Special Article

AIDS — THE FIRST 20 YEARS

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THE disease now known as the acquired immunodeficiency syndrome, or AIDS, was first reported 20 years ago this week in the ***Morbidity and Mortality Weekly Report*** under the quiet title "***Pneumocystis*** pneumonia — Los Angeles."[1] The description was not the lead article; that distinction went to a report of dengue infections in vacationers returning to the United States from the Caribbean.

Not even the most pessimistic reader could have anticipated the scope and scale the epidemic would assume two decades later. By December 2000, 21.8 million people worldwide had died of the disease, including more Americans (438,795) than died in World War I and World War II combined.[2] This article reviews the many important developments in the first 20 years of AIDS.

EARLY YEARS: FREE FALL

The initial report described five young homosexual men in whom a rare disease, ***Pneumocystis carinii*** pneumonia, and other unusual infections had developed. Each had abnormal ratios of lymphocyte subgroups and was actively shedding cytomegalovirus. This report was followed quickly by more series, and within a few months, the basic outline of the epidemic was established (Table 1). Although the disease was first encountered in homosexual men and injection-drug users, the risk groups soon included Haitians,[5] transfusion recipients, including those with hemophilia,[6,10] infants,[11] female sexual contacts of infected men,[8,12] prisoners,[13] and Africans.[15]

Additional opportunistic complications were soon described, including mycobacterial infections, toxoplasmosis, invasive fungal infections, Kaposi's sarcoma, and non-Hodgkin's lymphoma. The working definition for AIDS, developed by the Centers for Disease Control,[21] has required just a single revision in the past decade.[22]

Causation

In the early years, there were numerous theories regarding the cause of AIDS, many of which now seem eccentric. The evidence that the disease was caused by cytomegalovirus, as posited in the early reports,[1,23] was straightforward: groups with the new immunodeficiency had extremely high rates of infection with cytomegalovirus, a potentially immunosuppressive virus. Some hypothesized that the virus had inexplicably become more virulent. Yet this theory failed to account for all cases, and attention turned elsewhere.

A case was made for attributing causality to amyl nitrite, a prescription drug, and to isobutyl nitrite, a closely related chemical marketed as a room deodorizer.[24] Both were used as sexual stimulants but were also known immunosuppressive agents. This theory had scientific plausibility and suggested a simple solution. But soon cases were reported among nonusers.

A sophisticated theory developed around the notion that repeated exposure to another's sperm could trigger an immune response, resulting in a condition resembling chronic graft-versus-host disease and, ultimately, opportunistic infections.[25] Another hypothesis invoked a general overloading of the immune system — a sort of physiological battle fatigue in which the immune system simply wore out.[26,27] Outside the scientific community, there were suggestions that the disease was a punishment for homosexual men and injection-drug users.[28]

A novel viral cause of the disease was only one of many plausible theories in the early years. It was favored by those familiar with the epidemiology of hepatitis B infection,[8,29,30] which affected the same groups, and by those who worked with animal retroviruses. Feline leukemia virus had been described in the 1970s as a cause of general immunodeficiency (the "fading-kitten syndrome") and was associated with lymphoma and leukemia as well.[31,32] For the researchers in this field, the notion that a human retrovirus might cause a similar syndrome was a simple intellectual leap.

Nonetheless, doubt about a viral cause persisted until the actual virus was detected,[16] confirmatory studies were performed,[18] and the reports of transmission through blood and blood products became too numerous to ignore.[8,9] The complicated and rivalrous story that culminated in the isolation of the virus has been well described. High-stakes scientific inquiry has seldom been placed in a less attractive light.

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TABLE 1. IMPORTANT DATES IN THE FIRST DECADE OF THE AIDS EPIDEMIC.*

DATE	REPORTED EVENT	COMMENT†
June 5, 1981	5 Cases of *Pneumocystis carinii* pneumonia in homosexual men[1]	Initial report
July 3, 1981	26 Additional cases of new immunodeficiency syndrome[2]	Cases in New York and California
June 18, 1982	Cluster in southern California[3]	First report that "infectious agents [may be] sexually transmitted"
July 9, 1982	Initial cases in 34 Haitians[4]	Mode of transmission unclear
July 16, 1982	Initial cases in 3 persons with hemophilia[5]	Possibility of tainted blood supply
September 24, 1982	Term "acquired immune deficiency syndrome" (AIDS) used for first time[6]	Term coined at July 1982 meeting, replacing "gay related immune deficiency" (GRID)
October 1982	5 Cases in women reported, including 1 with only heterosexual exposure[8]	First possibly heterosexually transmitted case
November 5, 1982	Precautions published for clinical and laboratory staff[9]	"Patterns resemble the distribution and modes of spread of hepatitis B"
December 10, 1982	Initial transfusion related case, in an infant[10]	Further evidence of tainted blood supply
December 17, 1982	Initial vertically transmitted cases reported in 4 infants[11]	Reported as "Possible that these infants had AIDS"
January 7, 1983	Report of heterosexual transmission to 2 female partners of injection drug users[12]	"Supports infectious agent hypothesis"
January 7, 1983	Initial cases in 16 prisoners[13]	Given known risk groups, occurrence in prisoners "might have been anticipated"
March 4, 1983	CDC releases prevention recommendations[14]	Groups at risk advised not to donate blood
March 19, 1983	Initial cases in 5 persons from Central Africa[15]	"Black Africans may be another group predisposed to AIDS"
May 20, 1983	Isolation of a virus from a patient with AIDS[16]	Retrovirus belongs to HTLV group, but is "clearly distinct from each previous isolate"
July 15, 1983	Report of 4 possibly occupational cases among health care workers[17]	Occupational transmission suspected but not proven
September 22, 1983	Infection control guidelines published for care of patients with AIDS[18]	"Measures consistent with those suggested for prevention of hepatitis B should be followed"
January 13, 1984	AIDS tabulated as "notifiable disease" for first time[19]	25 Cases reported in first week
May 4, 1984	Frequent detection of HTLV-III in patients at risk[20]	"HTLV-III may be the primary cause of AIDS"
March 1985	FDA approves commercial test to detect HIV	Tremendous impact on patients at risk and blood supply
1986	CDC provides working definition of AIDS[21]	Updated in 1993[22]
1986	AIDS Clinical Trials Group established by NIH	Now largest clinical trials group in the United States
March 1987	FDA approves AZT (zidovudine)	First drug active against HIV

*CDC denotes Centers for Disease Control, FDA Food and Drug Administration, HIV human immunodeficiency virus, HTLV human T-cell lymphotropic virus, and NIH National Institutes of Health.

†Each quoted statement is from the reference cited under the corresponding Reported Event.

The delay on the part of some in accepting a novel viral cause may appear puzzling now, but investigators may have been intimidated by the enormous implications that a new virus would carry for blood banking, the safety of health care workers, and the overall public health. There was also a hesitancy, particularly among those outside the medical community, to acknowledge that the infection could be spread through heterosexual contact. Indeed, many preferred to invoke any but the obvious cause. The spread of the disease in Haiti, for example, was postulated to be a result of voodoo practices rather than heterosexual sex.[33] Today, most human immunodeficiency virus (HIV) infections in the world derive from heterosexual transmission — a fact that is still overlooked by many.

In some quarters, doubt persists that HIV causes AIDS. One prominent dissident has theorized that the disease occurs because of long-term use of recreational drugs and is exacerbated by nucleoside analogues given as treatment.[34] The improvements that have been made in antiviral therapies for HIV disease have, paradoxically, only intensified the debate.[35,36]

Treatment

Recent advances in therapy have obscured the difficult and often demoralizing character of the early

years of therapies for HIV. As the 1980s wore on, a hard-boiled fatalism settled in. Although patients and physicians did their best, they were all just playing out the same grim script.

Many of the agents that were studied in the first years of the epidemic are shown in Table 2. The list is incomplete; dozens and possibly hundreds of other concoctions were tried. The story for most was remarkably similar: a few patients in San Francisco, Los Angeles, or New York took a certain medication; some felt better; a few had improvements in CD4 cell counts. With the first whisper of encouragement, others joined in, a clinical trial was organized, and another great hope was born.

After the intense excitement came tempered optimism, then fading expectations, and finally an unsentimental assignment of the treatment to the scrap heap. Two agents, compound Q (Chinese cucumber plant root)[37] and peptide T,[38] are particularly representative. Each was briefly the darling of the emerging community of patients and activists seeking an effective therapy, but each moved slowly into formal clinical trials, prompting patients to criticize the medical–industrial complex as uncaring and uncooperative.[46] When studied, neither drug proved to be effective.

The growing sense of despair and frustration opened the door for charlatans. A typical fraudulent therapy was MM-1, promoted by an Egyptian rectal surgeon with "unbelievable claims of cure," but support for the claims was never presented.[47] The cost of the therapy, however, was presented: $75,000, including the trip to Zaire, where the treatment was administered.

THE LATE 1980s: SLOW PROGRESS

Once a retrovirus had been identified, the search began for agents that might act on reverse transcriptase, the enzyme necessary for transcribing HIV RNA to DNA. To study potential therapies, the National Institutes of Health (NIH) organized the AIDS Clinical Trials Group (ACTG) in 1986. Since its inception, the ACTG has systematically studied dozens of candidate therapies in adults and children. This research, along with trials sponsored by pharmaceutical companies, has led to the current guidelines that advocate triple-drug therapy.[48]

Zidovudine (earlier known as azidothymidine, or AZT) was among the earliest compounds tested[49] and, in 1987, became the first drug approved for the treatment of AIDS. After initial exuberance, many in the community of AIDS patients turned against the drug.[46] They came to see its promotion as an almost hostile act on the part of the NIH, Burroughs Wellcome, and treating physicians. Accusations abounded that cheap and simple treatments had been overlooked in favor of a mediocre, costly, and toxic agent. Patients soon claimed that everyone they knew who took zidovudine was dead — still a familiar lament.

This was the time of greatest tension between the community of patients and the medical establishment.[50] There was discord about access to study drugs, protocol selection, design, and interpretation, and perhaps most of all, the overall pace and sincerity of scientific investigation. Even the bedrock concept of the placebo-controlled trial became a point of contention, because it struck many as unethical.

Progress was very slow in the years after the ap-

Table 2. Early Therapies for the Management of HIV Infection.

Drug	Source	Possible Mechanism	Findings	Comment
Putative antiviral drugs				
Compound Q	Chinese cucumber root	Enters macrophage to eradicate virus	Ineffective[37]	Increase of 1 CD4 cell per cubic millimeter per month
Peptide T	Synthetic	Competitive receptor blockade[38]	Never published	Trials continue for HIV related cognitive impairment
AL 721 (active lipids at 7 2 1 ratio)	Hen's egg yolks	Destabilizes cell membrane	Ineffective[39]	Transient weight gain
Soluble CD4	Synthetic	Competitive receptor blockade	Ineffective[40]	No oral form
Dextran sulfate	Synthetic	Anticoagulant, blocks attachment	Ineffective[41]	Not absorbed orally
Putative immune modulators				
Isoprinosine	Synthetic	Immune stimulation, possible antiviral activity	Minimally effective[42]	Prolonged controversy regarding efficacy
Imuthiol	Metal chelator similar to disulfiram	Modulates T cell differentiation	Ineffective[43]	Investigators reported, "Use of [drug] should be discontinued"
Ampligen	Antisense RNA	Enhancement of killer cells	Ineffective[44]	Prolonged controversy regarding efficacy
Imreg 1	Synthetic	Enhanced production of interferon, interleukin 2	Minimally effective[45]	Prolonged controversy regarding efficacy; slower CD4 cell decrease with drug