1. Acquired Immune Deficiency Syndrome (AIDS)

Acquired immune deficiency syndrome (AIDS), first identified in 1981, is an infectious disease characterized by failure of the body's immunologic system. Affected individuals become increasingly vulnerable to many normally harmless microorganisms, eventually leading to severe morbidity and high mortality. The infection, spread sexually and through blood, has a high fatality rate, approaching 100 percent. Caused by a human retrovirus known as HIV-1, AIDS can now be found throughout the world – in both industrialized countries and developing nations. Public-health officials throughout the world have focused attention on this pandemic and its potentially catastrophic impact on health, resources, and social structure. Treatments for the disease have been developed, but no cure or vaccine currently exists.

Characteristics

Beginning in the late 1970s, physicians in New York and California reported increasing incidence of a rare cancer, **Kaposi's sarcoma**, and a variety of infections including **pneumocystis pneumonia** among previously healthy young homosexual men. Because of the unusual character of these diseases, which are typically associated with failure of the immune system, epidemiologists began seeking clues that might link these cases. AIDS was first formally described in 1981, although it now appears that the virus causing the disease was silently spreading in a number of populations during the previous decade. Early epidemiological studies suggested that homosexual men, blood recipients (especially hemophiliacs), and intravenous drug users were at greatest risk. Research focused on searching for an infectious agent transmitted sexually or through blood. In 1983, in French and American laboratories, an unknown human retrovirus was identified and named HIV-1 for "human immunodeficiency virus." Although the biological and geographic origins of the organism remain obscure, the AIDS epidemic appears to mark the first time it has spread widely in human populations. No evidence exists for casual transmission of HIV.

Following identification of HIV-1, tests to detect antibodies against it were devised in 1984. Although these tests do not detect the virus itself, they are generally effective in identifying infection because high levels of antibody are produced in most infected individuals. The enzyme-linked immunosorbent assay (ELISA), followed by Western blot testing, has enabled the screening of donated blood to protect the blood supply from HIV, as well as testing for epidemiological and diagnostic purposes.

As **HIV infection** precedes the development of AIDS, often by several years, the precise parameters of the epidemic have been difficult to define. Although "cofactors" that may determine the onset of symptoms remain unknown, evidence suggests that HIV-infected individuals will eventually develop AIDS.

Researchers have identified three epidemiological patterns of HIV transmission, which roughly follow geographic boundaries. Pattern I includes North America, Western Europe, Australia, New Zealand, and many urban centers in Latin America. In these industrial, highly developed areas, transmission has been predominantly among homosexual and bisexual men. Since the introduction of widespread blood screening, transmission via blood in

these areas now occurs principally among intravenous drug users who share injection equipment. Although little evidence exists of widespread infection among heterosexuals in these countries, heterosexual transmission from those infected intravenously has increased, leading to a rise in pediatric cases resulting from perinatal transmission.

Within the United States, distribution of AIDS has been marked by disproportionate representation of minorities and the poor. As the principal mode of transmission has shifted to intravenous drug use, AIDS has increasingly become an affliction of the urban underclass. Surveys reveal that 50 percent or more of intravenous drug users in New York City are infected with HIV. Women are typically infected by intravenous drug use or by sexual contact with a drug user.

In pattern II countries, comprised of sub-Saharan Africa and, increasingly, Latin America, transmission of HIV occurs predominantly through heterosexual contact. In some urban areas in these countries, up to 25 percent of all sexually active adults are reported to be infected, and a majority of female prostitutes are seropositive. Transfusion remains a mode of transmission because universal blood screening is not routine. Unsterile injections and medical procedures may also contribute to the spread of infection. In these areas, perinatal transmission is an important aspect of the epidemic.

Pattern III countries, including North Africa, the Middle East, Eastern Europe, Asia, and the Pacific, initially experienced less morbidity and mortality from the pandemic. Apparently, HIV-1 was not present in these areas until the mid-1980s. The nature of world travel, however, has diminished the significance of geographic isolation as a means of protecting a population from contact with a pathogen.

In 1985, a related virus, HIV-2, was discovered in West Africa. Although early reports suggested that HIV-2 is less pathogenic, the natural history of this agent remains unclear, as does its prevalence.

HIV cripples the body's immunologic system, making an infected individual vulnerable to other disease-causing agents in the environment. The most common of these opportunistic infections in AIDS patients has been pneumocystis pneumonia, previously seen principally in patients receiving immunosuppressive drugs. In addition to pneumocystis, AIDS patients are prone to other infectious agents such as **cytomegalovirus**, *Candida albicans* (a yeastlike fungus), and *Toxoplasma gondii* (a protozoan parasite). Moreover, a resurgence of **tuberculosis** has been reported in nations with high AIDS incidence.

Immunologic damage occurs by depletion of a specific type of white blood cell called a helper T4 lymphocyte. Destruction of these cells accounts for the vulnerability to normally harmless infectious agents. In some cases, infection of the central nervous system with HIV may cause damage to the brain and spinal column, resulting in severe cognitive and motor dysfunction. In its late manifestations, AIDS causes severe wasting. Death may occur from infection, functional failure of the central nervous system, or starvation.

HIV infection has a wide spectrum of clinical manifestations. After infection, an individual may remain free of symptoms for years, even a decade or longer. Some individuals experience fever, rash, and malaise at the time of infection when antibodies are first produced. Patients commonly present with general **lymphadenopathy**, weight loss, diarrhea, or an opportunistic infection. Diagnosis is confirmed by finding antibodies for HIV or by a decline in T4 cells. Most experts now agree that HIV infection itself be considered a disease, regardless of symptoms.

Because the virus becomes encoded within the genetic material of the host cell and is highly mutable, the problem of finding safe and effective therapies has been extremely difficult. Studies have attempted to determine the anti-HIV properties of many drugs, but the ethical and economic obstacles to clinical trials with experimental drugs are formidable. Given the

immediacy of the epidemic, it is difficult to structure appropriate randomized clinical trials, which often take considerable time, to assess the safety and efficacy of a drug. Since the beginning of the epidemic, clinical research has refined the treatment of opportunistic infections.

History

In its first decade, AIDS created considerable suffering and generated an ongoing worldwide health crisis. During this brief period, the epidemic was identified and characterized epidemiologically, basic modes of transmission specified, a causal organism isolated, and effective tests for infection developed. In spite of this remarkable progress, which required the application of sophisticated epidemiological, clinical, and scientific research, the barriers to controlling AIDS are imposing and relate to the most complex biomedical and political questions. AIDS has already sorely tested the capabilities of research, clinical, and public-health institutions throughout the world.

Because HIV is related to other recently isolated primate retroviruses, such as simian T lymphotropic virus (STLV)-III in African green monkeys, many have speculated that HIV originated in Africa. Antibodies to HIV were discovered in stored blood dating back to 1959 in Zaire. According to experts, it is likely that HIV has existed for many years in isolated groups in central Africa. Because outside contacts were minimal, the virus rarely spread, and epidemics could not be sustained. Once a sizable reservoir of infection was established, however, HIV became pandemic. As with other sexually transmitted diseases, such as **syphilis**, no country wished the stigma of association with the virus's "origin."

The epidemic began at a moment of relative complacency, especially in the developed world, concerning epidemic infectious disease. Not since the **influenza** of 1918–20 had an epidemic appeared with such devastating potential. The developed world had experienced a health transition from infectious to chronic disease and had focused its resources and attention on systemic, noninfectious ailments. Thus, AIDS appeared at a historical moment comprising little social or political experience in confronting such a public-health crisis. The epidemic fractured a widely held belief in medical security.

Not surprisingly, early sociopolitical responses were characterized by denial. Initial theories, when few cases had been reported, centered on aspects of "fast-track" gay sexual culture that might explain the outbreak of immune-compromised men. Additional cases among blood recipients, however, soon led the U.S. Centers for Disease Control and Prevention to the conclusion that an infectious agent was the likely link. Nevertheless, in the earliest years of the epidemic, few wished to confront openly the possibility of spread beyond the specified "high-risk" groups. During this period, when government interest and funding lagged, grassroots organizations, especially in the homosexual community, were created to meet the growing need for education, counseling, patient services, and – in some instances – clinical research. Such groups worked to overcome the denial, prejudice, and bureaucratic inertia that limited governmental response.

As the nature and extent of the epidemic became clearer, however, hysteria sometimes replaced denial. Because the disease was powerfully associated with behaviors identified as immoral or illegal (or both), the stigma of those infected was heightened. Victims were often divided into categories: those who acquired their infections through transfusions or perinatally, the "innocent victims"; and those who engaged in high-risk, morally condemnable behaviors, the "guilty perpetrators" of disease. Since the early recognition of behavioral risks for infection, there has been a tendency to blame those who became infected through drug use or homosexuality, behaviors viewed as "voluntary." Some religious groups in the United States and elsewhere saw the epidemic as an occasion to reiterate particular moral views about sexual behavior, drug use, sin, and disease. AIDS was viewed as "proof" of a certain moral order.

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AIDS victims have been subjected to a range of discriminatory behavior, including loss of employment, housing, and insurance. Since the onset of the epidemic, violence against gays in the United States has increased. Despite the well-documented modes of HIV transmission, fears of casual transmission persist. In some communities, parents protested when HIV-infected schoolchildren were permitted to attend school. In one instance, a family with an HIV-infected child was driven from a town by the burning of their home.

By 1983, as potential ramifications of the epidemic became evident, national and international scientific and public-health institutions began to mobilize. In the United States, congressional appropriations for research and education began to rise significantly. The National Academy of Sciences issued a consensus report on the epidemic in 1986. A presidential commission held public hearings and eventually issued a report calling for protection of AIDS sufferers against discrimination and a more extensive federal commitment to drug treatment. The World Health Organization (WHO) established a Global Program on AIDS in 1986 to coordinate international efforts in epidemiological surveillance, education, prevention, and research.

Despite growing recognition of the epidemic's significance, considerable debate continued over the most effective public-health responses. Although some nations – such as Cuba – experimented with programs mandating isolation of HIV-infected individuals, the World Health Organization lobbied against coercive measures. Given the lifelong nature of HIV infection, effective isolation would require lifetime incarceration. With the available variety of less restrictive measures, most nations rejected quarantine as both unduly coercive and unlikely to achieve control. Traditional public-health approaches to communicable disease, including contact tracing and mandatory treatment, have less potential for control because no means exist to render an infected individual noninfectious.

Because biomedical technologies to prevent transmission appear to be some years away, the principal public-health approaches to controlling the pandemic rest on education and behavior modification. Heightened awareness of the dangers of unprotected anal intercourse among gay men, for example, has led to a significant decline in new infections among this population. Nevertheless, as many public-health officials have noted, encouraging the modification of risk behaviors, especially those relating to sexuality and drug abuse, presents no simple task, even in the face of a dread disease.

In the developing world, AIDS threatens to reverse recent advances in infant and child survival. The epidemic is likely to have a substantial impact on demographic patterns. Because the disease principally affects young and middle-aged adults (ages 20–49), it has already had tragic social and cultural repercussions. Transmitted both horizontally (via sexual contact) and vertically (from mother to infant), it has the potential to depress the growth rate of human populations, especially in areas of the developing world. In this respect, the disease could destabilize the work force and depress local economies.

AIDS has clearly demonstrated the complex relationship of biological and behavioral forces in determining patterns of health and disease. Altering the course of the epidemic by human design has already proved to be no easy matter. The lifelong infectiousness of carriers; the private, biopsychosocial nature of sexual behavior and drug abuse; and the stigma already attached to those at greatest risk – all have made effective public policy intervention even more difficult. Finally, the very nature of the virus itself – its complex and mutagenic nature – makes a short-term technological breakthrough unlikely.

The remarkable progress in understanding AIDS is testimony to the sophistication of contemporary bioscience; the epidemic, however, is also a sobering reminder of the limits of that science. Any historical assessment of the AIDS epidemic must be considered provisional.

Nevertheless, it is already clear that AIDS has forced us to confront a new set of biological imperatives.

Allan M. Brandt

Postscript

By way of a caveat, recent estimates of the number of HIV/AIDS infections, the competing theories of origin, conflicting interpretations of new evidence, and announcements of therapeutic and preventive progress are sometimes contradictory and thus constitute especially treacherous terrain.

Beginning with the estimates, in June of 1990 the WHO estimated that there were some 8 million HIV cases worldwide; the following year that estimate was raised to between 10 million and 12 million. Toward the end of the decade the WHO warned that the number of cases would reach between 20 million and 30 million cases by the year 2000. In retrospect, it seems that this estimate was much too conservative; by 1997 the number of cases already exceeded 30 million. By 2001, HIV had infected some 56 million individuals worldwide and killed more than 20 million of them. Left behind were an estimated 36 million living with HIV/AIDS and millions more expected to become infected in the early years of the twenty-first century.

Of the 30 million cases in 1997, almost 21 million were in sub-Saharan Africa alone (where in some places, such as Botswana, upwards of 36 percent of the adult population has become infected with HIV), while South and Southeast Asia and the Pacific accounted for another 6 million cases. In all, the developing world contained 95 percent of the cases, and in 1998 it was estimated that 70 percent of all new infections and 80 percent of all AIDS deaths occurred in sub-Saharan Africa. By 2001, average life expectancy south of the Sahara had declined by 10 years and infant death rates had doubled. Illustrative of the impact of AIDS mortality is the example of Zambia, where a dire shortage of schoolteachers has developed because they are dying of AIDS faster than replacements can be trained.

In the United States – although the millions of cases of HIV infection that had been gloomily predicted by some did not materialize – 774,647 cases were reported between 1981 and 2001, and there were 448,060 deaths. By age and sex, the breakdown of those infected was 79 percent adult males, and by ethnicity 61 percent were black or Hispanic. The major avenues of transmission have been through male homosexual contact (48 percent) and intravenous drug abuse (26 percent), although HIV infection via heterosexual contact – generally between infected males and uninfected females – is on the rise. Today the fastest growing groups of newly infected individuals are reported to be women and their children, and gay black males – the latter group accounting for 42 percent of all new infections. The U.S. cases are almost all HIV-1. Despite fears of HIV-2 also spreading in North America, only 64 cases have been documented, and these were all directly linked with West Africa.

Among HIV/AIDS researchers a consensus gradually emerged that **simian immunodeficiency virus** (SIV) had somehow managed to jump the species barrier from African primates (for whom it seems to be a relatively benign infection) to first infect humans in Central and West Africa and, somewhere along the line, became human immunodeficiency virus or HIV-1 and its subtypes (the most common form worldwide) and HIV-2.

Another question had to do with how the species barrier was hurdled. Again a consensus took shape; SIV had entered the blood of Africans engaged in chimpanzee butchering, after which it became HIV-1 (although the possibility of SIV evolving into HIV in the chimpanzee was not ruled out). Moreover, lineages of HIV transmitted by sooty mangabeys (also called the green monkey) were believed to have reached humans in like fashion to become HIV-2. Some, however, suspected that medicine had something to do with HIV becoming a human

infection and, therefore, that AIDS had an iatrogenic or medical cause.

Initially, the WHO **smallpox** vaccination campaign in Africa from 1967 to 1980 came under scrutiny for the possibility that HIV had been propelled through countless bodies with the repeated use of inadequately sterilized needles, or even that the vaccine had been contaminated. These hypotheses, of course, dealt with HIV transmission and did not really confront the question of its origin. Another hypothesis, however, did – this one focusing on the **polio** vaccination campaign conducted in Africa (and elsewhere) during the late 1950s. In the (then Belgian) Congo, chimpanzee kidneys were used to culture the poliovirus, which in turn, it was argued, could have contaminated the oral polio vaccine used in a widespread vaccination effort during 1957–58. Buttressing the case was that this region subsequently became the major epicenter of the burgeoning AIDS epidemic. Also bolstering it was the announcement in 1999 by a group of University of Alabama researchers that they had determined that a kind of chimpanzee once common in West Africa was indeed the source of HIV.

Yet other recent evidence was not so supportive. Most recently, in 2001, it was announced that a vial of the suspected polio vaccine had been found and that analysis had revealed no trace of HIV. Moreover, a study published in 2000 in *Science* had already cast considerable doubt on the contaminated vaccine hypothesis by showing that HIV-1 may well have been present in human African populations since at least the 1930s – almost 30 years before the polio vaccination campaign in the Congo. That date, however, is for the time that the HIV-1 group of viruses began to diversify, and not for when they were transmitted to humans. Thus, vital questions of transmission and origin remain unresolved – that of origin because even if chimpanzees did pass on HIV to humans, they may also have been infected from yet another source.

Great strides have been made recently toward the goals of treatment and prevention. In 1986, the drug azidothymidine (AZT) was shown to extend the period of latency for AIDS. It is one of five drugs called nucleosides licensed by the U.S. Food and Drug Administration, all of which are inhibitors of the viral enzyme reverse transcriptase (RT), which performs reverse transcription – the conversion of RNA into DNA that HIV must undergo to be infective. In the second half of the 1990s, protease inhibitors (which cripple a viral enzyme vital to HIV reproduction) came into use and two nucleoside inhibitors and one protease inhibitor were blended together into what was called the "antiviral cocktail." The results were miraculous. Individuals on the verge of death were going back to jobs and resuming normal lives, the mortality rate from AIDS in the United States fell dramatically, and it seemed that a major battle against the disease had been won.

But it was an incomplete victory, because the "cocktail" can produce unpleasant side effects, and just one missed dose can give the virus the opportunity to quickly mutate into a strain that resists the drugs. In fact, drug-resistant strains of HIV are already complicating AIDS treatment, which has led to different combinations of "cocktail" ingredients, each of which interferes with certain steps in the HIV infection process. Still other drugs have been brought effectively to bear on some of the "killer" opportunistic infections such as pneumocystis pneumonia and tuberculosis, which are the principal cause of AIDS deaths worldwide. But whether the miracle will continue indefinitely remains to be seen. The therapy is new and consequently the long-term success rate is unknown. Moreover, a per-patient annual cost of some 10,000–12,000 U.S. dollars limits this costly drug treatment to a relatively few victims in the developed world. Thus far, pressure on pharmaceutical manufacturers to make low- or no-cost drugs available to the developing world's millions stricken with HIV/AIDS has produced little in the way of results.

Work is also being done to develop a vaccine that could be both protective by preventing infection and therapeutic for those infected,

by prolonging survival and decreasing immune system destruction. At the turn of the twenty-first century, vaccines were being tested that had proven effective in protecting monkeys from HIV, and large-scale trials were under way to test them for human safety. In addition, Merck and Company, with its enormous resources, announced in 1999 that it would begin human trials on two vaccines. However, provided that a safe vaccine does become available, the problems of administering it – especially to the millions at high risk in the developing world – are daunting because it appears that one primary injection will be required, followed by three booster shots. The good news, of course, is that the question seems no longer to be whether there will be a vaccine, but rather when a vaccine will be available.

Moreover, gene therapy holds out promise of inhibiting HIV by introducing a gene into cells that interferes with the viral regulatory proteins, or even one that will protect cells from HIV infection. But all of these measures, even when they do bear fruit, will probably be too late to stop AIDS from becoming the biggest killer-disease in human history.

Kenneth F. Kiple

2. African Trypanosomiasis (Sleeping Sickness)

African trypanosomiasis, or "sleeping sickness," is a fatal disease caused by a protozoan hemoflagellate parasite, the trypanosome. It is transmitted through the bite of a tsetse fly, a member of the genus *Glossina*. Sleeping sickness is endemic, sometimes epidemic, across a wide band of sub-Saharan Africa, the so-called tsetse belt that covers some 11 million square kilometers. Although the disease was not scientifically understood until the first decade of the twentieth century, it had been recognized in West Africa as early as the fourteenth century.

Chemotherapy to combat trypanosomiasis has remained archaic, with no significant advances made and, indeed, very little research done between the 1930s and the 1980s. However, in the mid-1980s field trials of a promising new drug demonstrated its efficacy in late-stage disease when there is central nervous system involvement. In addition, there have been exciting recent developments in the field of tsetse eradication with the combined use of fly traps and odor attractants.

Characteristics

An acute form of sleeping sickness caused by *Trypanosoma brucei rhodesiense* with a short incubation period of 5–7 days occurs in eastern and southern Africa. A chronic form (*Trypanosoma brucei gambiense*) of western and central Africa can take from several weeks to months or even years to manifest itself. There are many species of tsetse flies, but only six act as vectors for the human disease. The *Glossina palpalis* group, or riverine tsetse, is responsible for the transmission of *T. b. gambiense* disease. The *Glossina morsitans* group, or savanna tsetse, is the vector for *T. b. rhodesiense*, the cause of the rhodesiense form of sleeping sickness. Although tsetse flies are not easily infected with trypanosomes, once infected they remain vectors of the disease for life.

After being bitten by an infected fly, most victims experience local inflammation, or the trypanosomal chancre; parasites migrate from this site to multiply in blood, lymph, tissue fluids, and eventually the cerebrospinal fluid. The blood trypanosome count oscillates cyclically, with each successive wave, manifesting different surface antigens. In this manner, trypanosomes evade the antibodies raised against them by the host. Eventually, all organs are invaded, with central nervous system involvement, ultimately leading to death.

The epidemiological pattern of sleeping sickness varies considerably from place to place, but two features are well recognized. First, trypanosomiasis is exceptionally focal, occurring at or around specific geographic locations; and second, the number of tsetse flies is apparently not as important for disease

incidence as is the nature of the human-fly contact.

The focal nature of sleeping sickness means that the ecological settings in which it occurs are of vital importance for understanding its epidemiology. Seemingly impossible to destroy, many historical foci tend to flare up in spite of concentrated eradication efforts since the 1930s. Very often, villages and regions that were affected decades ago remain problem areas today. The disease involves humans, parasites, tsetse flies, and wild and domesticated animals, and increasing population movements have complicated the epidemiology. Tsetse species have varying food preferences, ranging from the blood of wild and domestic animals to that of humans, but they require a daily blood meal, thereby making a single fly potentially highly infective.

Gambiense sleeping sickness is classically a disease of the frontier of human environments, where human-created habitat meets sylvan biotope. Humans are the principal reservoir of *T. b. gambiense*, and they maintain the typical endemic cycle of the disease. It is now known, however, that some animals, including domestic pigs, cattle, sheep, and even chickens, can act as reservoirs. The key to understanding the gambiense form is its chronicity and the fact that there are usually very low numbers of parasites present in the lymph and other tissue fluids. Gambiense disease can be maintained by a mere handful of peridomestic flies – that is, those that have invaded bush or cultivations near human settlements. This is known as close human-fly contact.

Riverine *G. palpalis* are most commonly found near waterways and pools; during dry seasons, when humans and flies are brought together through their shared need for water, the flies become particularly infective. Other common foci for the disease are sacred groves, which are often small clearings in the forest where the high humidity allows the flies to venture farther from water sources.

The virulent rhodesiense sleeping sickness is a true zoonosis maintained in wild animal reservoirs in the eastern African savannas. In the case of *T. b. rhodesiense*, the usual mammalian hosts are wild ungulates, with humans as adventitious hosts. Transmission of rhodesiense disease is more haphazard and directly relates to occupations such as searching for firewood, hunting, fishing, honey gathering, poaching, cultivation, cattle keeping, and being a game warden or a tourist. Whereas the gambiense form of the disease is site related, the rhodesiense form is occupation related, which helps to explain why the latter characteristically affects many more men and boys than women and girls. However, when a community moves near bush infested with infected flies, the entire population is at risk.

The animal reservoir of trypanosomes is an important factor in the epidemiology and history of sleeping sickness. It is well established that the trypanosomiases are ancient in Africa. Indeed, it is conjectured that the presence of sleeping sickness may explain why the ungulate herds of the African savanna have survived human predators for so long; the wild-animal reservoir of trypanosomes firmly restricted the boundaries of early human settlement. Although the wild ungulate herds became trypotolerant, domestic cattle still succumb to the disease, and the vast majority of research and funding has been aimed at solving the problem of animal – not human – sleeping sickness.

In evolutionary terms, the presence of trypanosomes in Africa may have precluded the development of some ground-dwelling faunas, thus encouraging certain resistant primates, including the early ancestors of humankind, to fill the empty ecological niches. If so, then humans were exposed to trypanosomal infection at the time of their very remote origin. The parasites are on the whole poorly adapted to humans, which accounts for the variety of clinical symptoms and ever-changing epidemiological patterns. A perfectly adapted parasite does not kill its host – at least in the short run.

An estimated 50 million people in 42 countries are at risk for trypanosomal infection, while it is estimated that only about 5 million to 10 million people have access to some form of

protection against or treatment for the disease. Sleeping sickness is endemic across the wide band of sub-Saharan Africa known as the "tsetse belt" lying roughly between 20° north and 20° south of the equator, where it also can attain epidemic proportions.

The actual number of cases will never be known, as it is a disease of remote rural areas, and even today people in such places often die undiagnosed and uncounted. Most national statistics are grossly underreported, with the World Health Organization being notified of about only 10 percent of new cases. The current estimate of incidence is 20,000 to 25,000 cases annually. Most of the victims are concentrated in Zaire, Uganda, and southern Sudan. Some villages had infection rates of up to 25 percent. In the late 1970s and 1980s, severe outbreaks occurred in Cameroon, Angola, the Central African Republic, the Ivory Coast, and Tanzania, as well as in Sudan, Zambia, Uganda, and Zaire.

Although trypanosomiasis has been studied for more than 80 years, much is still unknown about the pathology of the disease. Three phases follow the bite of an infected fly: first the chancre itself; then the hemolymphatic or "primary stage"; and finally the meningocephalitic or "secondary stage." On average, people infected with *T. b. gambiense* live 2–3 years before succumbing, although there are recorded cases of infection spanning as much as 2 decades. In contrast, infection with the more virulent *T. b. rhodesiense*, if untreated, usually leads to death within 6–18 weeks.

The disease manifests a bewildering array of clinical symptoms, which can vary from place to place. Progressing through the two stages, there is increasing parasitemia with eventual involvement of the central nervous system. Clinical symptoms can include fever, headache, and psychiatric disorders such as nervousness, irascibility, emotionalism, melancholia, and insomnia, which reflect neuronal degeneration. Other symptoms include loss of appetite, gross emaciation, sleep abnormalities, stupor, and the characteristic coma from which sleeping sickness derives its name. Some of the initial symptoms of sleeping sickness are also characteristic of early **malaria**, which can make differentiation between the two diseases difficult in the field. A common, easily recognizable symptom is swelling of lymph nodes. Another common symptom is called "moon face," an edema caused by leaking of small blood vessels. A most common complication during trypanosomiasis is **pneumonia**, which is a frequent cause of death. The chronic gambiense form can take as long as 15 years to develop after the victim has left an endemic area.

The prospect of a vaccine for human trypanosomiasis is bleak. The phenomenon of "antigenic variation" greatly reduces the prospect of producing an effective vaccine, and at present very little research is under way on vaccine development.

History

The history of sleeping sickness in Africa is long and complex, and its complicated ecology has dramatically affected demographic patterns in sub-Saharan Africa. The parameters and density of human settlement have been limited in many regions until the present time, while cattle-keeping has been prevented across vast regions of the continent, thereby seriously affecting the nutrition of entire populations.

The "African lethargy," or "sleepy distemper," as trypanosomiasis has been called, was well known to Europeans in West Africa from as early as the fourteenth century, through good descriptions given by Portuguese and Arab writers. For centuries slave traders rejected Africans with the characteristic swollen cervical glands, for it was common knowledge that those with this symptom sooner or later died in the New World or North Africa. As European exploration and trade along the West African coast increased between 1785 and 1840, the disease was reported in Gambia, Sierra Leone, and western Liberia, whereas between 1820 and 1870 it was also commonly noted along the Liberian coast.

Certainly the disease was an important factor in the history of colonial Africa. In the beginning, colonial administrators were concerned mainly with the health of Europeans and those few Africans in their service. But the threat of epidemics of sleeping sickness eventually forced colonial authorities to take much more seriously the health of entire African populations.

In those colonies affected by sleeping sickness, medical services often developed in direct response to this one disease, which resulted in the development of "vertical" health service – programs aimed at controlling a specific disease while neglecting other crucial public health issues. As recently as the 1970s, the World Health Organization urged developing countries to move toward "horizontal" health services that take into account the multifactoral nature of disease and health.

Sleeping sickness, along with malaria and **yellow fever**, played an important role in the development of the new specialties of parasitology and tropical medicine. In 1898, Patrick Manson, the "father of tropical medicine," published the first cogent discussion of the new scientific discipline. He explained that tropical diseases were very often insect-borne parasitical diseases, the chief example being trypanosomiasis.

Trypanosomiasis at the time was very much on the minds of colonial officials. In the decade between 1896 and 1906, devastating epidemics killed more than 250,000 Africans in the new British protectorate of Uganda, as well as an estimated 500,000 residents of the Congo basin. Understandably, the new colonial powers, including Britain, France, Germany, Portugal, and King Léopold's Congo Free State, perceived sleeping sickness to be a grave threat to African laborers and taxpayers, which in turn could dramatically reduce the utility of the new territories. Moreover, the fears were not limited to the continent of Africa; the British also speculated that sleeping sickness might spread to India, the "jewel" of their empire.

Thus ensued one of the most dramatic campaigns in the history of medicine, as scientific research teams were dispatched to study sleeping sickness. They began with the Liverpool School of Tropical Medicine's expedition to Senegambia in 1901 and the Royal Society's expedition to Uganda in 1902; other expeditions followed until World War II.

Many of these were sent by new institutions especially designed to investigate the exotic diseases of warm climates. The British, for example, opened schools of tropical medicine at Liverpool and London in 1899, while other such schools came into being in Germany, Belgium, France, Portugal, and the United States. This new field of scientific endeavor offered the opportunity for bright young men to gain international acclaim and a place in the history of medicine.

It should be noted that sleeping sickness was not the only disease to receive such attention as Europeans sought to establish themselves permanently in regions of the globe where health conditions were difficult and mortality was high. There were major discoveries by Manson, who was the first to demonstrate insects as vectors of human disease (**filariasis**); and by Ronald Ross, who found that the malaria parasite was transmitted by the *Anopheles* mosquito. Yet, despite the fact that endemic malaria was probably the cause of far more morbidity, the trypanosomiases attracted much attention in the new field of tropical medicine for the next 2 or 3 decades.

International meetings were convened to discuss sleeping sickness, beginning with one at the British Foreign Office in 1907. As the number of "tryps" specialists increased, sleeping sickness became a key factor in the international exchange of research findings in tropical medicine. The Sleeping Sickness Bureau was opened in London in 1908 to facilitate communication of research findings on all aspects of the disease. Its work continues to the present time.

After World War I and the formation of the League of Nations' Health Organization (the antecedent of the World Health Organization), two major conferences in 1925 and 1928 were convened to focus on African sleeping