whom are untested, untreated, or both.[14] The really sobering issue about HIV/AIDS in the United States is the 40,000 new infections that occur each year. In the mid-1980s the number of new infections each year peaked at 150,000, then through prevention efforts fell to a plateau of about 40,000, which is still an unacceptable level.[15] The demographics of new HIV infections have changed. One percent of new infections occurred in women in the 1980s, but today more than a quarter of new infections are among women. Half of all new infections today occur in people under the age of 25, and the rates of infection are significantly higher among minorities, particularly African Americans and Hispanics.[14]

Despite these challenges, much has been accomplished in the fight against HIV/AIDS. One of the great triumphs of our investment in basic biomedical research is the development of potent antiretroviral drugs that have prolonged and improved the lives of HIV-infected individuals. The AIDS research model serves as a valid paradigm for approaching other diseases of global importance. When adequate resources are invested in attacking a problem, you get results, as evidenced by the more than 20 drugs that have been approved by the Food and Drug Administration for the treatment of HIV/AIDS. As shown in Figure 3, we have seen a dramatic decline in AIDS deaths in the USA since the mid-1990s, when combination antiretroviral therapy (ART) was introduced. However, as fewer people die and a consistent 40,000 people become infected each year, the number of people living with AIDS continues to increase.

AIDS patients in other countries have not fared as well. Of the estimated 6.5 million low- and middle-income people in other countries who need treatment, most of whom live in sub-Saharan Africa, only 15 percent are receiving antiretroviral drugs.[16] However, we are making some progress. Two or three years ago, only 1 percent of those in need in developing countries were treated. We progressed from treating 5,000 to 10,000 patients to treating 970,000 globally as a result of a very aggressive effort by the Global Fund to Fight AIDS, Tuberculosis, and Malaria and the President's Emergency Plan for AIDS Relief (PEPFAR).[16] The president's program, which aims to prevent 7 million infections, treat 2 million people, and care for 10 million patients, is on target. As of March 31, 2005, 235,000 people in 15 countries, more than half of them women, were receiving ART through PEPFAR. However, it is important to realize that these people need to be treated for life. Unless we slow the rate of new HIV infections, continued treatment of significant numbers of AIDS patients throughout the world will not be feasible, neither logistically nor financially. This brings us to the issue of HIV prevention.

FIGURE 3 AIDS IN THE UNITED STATES. ESTIMATED NUMBER OF CASES, DEATHS, AND PEOPLE LIVING WITH AIDS IN THE UNITED STATES, 1981–2003.



Source: Centers for Disease Control and Prevention. 2004. Cases of HIV Infection and AIDS in the United States, 2003: HIV/AIDS Surveillance Report http://www.cdc.gov/hiv/stats/2003SurveillanceReport.pdf.

We often lose sight of the fact that HIV/AIDS is a totally preventable disease. There are multiple modalities of prevention, and some of them work very well. The various strategies, including education, behavior modification, treatment of drug users, distribution of condoms, clean syringes, needle exchange programs, topical microbicides, antiretroviral therapy, and abstinence, can prevent HIV/AIDS, but all of these approaches must be pursued concomitantly.

In a perfect world, we would not need an HIV/AIDS vaccine, but we do not live in a perfect world and people continue to put themselves and others at risk. Hence, a vaccine is needed. The scientific challenge of developing an effective HIV vaccine is formidable. For every other major infectious disease — even the great killers and maimers, such as smallpox, polio, and measles — the body handles the invading microbes the vast majority of the time without a vaccine. Historically, only 25 to 30 percent of people infected with the smallpox virus die; 70 to 75 percent of those infected recover spontaneously.[17,18] Similarly, more than 98 percent of people infected with poliovirus never experience serious complications.[19,20] The reason is that the body has the capability of ultimately mounting an effective immune response, generally an antibody response, to eliminate the microbe.

No such luck with HIV. Of the more than 60 million people who have been infected with HIV since the beginning of the epidemic, there is not a single well-documented case of someone who has completely cleared the virus after having had an established infection.[15] Lymphocyte cultures from people who clinically are doing very well still yield the virus. Even for people on drug therapy for eight to nine years with undetectable viral loads, the virus can be cultured from their lymphocytes.[15]

To address the many hurdles in HIV vaccine development, the Global HIV/AIDS Vaccine Enterprise was proposed in 2003 and endorsed by the G8 summit in June 2004. The Enterprise, an international consortium of independent parties, is part of an effort to encourage the global scientific community to pursue common goals using complementary strategies and to avoid doing overlapping or repetitive experiments. The international group has met regularly since the summer of 2003 and has developed a strategic plan that is freely accessible on the Internet.[21]

MALARIA AND TUBERCULOSIS

Malaria is one of those diseases that most people in the developed world just do not think about. Yet more than one million people with malaria die each year. Every 30 seconds, a child dies of malaria.[22] Over the past few years we have made considerable progress in malaria research. Scientists now have completed the genomic sequence of the most virulent malaria-causing parasite, *Plasmodium falciparum*, as well as that of *Anopheles gambiae*, one of the important mosquito species that carries the parasite.[23,24] With the human genome sequence also available, we have the genomes of the host, the vector, and the microbe completely sequenced. This information can now be helpful in the design of effective drugs and vaccines as well as in other areas of malaria control. More recently, a trial of a malaria vaccine conducted among children in Mozambique showed 30 percent efficacy in preventing infection and nearly 60 percent efficacy in preventing severe disease.[25] Although the vaccine is not as efficacious as most commonly used childhood vaccines, it has the potential for saving millions of lives.

Tuberculosis is another major killer, causing the deaths of about two million people each year.[26] About one third of the world's population is infected with the mycobacterium that causes tuberculosis, and almost four million have the active disease at any time, including the 300,000 new cases of multiple-drug-resistant tuberculosis that develop each year.[26] Tuberculosis is especially prevalent among patients with HIV/AIDS: about 46 percent of people in the developing world with HIV are co-infected with tuberculosis, and 13 percent of the deaths among HIV-infected individuals are from disseminated tuberculosis.[26]

INFLUENZA

Influenza, as common as it is, is a greatly misunderstood disease. Each year we confront seasonal, or interpandemic, influenza. Seasonal influenza kills about 250,000 to 300,000 people each year throughout the world.[27] In the United States 36,000 people die each year, more than 90 percent of

whom are 65 years or older.[28] Superimposed on this yearly cycle is the ever-present threat of an influenza pandemic. A pandemic occurs through exposure to a microbe for which there is no baseline immunity in the population.

The worst influenza pandemic in history occurred in 1918–1919.[29] There were 40 million deaths throughout the world and a half-million deaths in the United States. Unlike the seasonal flu that typically kills the elderly, the 1918 pandemic killed young people as well. Even though they were fundamentally healthy, 20-, 30-, and 40-year-old people were dying because they had no background immunity to the virus, and the virus was particularly virulent.

Influenza virus strains are designated by the composition of their hemagglutinin and neuraminidase proteins. The major influenza strain circulating in 2005 was an H3N2 strain. Virtually every year, the sequence of the prevalent strain mutates slightly in a process known as drift. A drift from an H3N2 Panama strain to an H3N2 Fujian strain (as occurred in the 2003–2004 influenza season) represents a relatively minor mutation; if you were vaccinated or are immune to a Panama strain, you would also harbor some degree of cross-reacting, baseline immunity to a Fujian strain.

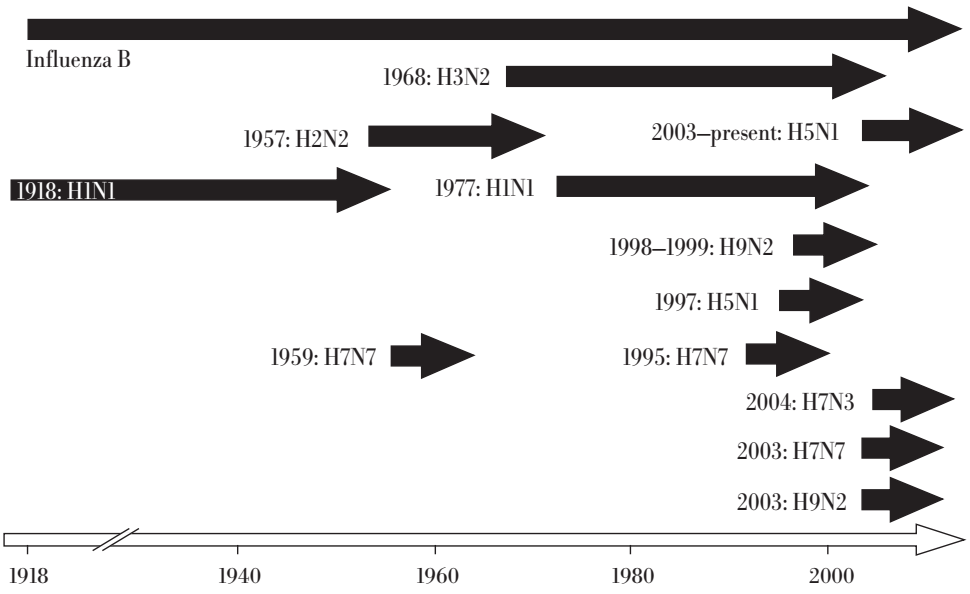
However, an antigenic shift occurs when an influenza strain emerges that is substantially different from anything to which the population has been previously exposed. Figure 4 illustrates the timetables of the three influenza pandemics that occurred in the 20th century. In 1918, H1N1 first appeared; in 1957 H2N2 emerged, and in 1968, we first saw H3N2.[29]

Over the past few years, many more influenza strains have emerged with the capability of infecting humans. The H5N1 strain likely evolved from a few flocks of chickens in Hong Kong (where it was first noticed in 1996 and infected a small number of humans in 1997) to the situation today where it has infected numerous flocks, as well as wild birds throughout Southeast Asia.[30] Hundreds of millions of birds have been infected; more than 100 million chickens have died or have been culled to slow the spread of the H5N1 virus.

We are now faced with what I call an escalating scale of compounding probabilities. If a few birds are infected, there is a problem, but not a big problem. When more birds are infected, the problem is getting bigger. When the virus jumps to humans, the problem is getting even more serious. If it jumps to significant numbers of humans, the threat becomes more serious still.

Between December 2003 and June 28, 2005, 108 laboratory-confirmed cases of human infection with the H5N1 avian influenza virus and 54 deaths were reported to the World Health Organization.[30] Not long ago, the first documented cases of human-to-human transmission were reported in a Thai family.[31] Clearly, the virus is percolating among avian populations in Southeast Asia. If the virus develops the capability of efficiently transmitting from human to human, then we have the makings of an influenza pandemic. Is it likely that will happen? No, it is not likely, but it is quite possible and significantly more probable than it was 10 years ago. In response, we are doing what we should be doing: basic research to understand virulence factors, the factors that allow transmission from one animal species to another animal species, and the mechanisms of transmissibility.

FIGURE 4: INFLUENZA VIRUS TIME LINE. APPEARANCE OF INFLUENZA VIRUSES INFECTING HUMANS, 1918–2005.



Source: World Health Organization. 2005. Avian Influenza: Assessing the Pandemic Threat; http://www.who.int/csr/disease/influenza/WHO_CDS_2005_29/en/.

We have developed an H5N1 vaccine based on the virus that is currently circulating in Asia; a clinical trial of this vaccine was initiated in April 2005. Initial results show that the vaccine is safe and immunogenic. The U.S. government has purchased two million doses of the H5N1 vaccine for the strategic national stockpile and has also begun to stockpile the antiviral compound known as Tamiflu, which is effective against the H5N1 virus. These efforts are part of the HHS Pandemic Influenza Response and Preparedness Plan.[32]

SARS

Nearly three years ago, the world experienced another newly emerging microbe — a previously unknown coronavirus — that caused severe acute respiratory syndrome (SARS). Fortunately, the morbidity and mortality associated with the SARS outbreak were not as great as what we observe every year with influenza. The SARS outbreak turned out to be a classic study in epidemiology with regard

to tracking the point source, the spread, and the containment. SARS first appeared in Guangdong Province in China. It was not reported to authorities until it emerged in Hong Kong, when an index case, who traveled from Guangdong to Hong Kong, stayed at the Metropole hotel and infected at least 14 people.[33] Those individuals did some traveling throughout the world. Within months we had an epidemic that temporarily transfixed the world and did extraordinary economic damage in Canada, China, and Hong Kong, and other countries. There were 8,098 reported cases and 774 deaths.[33]

SARS taught us an important lesson. Academic scientists, public health officials, and pharmaceutical companies acted together in a way that was unprecedented, leading to the development of promising vaccine candidates in record time. The new microbe was identified in March 2003 and was rapidly sequenced; a vaccine was developed by the following March. In December 2004, a clinical trial of the SARS vaccine began.[34] This likely was the fastest time frame in the history of biomedical research from the identification of a previously unknown microbe to the beginning of a clinical trial. Such rapid progress could not have occurred 30 to 40 years ago. Thus, as microbes continue to emerge, we continue to develop technological advances that will, hopefully, keep us one step ahead of our microbial foes.

WEST NILE VIRUS

Whereas SARS is an emerging infection, West Nile virus is a re-emerging infection. It has existed in Africa and the Middle East for decades, if not centuries. In 1999, it landed in Queens, New York, via an unknown route. The infection then proceeded to move across the country, with different hot spots each year.[35,36] In 1999, the hotspot was Long Island and New York City. In the year 2000, it spread a little bit, and many people were not terribly worried. However, all the makings for an epidemic were in place: the right mosquito, the right microbe, and suitable hosts. In 2001, the hotspots expanded throughout New York State and to Connecticut, Maryland, and Florida. In 2002, hotspots appeared in the Midwest, and farther west in 2003. By 2004, the epidemic had crossed the Rocky Mountains and emerged in California, Arizona, and Colorado. In 2004, 2,470 cases and 88 deaths were reported.[36] West Nile is likely to follow the path of other infectious encephalopathies such as St. Louis encephalitis and eastern equine encephalitis, becoming part of the background matrix of infectious diseases.

The research enterprise also has moved rapidly to respond to West Nile virus. In particular, scientists have created a chimeric vaccine against West Nile virus. Genes coding for the immunodominant antigens of the West Nile virus (a flavivirus) were spliced into the genome of an attenuated yellow fever virus (another flavivirus) vaccine to yield a chimeric yellow fever/West Nile virus vaccine. This vaccine is now in clinical trials with promising early results. A similar chimeric vaccine has also been created with an attenuated dengue virus vector. Other West Nile vaccine approaches also are being pursued, including a DNA vaccine and recombinant subunit vaccines, as well as new approaches to therapy.[37]

MARBURG VIRUS

We recently experienced an outbreak of Marburg virus in Angola. This virus, related to Ebola virus, was first detected in 1967 in Marburg, Germany, when people working with monkeys from Uganda became infected, resulting in seven deaths. Throughout the years in Kenya, South Africa, the Democratic Republic of the Congo, and most recently, Angola, the virus has re-emerged. Fortunately, Marburg and Ebola outbreaks tend to appear in localized regions and have not triggered epidemics throughout the world. Unlike influenza, which spreads even when people are relatively asymptomatic, Ebola and Marburg are generally transmitted from people who are deathly ill. The people at greatest risk of contracting disease are family members, physicians, and nurses in hospitals, undertakers, and other people who come in close contact with infected individuals. Unless the virus is used as an agent of bioterrorism, it is unlikely that the world will experience an epidemic of Ebola or Marburg, merely because of the somewhat restricted manner of its transmission.[38]

BIOTERRORISM

One of those days in history that we will never forget is September 11, 2001. Barely had the dust settled on Ground Zero in New York City and the Pentagon when an unknown bioterrorist sent anthrax spores through the mail, resulting in 22 anthrax cases and five deaths.[39] Unlike other infectious diseases, anthrax is not communicable, yet it virtually immobilized Washington D.C. People were afraid to open their mail, and several mail facilities were closed down. Congressional office buildings were closed for months. A large infusion of resources was invested in bioterrorism research, and the issue of how such research should be conducted was the subject of much debate. Should it be done openly or covertly? I made the argument that such research should be done openly and transparently by researchers who are studying emerging and re-emerging diseases anyway. With an infusion of resources, we developed a strategic plan and research agendas, now widely transparent and available, which call for fundamental basic research as the matrix for the development of countermeasures against agents of bioterror.[40]

A NEW PARADIGM

One of the goals of infectious disease research is the development and production of countermeasures. The academic community has been fundamentally concerned with basic research and concept development, and for the most part has left the development of products to industry. When industry has a product that they know will generate a major profit margin, they do not need much outside incentive to do advanced product development. However, if faced with the choice of putting $200 million into a new area, will pharmaceutical companies make a product to combat an emerging microbe, for which there is an uncertain market, or will they develop a new Viagra or a better Lipitor? The answer, at least in terms of answering to shareholders, is obvious. So in developing products for public health issues, a new paradigm is needed. In the present paradigm, the biomedical research community provides the push in the form of concept development. The pull is generally the marketplace demand. However there is not a large marketplace demand for countermeasures for emerging infections. Hence, we have to do things differently, and we are starting to observe a shift. We are now seeing partnerships with industry fueled in part by programs that developed as a result of the Project Bioshield bill that was signed in the summer of 2004. Through this project, $5.6 billion has been put aside as a guarantee to industry that if they make a product that serves an important public health need, the government will buy it at a fair price, even if it is never used. This provides an important incentive for industry to get involved.[41]

As a result of these efforts, several critical countermeasures have been developed. We started out with 18 million doses of the classic, proven smallpox vaccine, but now have more than 300 million doses, enough for everyone in the country. Although it is a very effective vaccine, there are rare but serious side effects, which have prompted the biomedical research community and the public health community to develop a second-generation vaccine that is much safer. In addition, new antiviral drugs are being developed. For example, several months ago, researchers found that a potential anticancer drug that blocks a cellular signal transduction cascade also interferes with smallpox growth factor, essential to the entry and replication of the smallpox virus.[42] Thus, purely fundamental science has opened up a new possible route for developing countermeasures to smallpox and other viruses that block cellular pathways. Other developments include a next-generation anthrax vaccine, Ebola vaccine, and monoclonal antibodies against botulism toxin.

As we educate the next generation of physicians and researchers, it is important to keep this paradigm shift in mind. We need to help today's medical students understand that they are part of a global enterprise encompassing multiple facets of patient care and drug development. As we struggle to keep a step ahead of the diseases that challenge us, it may not be sufficient to simply be a good doctor or a good scientist. We must develop partnerships among clinicians, researchers, government, and industry to detect and diagnose disease; to conduct basic, applied, and clinical research; to develop effective countermeasures; to manufacture vaccines and drugs to prevent and treat disease; and to deliver these therapies to the patients who need them. Today's medical students will play an important role in all aspects of our efforts to combat infectious diseases.

It is clear that we will rely heavily on fundamental science, its applications, intellectual capital, and research facilities in the ongoing struggle between microbes and humans, a challenge that is

perpetual. I would like to close by quoting Dr. Joshua Lederberg, a person whom I have admired for many years, who has said it much better then I could:

> *The future of humanity and microbes likely will unfold as episodes of a suspense thriller that could be titled* Our Wits Versus Their Genes.[43]

REFERENCES

1. Cockburn, T.A. 1963. *The Evolution and Eradication of Infectious Diseases*. Baltimore, MD: Johns Hopkins Press.

2. Garrett, L. 1994. *The Coming Plague*. New York: Farrar, Straus and Giroux.

3. World Health Organization. 2004. The World Health Report 2004 — Changing History. http://www.who.int/whr/2004/en/. Accessed on September 8, 2005.

4. Morens, D.M., G.K. Folkers, and A.S.Fauci. 2004. The Challenge of Emerging and Re-emerging Infectious Diseases. *Nature* 430:242–49.

5. Morse, S.S. 1995. Factors in the Emergence of Infectious Diseases. *Emerging Infectious Diseases* 1:7–15.

6. Taylor L.H., S.M. Latham, and M.E. Woolhouse. 2001. Risk Factors for Human Disease Emergence. *Philosophical Transactions of the Royal Society B: Biological Sciences* 356:983–89.

7. Fauci, A.S. 2001. Infectious Diseases: Considerations for the 21st Century. *Clinical Infectious Diseases* 32:675–85.

8. Fraser, C.M., J.A. Eisen, K.E. Nelson, I.T. Paulsen, and S.L. Salzberg. 2002. The Value of Complete Microbial Genome Sequencing (You Get What You Pay For). *Journal of Bacteriology* 184:6403–05.

9. Centers for Disease Control and Prevention. 1981. Pneumocystis Pneumonia — Los Angeles. *Morbidity and Mortality Weekly Report* 30:250–52.

10. Centers for Disease Control and Prevention. 1981. Kaposi's Sarcoma and Pneumocystis Pneumonia among Homosexual Men — New York City and California. *Morbidity and Mortality Weekly Report* 30:305–8.

11. UNAIDS. 2004. AIDS Epidemic Update. http://www.unaids.org/wad2004/EPI_1204_pdf_en/EpiUpdate04_en.pdf. Accessed on September 8, 2005.

12. UNAIDS. 2004. UNAIDS at Country Level: Progress Report.

13. Central Intelligence Agency. 2005. The World Factbook 2005. http://www.cia.gov/cia/publications/factbook/index.html. Accessed on September 8, 2005.

14. Centers for Disease Control and Prevention. 2004. Cases of HIV Infection and AIDS in the United States, 2003: HIV/AIDS Surveillance Report. http://www.cdc.gov/hiv/stats/2003SurveillanceReport.pdf.

15. Fauci, A.S. 2003. HIV and AIDS: 20 Years of Science. *Nature Medicine* 9:839–43.

16. World Health Organization. 2005. Progress on Global Access to HIV Antiretroviral Therapy: An Update on 3 by 5. http://www.who.int/3by5/fullreportJune2005.pdf. Accessed on September 8, 2005.

17. World Health Organization. Smallpox Fact Sheet. http://www.who.int/mediacentre/factsheets/smallpox/en/. Accessed on September 8, 2005.

18. Kasper, D.L., E. Braunwald, A.S. Fauci, S.L. Hauser, D.L. Longo, and J.L. Jameson, Eds. 2005. *Harrison's Principles of Internal Medicine: Microbial Bioterrorism*, p. 1284. New York: McGraw Hill.

19. World Health Organization. Poliomyelitis Fact Sheet. http://www.who.int/mediacentre/factsheets/fs114/en/. Accessed on September 8, 2005.

20. Kasper, D.L., E. Braunwald, A.S. Fauci, S.L. Hauser, D.L. Longo, and J.L. Jameson, Eds. 2005. *Harrison's Principles of Internal Medicine: Enteroviruses and Reoviruses*, page 114. New York: McGraw Hill.

21. PLoS Medicine. 2005. The Global HIV/AIDS Vaccine Enterprise: Scientific Strategic Plan. http://medicine.plosjournals.org/archive/1549-1676/2/2/pdf/10.1371_journal.pmed.0020025-S.pdf. Accessed on September 8, 2005.

22. World Health Organization. Roll Back Malaria. http://www.rbm.who.int/cmc_upload/0/000/015/367/RBMInfosheet_6.htm. Accessed on September 8, 2005.

23. Gardner, M.J., N. Hall, E. Fung, et al. 2002. Genome Sequence of the Human Malaria Parasite *Plasmodium falciparum*. *Nature* 419:498–511.

24. Holt, R., G.M. Subramanian, A. Halpern, et al. 2002. The Genome Sequence of the Malaria Mosquito *Anopheles gambiae*. *Science* 298:129–49.

25. Alonso, P.L., J. Sacaral, J.J. Aponte, et al. 2004. Efficacy of the RTS, S/AS02A Vaccine against *Plasmodium falciparum* Infection and Disease in Young African Children: Randomized Controlled Trial. *Lancet* 364:1411–20.

26. World Health Organization. Tuberculosis Fact Sheet. http://www.who.int/mediacentre/factsheets/fs104/en/. Accessed on September 8, 2005.

27. World Health Organization. Influenza Fact Sheet. http://www.who.int/mediacentre/factsheets/fs211/en/. Accessed on September 8, 2005.

28. Centers for Disease Control and Prevention. 2004. Fact Sheet: Key Facts about the Flu and Flu Vaccine. http://www.cdc.gov/flu/keyfacts.htm. Accessed on September 8, 2005.

29. World Health Organization. 2005. Avian Influenza: Assessing the Pandemic Threat. http://www.who.int/csr/disease/influenza/WHO_CDS_2005_29/en/. Accessed on September 8, 2005.

30. World Health Organization. Avian Influenza. http://www.who.int/csr/disease/avian_influenza/en/. Accessed on September 8, 2005.

31. Ungchusak, K., P. Auewarakul, S.F. Dowell, et al. 2005. Probable Person-to-Person Transmission of Avian Influenza A (H5N1). *New England Journal of Medicine* 352:333–40.

32. Department of Health and Human Services. Pandemic Influenza Response and Preparedness Plan. http://www.hhs.gov/nvpo/pandemicplan/. Accessed on September 8, 2005.

33. World Health Organization. SARS: Breaking the Chain of Transmission. http://www.who.int/features/2003/07/en/. Accessed on September 8, 2005.

34. National Institute of Allergy and Infectious Diseases. Factsheet: NIAID Research on Severe Acute Respiratory Syndrome (SARS). http://www.niaid.nih.gov/factsheets/sars.htm. Accessed on September 8, 2005.

35. Komar, N. 2003. West Nile Virus: Epidemiology and Ecology in North America. *Advances in Virus Research* 61:185–234.

36. Centers for Disease Control and Prevention. West Nile Virus. http://www.cdc.gov/ncidod/dvbid/westnile/index.htm. Accessed on September 8, 2005.

37. National Institutes of Allergy and Infectious Diseases. Factsheet: NIAID Research on West Nile Virus. http://www.niaid.nih.gov/factsheets/westnile.htm. Accessed on September 8, 2005.

38. Peters, C.J. 2005. Marburg and Ebola: Arming Ourselves against the Deadly Filoviruses. *New England Journal of Medicine* 352:2571–73.

39. Jernigan, D.B., P.L. Raghunathan, B.P. Bell, et al. 2002. Investigation of Bioterrorism-Related Anthrax, United States, 2001: Epidemiologic Findings. *Emerging Infectious Diseases* 8:1019–28.

40. Hirschberg, R., J. La Montagne, and A.S. Fauci. 2004. Biomedical Research — An Integral Component of National Security. *New England Journal of Medicine*. 350:2119–21.

41. Meadows, M. 2004. Project Bioshield: Protecting Americans from Terrorism. *FDA Consumer* 38:32–33.

42. Yang H, S.K. Kim, M. Kim, et al. 2005. Antiviral Chemotherapy Facilitates Control of Poxvirus Infections through Inhibition of Cellular Signal Transduction. *The Journal of Clinical Investigation* 115:379–87.

43. Lederberg, J. 2000. Infectious History. *Science* 288:287–93.

ABOUT THE AUTHOR

Dr. Anthony S. Fauci, a native of Brooklyn, New York, received his MD degree from Cornell University Medical College in 1966. He then completed an internship and residency at the New York Hospital — Cornell Medical Center. In 1968, Dr. Fauci came to the National Institutes of Health (NIH) as a clinical associate in the Laboratory of Clinical Investigation (LCI) at the National Institute of Allergy and Infectious Diseases (NIAID). In 1974, he became head of the Clinical Physiology Section, LCI, and in 1980 he was appointed chief of the Laboratory of Immunoregulation, a position he still holds. In 1984, Dr. Fauci became director of NIAID, where he oversees an extensive research portfolio of basic and applied research to prevent, diagnose, and treat infectious and immune-mediated illnesses, including HIV/AIDS and other sexually transmitted diseases; illness from potential agents of bioterrorism; tuberculosis; malaria; autoimmune disorders; asthma; and allergies. Dr. Fauci serves as one of the key advisors to the White House and the U.S. Department of Health and Human Services on global AIDS issues, and on initiatives to bolster medical and public health preparedness against possible future bioterrorist attacks.

Dr. Fauci has made many contributions to basic and clinical research on the pathogenesis and treatment of immune-mediated diseases. He has pioneered the field of human immunoregulation by making a number of basic scientific observations that serve as the basis for current understanding of the regulation of the human immune response. In addition, Dr. Fauci is widely recognized for delineating the precise mechanisms whereby immunosuppressive agents modulate the human immune response. He has developed effective therapies for formerly fatal diseases such as polyarteritis nodosa, Wegener's granulomatosis, and lymphomatoid granulomatosis. A 1985 Stanford University Arthritis Center Survey of the American Rheumatism Association ranked the work of Dr. Fauci on the treatment of polyarteritis nodosa and Wegener's granulomatosis as one of the most important advances in patient management in rheumatology over the previous 20 years.

Dr. Fauci has made seminal contributions to the understanding of how the AIDS virus destroys the body's defenses leading to its susceptibility to deadly infections. He has also delineated the mechanisms of induction of HIV expression by endogenous cytokines. Furthermore, he has been instrumental in developing strategies for the therapy and immune reconstitution of patients with this serious disease, as well as for a vaccine to prevent HIV infection. He continues to devote much of his research time to identifying the nature of the immunopathogenic mechanisms of HIV infection and the scope of the body's immune responses to the AIDS retrovirus.

Dr. Fauci is a member of the National Academy of Sciences, the American Academy of Arts and Sciences, the Institute of Medicine (council member), the American Philosophical Society, and the Royal Danish Academy of Science and Letters, as well as a number of other professional societies, including the American College of Physicians, the American Society for Clinical Investigation, the Association of American Physicians, the Infectious Diseases Society of America, the American Association of Immunologists, and the American Academy of Allergy, Asthma, and Immunology. He serves on the editorial boards of many scientific journals; as an editor of *Harrison's Principles of Internal Medicine*; and as author, coauthor, or editor of more than one thousand scientific publications, including several textbooks.

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