

Special Article

THE AIDS EPIDEMIC

Considerations for the 21st Century

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**H**UMANKIND has been besieged throughout its evolution by microorganisms that pose a continual challenge to the survival of the species.<sup>1</sup> Although such ancient killers as tuberculosis and malaria persistently take a toll of millions of lives per year, occasionally the emergence or reemergence of a microbe results in an unexpected, catastrophic pandemic with global public health consequences. As we prepare to leave the 20th century, it is worth reflecting on the fact that within the framework of an enormous but constant burden of a variety of infectious diseases, as well as a number of mini-epidemics, this century has witnessed two such unexpected cataclysmic events.

One, the influenza A pandemic of 1918, was due to an old, but reemerging microbe. Influenza had been a problem for centuries, but in that one winter of 1918–1919, it was responsible for the deaths of approximately 25 million people worldwide and 550,000 people in the United States.<sup>2</sup>

The other pandemic, the acquired immunodeficiency syndrome (AIDS), is due to a newly recognized microbe, the human immunodeficiency virus (HIV).<sup>3</sup> The world first became aware of this new disease in the summer of 1981, and it has exploded in successive waves in various regions of the world. Still, as we enter the 21st century, the catastrophic potential of the pandemic may still not have been fully realized. As we prepare to enter the new millennium, it is appropriate to reflect on the origins of this epidemic, what has occurred over the past 18 years, what has been accomplished from a scientific and public health perspective, and what the prospects are for the future.

THE ORIGINS OF HIV

Recent molecular epidemiologic data have clearly indicated that HIV type 1 (HIV-1) evolved with the *Pan troglodytes troglodytes* subspecies of chimpanzee and was present in that subspecies for centuries.<sup>4</sup> The virus apparently does not readily cause disease in the chimpanzee. As is the case with many viruses, HIV at a particular point (or points) in time “jumped” species to infect human beings; hence, it almost certainly originated as a zoonotic infection. HIV type 2, the less prevalent and less virulent species of HIV,

is remarkably similar genetically to the simian immunodeficiency virus that is endemic among sooty mangabeys.<sup>5</sup>

The most likely mechanism of transmission of HIV-1 from chimpanzees to humans was by contamination of a person’s open wound with the infected blood of a chimpanzee, probably when the chimpanzee was being butchered for the purposes of consumption.<sup>6</sup> Chimpanzees have traditionally served as a source of nutrition for humans in certain parts of sub-Saharan Africa. Any of a number of mutations in the viral genome that would have allowed successful transmission of the virus from chimpanzees to humans probably took place intermittently over the centuries.<sup>4</sup> Indeed, it is likely that sporadic cases of transmission to humans were continually occurring unnoticed over the course of decades, and perhaps centuries.

As with other microbes, transmission may not result in an epidemic unless certain conditions are present.<sup>1</sup> An intermittent HIV infection in a rural village in Africa might have been passed on to an infected person’s sexual partner and would probably have resulted in the deaths of the infected persons without further spread, thus representing a dead end for the virus. Only when demographic and social conditions allowed rapid spread of the virus among people did an epidemic actually begin to emerge. These conditions included massive migration from rural areas to urban areas; the breakup of family units due to the migratory nature of employment opportunities, with its attendant sexual promiscuity and extensive frequenting of commercial sex workers; and contamination of the blood supply.<sup>7</sup>

Such were the seeds of the epidemic in Africa. The introduction of the epidemic to developed countries, such as the United States, followed relatively soon after the “gay revolution” that had its origins in the riot at the Stonewall Inn, a bar frequented by homosex-

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ual men, in New York City in 1969.<sup>8</sup> The demographic setting of the high-risk homosexual practices that were concentrated in cities such as New York, San Francisco, and Los Angeles in the 1970s and early 1980s unfortunately made this population of predominantly young adults a perfect target for an epidemic of sexually transmitted disease. Similar patterns soon followed in other developed countries, such as Canada, Australia, and those of western Europe.

#### SCOPE OF THE EPIDEMIC

AIDS continues to exact an enormous toll throughout the world, in both human and economic terms. In the United States, an estimated 650,000 to 900,000 people are infected with HIV,<sup>9</sup> of whom more than 200,000 are unaware of their infection.<sup>10</sup> Through 1998, 688,200 cumulative cases of AIDS and 410,800 AIDS-related deaths had been reported to the Centers for Disease Control and Prevention (CDC).<sup>11</sup>

The demographic characteristics of those affected by the epidemic have changed dramatically since the first cases were reported in 1981. Unlike the early days of the HIV and AIDS epidemic in the United States, when the affected population consisted overwhelmingly of homosexual men, leading some to assume incorrectly that the epidemic would remain contained within the gay population, today new cases of HIV infection result predominantly from injection-drug use and heterosexual contact, with a disproportionate representation among minority populations.<sup>11</sup> The numbers of cases of AIDS (per 100,000 population) reported in 1998 in the United States were 66.4 for non-Hispanic blacks, 28.1 for Hispanics, 8.2 for non-Hispanic whites, 7.4 for American Indians and Alaska Natives, and 3.8 for Asians and Pacific Islanders. Women are increasingly affected; the proportion of U.S. cases reported among women and adolescent girls more than tripled between 1985 and 1998, from 7 percent to 23 percent.<sup>11</sup>

It is often said that the HIV and AIDS epidemic in the United States and other developed countries has reached a plateau, since the number of new infections per year is no longer on an accelerating trajectory but has leveled off. However, in the United States it is estimated that this plateau has reached an unacceptable level of 40,000 new infections per year, a rate that is believed to have remained relatively constant throughout the 1990s.<sup>12</sup> Of these newly infected people, the CDC estimates that half are younger than 25 years of age and were infected sexually.<sup>13</sup> As the number of new cases per year among homosexual men has decreased dramatically, the number of new infections among heterosexuals, particularly among women, has accelerated greatly, producing a deceptive plateau. In the United States we are in fact seeing new waves of the epidemic among different demographic groups.

The same phenomenon of successive waves is reflected dramatically in the global pattern of the epidemic, with sub-Saharan Africa currently bearing the greatest burden of the epidemic worldwide.<sup>14</sup> In addition, the number of HIV infections in the countries of the former Soviet Union has escalated sharply over the past few years.<sup>14</sup> However, the trajectory of the infection rate in the Indian subcontinent and Southeast Asia indicates that without dramatically successful preventive measures, these regions will bear the greatest burden of the epidemic as we enter the 21st century.<sup>14</sup> The estimated number of infections in China is still relatively low; however, there is potential for an explosive spread of HIV in that nation of more than 1 billion people.

The magnitude of the epidemic is huge. As of the end of 1998, there were more than 33 million people worldwide with HIV infection or AIDS, 43 percent of them female, according to estimates by the Joint United Nations Programme on HIV/AIDS (UNAIDS).<sup>14</sup> An estimated 5.8 million new HIV infections occurred worldwide during 1998 — approximately 16,000 each day. More than 95 percent of these new infections occurred in developing countries. In 1998, HIV infection or AIDS was the fourth leading cause of death worldwide, resulting in an estimated 2.3 million deaths.<sup>15</sup> If the current trend in the incidence of HIV infection continues, more than 40 million people will be infected with HIV as we enter the new millennium.

In addition to the enormous human tragedy associated with HIV and AIDS, the economic costs of the epidemic are staggering, posing a serious impediment to the growth and economic stability of many developing countries. It is estimated that the annual economic burden of HIV infection is \$14 billion for costs associated with prevention and treatment alone.<sup>16</sup> In many countries, the epidemic is depleting a limited pool of skilled workers and managers and will neutralize previously realized gains in development by slashing life expectancy. According to the United Nations Population Division, by 2010 to 2015 life expectancy in the nine countries in Africa with the highest prevalence of HIV infection will fall on average by 16 years.<sup>17</sup> It is also clear that this epidemic will produce political instability in some nations and in communities within these nations.

#### THE SUCCESSES AND LIMITATIONS OF ANTIRETROVIRAL THERAPY

In the United States and other developed countries, the numbers of new AIDS diagnoses and deaths have fallen substantially during the past three years. The age-adjusted death rate from AIDS declined 48 percent from 1996 to 1997<sup>18</sup>; similar decreases have been noted in western Europe and Australia.<sup>19,20</sup> These trends are due to several factors, including improved prophylaxis against opportunistic infections and im-

proved treatment, the growing experience among health professionals in caring for HIV-infected patients, improved access to health care, and the decrease in the number of new HIV infections due to prevention efforts and to the fact that a substantial proportion of persons with high-risk behavior are already infected.

However, the most influential factor has clearly been the increased use of potent anti-HIV drugs, generally administered in combinations of three or more agents and usually including a protease inhibitor.<sup>19,21-23</sup> Such combinations are known as highly active antiretroviral therapy. The development of therapies for HIV infection has been remarkably successful, reflecting an effective synergy among government, industry, and academia. Sixteen anti-HIV drugs are now licensed by the Food and Drug Administration. These drugs have had dramatic effects in reversing the extent of illness in many patients with advanced disease, as well as in preventing the progression of disease in those who are relatively healthy.

Consensus guidelines have been developed for the use of highly active antiretroviral therapy in adults and adolescents, as well as in children and in HIV-infected pregnant women.<sup>24-26</sup> These guidelines, when appropriately applied, have greatly improved the prognosis for HIV-infected people and have markedly reduced the risk of HIV transmission from mother to baby.

Despite the enormous beneficial effects of highly active antiretroviral therapy, many HIV-infected people have unfortunately not had adequate responses to the regimens, cannot tolerate the toxic effects, or have difficulty complying with treatment that involves large numbers of pills, myriad interactions with other drugs, and complicated dosing schedules in which intake of food and liquids must be taken into account.<sup>24</sup> Even in patients who are successfully treated with highly active antiretroviral therapy and have extremely low levels of HIV-1 RNA in plasma, the virus persists in sanctuaries where the drugs cannot reach it or in a latent form on which drugs have no effect.<sup>27-30</sup> In addition, the emergence of strains of HIV that are resistant to currently available drugs is a widespread and growing problem.<sup>31</sup>

Although there is evidence of improvement in immune-system function in most patients who receive combination antiretroviral therapy, complete normalization of the immune system and complete eradication of the virus from the body appear unlikely with currently available therapies. The persistence of latent HIV despite therapy that successfully suppresses detectable levels of HIV-1 RNA in plasma is particularly problematic and suggests that lifelong treatment may be necessary with drugs that are currently expensive and difficult to tolerate for prolonged periods.<sup>32-36</sup> In patients in whom plasma HIV-1 RNA had been suppressed by highly active antiretroviral therapy to below detectable levels for a median of

390 days, levels invariably rebounded within 3 weeks after the cessation of therapy.<sup>37</sup>

Therefore, the development of a new generation of therapies remains a major priority. Currently, all licensed antiretroviral medications are directed at one of two viral enzymes, reverse transcriptase or protease. Many new treatment strategies are being developed and tested, including the use of drugs that prevent the virus from entering a cell and those that prevent the integration of the provirus into nuclear DNA. In addition, approaches to purging the virus from its latent reservoirs in certain cells and tissues are being vigorously pursued, as are methods to boost HIV-specific immune responses.<sup>38</sup>

### PREVENTION OF HIV INFECTION

In developing countries in which the per capita allocation for health care spending may be only a few dollars a year, anti-HIV therapies are invariably beyond the reach of all but the privileged few. This situation underscores the need for effective, low-cost tools for HIV prevention that can be used in these settings as well as in the United States and other developed countries. Even if such therapies were feasible on a global scale, it is clear that treatment is not the solution to the global HIV problem. Unlike microbial scourges, such as malaria and tuberculosis (among many others), for which there is very little that people can do to prevent infection, HIV infection in adults is entirely preventable by behavior modification. Researchers have shown that several approaches to prevention, when properly executed, can be effective. These approaches include education and behavior modification, the promotion and provision of condoms, the treatment of other sexually transmitted diseases, drug-abuse treatment (for example, methadone maintenance for injection-drug users), access to clean needles and syringes for injection-drug users, and the use of antiretroviral drugs to interrupt the transmission of the virus from mother to infant.<sup>39</sup>

The use of antiretroviral drugs in pregnant women with HIV infection and their infants is an extraordinarily successful prevention strategy.<sup>40</sup> The rate of mother-to-child transmission of HIV in the United States has been cut to negligible levels among women and infants treated with an extended regimen of zidovudine therapy. Recent studies by the CDC, the National Institutes of Health (NIH), and others have shown that substantially shorter regimens of antiretroviral drugs, which would be more feasible in poorer countries, can also reduce perinatal HIV transmission dramatically.<sup>41,42</sup> A brief and affordable regimen of therapy administered to the mother around the time of delivery could potentially prevent HIV infection in hundreds of thousands of babies per year. An interim analysis of a study in Uganda indicates that two doses of nevirapine — one given to

the mother at the onset of labor and one given to the infant within 72 hours after birth — can markedly reduce the incidence of perinatal transmission of HIV.<sup>43</sup>

Other methods of preventing HIV transmission may also help slow the epidemic of HIV and AIDS. For example, researchers are developing and testing topical microbicides, substances that a woman could use in her vagina before sexual intercourse to prevent the transmission of HIV and other sexually transmitted diseases.<sup>44</sup> UNAIDS and other organizations have also facilitated the widespread use of the female condom in Africa. These interventions may help empower women to protect themselves in situations in which they are unable to avoid sexual relations with HIV-infected partners or cannot persuade their partners to use a condom. This latter issue reflects the relation between the prevention of HIV transmission and human rights that was eloquently articulated by the late Jonathan Mann.<sup>45</sup>

#### DEVELOPMENT OF AN HIV VACCINE

Historically, vaccines have provided a safe, cost-effective, and efficient means of preventing illness, disability, and death from infectious diseases.<sup>46</sup> The solution to the HIV pandemic is the development and availability of a safe and effective vaccine against the infection. Indeed, such a goal remains the highest priority of AIDS research. A major scientific obstacle to the accomplishment of this goal has been the difficulty in establishing the precise correlates of protective immunity against HIV infection. To speed the pace of discovery, many public and private agencies have dramatically increased the resources devoted to research on HIV vaccines. For example, at the NIH, funding for HIV-vaccine research rose from \$100.5 million in fiscal year 1995 to an estimated \$194.1 million in fiscal year 1999. To date, more than 3000 uninfected volunteers have enrolled in more than 50 HIV-vaccine studies sponsored by the NIH (including two phase 2 intermediate-sized trials), involving 27 vaccines.

As part of a broad portfolio of research, recent NIH-supported studies have assessed so-called vectored vaccines: harmless viruses (e.g., canarypox) that are genetically altered to make HIV proteins. These vaccines have been administered to volunteers in combination with a separate vaccine made of a purified HIV envelope protein. Results have been encouraging. In phase 1 and phase 2 studies, the combination approach has appeared safe and has evoked both cellular and humoral immune responses that may have a role in providing protection from HIV infection.<sup>47</sup> Three vectors, as well as other HIV proteins, are currently being compared to determine which combination produces the most vigorous immune response.

Meanwhile, a large-scale study of a vaccine based

on the surface proteins of two strains of HIV was recently undertaken in the United States by a private company, with an additional phase 3 study to be conducted in Thailand.<sup>48</sup> Finally, a phase 1 trial of canarypox-vectored vaccine for HIV infection has been initiated in Uganda in a growing effort to involve scientists from developing countries in the research effort.

#### CONCLUSIONS

The HIV pandemic has posed a formidable challenge to the biomedical-research and public health communities of the world. What began as a handful of recognized cases among homosexual men in the United States has become a global pandemic of such proportions that it clearly ranks as one of the most destructive microbial scourges in history. We are at a pivotal point in the evolution of this historic event as we enter the new millennium. Biomedical research has provided the tools for the development of treatments as well as a still elusive vaccine. It has become apparent over the past few years that minimizing the destructive impact of this epidemic will require partnerships between the public and private sectors as well as a stronger political will among the nations of the world. Unless methods of prevention, with or without a vaccine, are successful, the worst of the global pandemic will occur in the 21st century.

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