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3

The Natural History of AIDS

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INTRODUCTION

This paper will describe the current state of knowledge of the natural history and pathogenesis of acquired immunodeficiency syndrome (AIDS). Several thousand articles have now been written on this subject since the epidemic was first recognized in 1981. In modern times no disease has had such a global impact on medical science and on society. The pace of research, and the progress attained to date, is unprecedented.

AIDS is a viral illness affecting the immune system that results in a wide array of secondary manifestations, including opportunistic infections, neoplasia, autoimmune phenomena, neurologic disorders, and hematologic abnormalities. Virtually every organ may be affected, and clinical care for AIDS patients is truly multidisciplinary. Prolonged and expensive hospitalization is often required, demanding creative use of community resources and psychosocial support systems. The epidemic forces policy decisions in political, social, journalistic, and ethical spheres. The cause, prevention, and cure of AIDS has induced collaboration between clinicians, virologists, immunologists, molecular biologists, epidemiologists and sociologists. Thus this epidemic has, in five short years, mobilized a response from virtually every arena of human society.

DEMOGRAPHY

The intensity of research in AIDS is steadily improving our understanding of etiology and pathogenesis. The stark demographic facts are reason alone to motivate a sense of urgency. Over 18,000 cases of AIDS are now reported in the USA, and several thousands more have occurred in Europe, Africa, and other countries.

In the USA an estimated one million persons are now infected, and the progression rates from asymptomatic infection to illness are estimated to be at least 2% anually. Because of the prolonged incubation period of 6 months to over 5 years, there will continue to be thousands of cases per year even if a totally effective vaccine is developed. The outcome appears almost invariably fatal, with actuarial mortality approaching 50%. Since many of the victims are in the prime of their lives, an estimate of years of potential life lost from AIDS in endemic cities approaches that of cancer and heart disease combined.[1]

THE AIDS RETROVIRUS

Following the original descriptions of the outbreak of opportunistic infections and neoplasms in homosexual men, attention turned immediately to the pathogenesis of immune impairment where a deficiency of T4 lymphocytes was disclosed. Epidemiologic evidence implicated person-to-person spread. Similar syndromes observed in intravenous drug abusers, recipients of blood transfusions, hemophiliacs, infants, Haitians, and Africans, led to the conclusion that this was a new, transmissible disease. In 1979, a novel human lymphotropic retrovirus (HTLV-I), was discovered in the cultured T4 lymphocytes of a patient with a rare T cell lymphoma.[2] The T4 cell defect in AIDS awakened interest in the possibility of a retroviral cause, and in 1983–84 three laboratories produced convincing evidence that a new human lymphotropic retrovirus (variously called LAV, HTLV-III, and ARV) was the etiologic agent of AIDS.[3-6]

The discovery of the AIDS virus led to antibody assays and opened the way to definitive seroepidemiologic studies. The first priority was to safeguard the blood supply by screening donors for AIDS antibody. While the ELISA antibody test yielded a small number of false-positive results (i.e. 'unconfirmed' by Western blot) in low-risk populations, it was possible to eliminate donors potentially infected with the AIDS virus. A few high-risk donors (perhaps 2–3%) are infected by the virus but lack antibody (i.e. false-negatives) because they either have been recently infected and have not yet seroconverted or simply do not produce specific antibody to the virus.[7,8] Culture of the AIDS virus is not a 'gold standard' of infection because

of cumbersome and time-consuming techniques and relatively low yield. Immunofluorescence methods and Western blot patterns remain the best 'confirmatory' methods.

NATURAL HISTORY

Mode of transmission

Serologic tools permit a clearer definition of the course of infection. The AIDS virus is found in many body fluids including sperm and vaginal secretions, but the major modes of transmission are sexual or by exposure to contaminated blood.[1,9,10] Remarkably, transmission of the AIDS virus has remained confined to the originally defined risk groups, despite fears from many quarters of spread to the general population.[1] There are probably two reasons for this: one is that exposure to the virus must be intense and associated with some degree of parenteral trauma; the other reason involves the presence of cofactors that influence the immune system. Among homosexual men, passive anal intercourse and number of partners remain dominant risk factors.[11] Among intravenous drug abusers, repeated exposure to shared needles in epidemic cities is the major risk factor.[12] Heterosexual spread in the USA is unusual, and is predominantly from infected men to their female partners rather than the other way.[13] In Africa, on the other hand, heterosexual spread appears to be the major mode of transmission: this difference is totally unexplained.[14] There is no documented case of infection from exposure to other body fluids (e.g. tears, saliva, milk) or of 'casual' spread within or outside of the major risk groups.

Clinical manifestations

It is now clear that a well-defined clinical syndrome may accompany acute infection by the AIDS virus.[15] Within 2 weeks of exposure the patient complains of a 'flu-like illness with fever, generalized lyphadenopathy, myalgia, arthalgia, and fatigue. A maculopapular rash, usually confined to the trunk, may appear transiently. Rarely headache and meningoencephalitic symptoms may dominate.[16] The acute illness is self-limited and usually subsides within 2–4 weeks of onset, although lymphadenopathy may persist.

The remaining chronic clinical syndromes that are associated with AIDS constitute a spectrum of illness, ranging from benign, asymptomatic lymphadenopathy to severe, life-threatening opportunistic infection. This spectrum has been subdivided into two rather arbitrary 'entities': AIDS-related complex (ARC), and AIDS classification of these conditions is shown in

Table 1.[17] Virtually all studies of the natural history of AIDS document a progression from ARC to AIDS, with a conversion rate that varies from 7% to as high as 17% each year.[18] There are no known cures.

Table 1 Classification of illness associated with infection by the AIDS virus

Category	Clinical features
1	Asymptomatic
2	Unexplained lymphadenopathy > 4 months
A	No systemic symptoms
B	Fever, night sweats, fatigue, weight loss
3	Idiopathic thrombocytopenic purpura
4	Minor opportunistic infection (thrush, herpes zoster, oral hairy leukoplakia, unexplained meningo-encephalitic syndrome, prolonged diarrhea, interstitial pneumonitis)
5	Kaposi's sarcoma
6	Non-Hodgkin's lymphoma
7	Severe opportunistic infection (*Pneumocystis carinii* pneumonia, cryptococcal meningitis, toxoplasmosis, *Mycobacterium avium* complex)

Modified from Haverkos *et al.*[17]

Immune abnormalities

Before turning to pathogenesis, we must address the plethora of immune abnormalities described in patients with ARC and AIDS. Several excellent reviews have summarized these data.[19-22] Basically, the immunologic studies describe three temporal phases of illness: proliferative, intermediate, and hypoplastic. In this regard, the immunologic observations bear a remarkable similarity to the graft-versus-host syndromes.[23]

Patients with ARC display follicular hyperplasia, hypergammaglobulinemia (with circulating immune complexes), elevated levels of acid-labile interferon, beta-2 microglobulin, and alpha-thymosin. B cells *in vitro* are unreactive to recall antigens, a finding consistent with a polyclonal, preactivated state.[24] As the illness progresses, enlarged lymph nodes begin to regress, gamma globulin levels fall, and 'follicle lysis' and lymph node atrophy supervene.[25]

Patients with ARC and Kaposi's sarcoma may have intact cutaneous hypersensitivity, but those with severe opportunistic infections are anergic. These clinical features parallel a progressive fall in absolute numbers of T4 lymphocytes, loss of antigen-processing dendritic cells, and a progressive rise in cytotoxic TB lymphocytes.[26,27] Circulating T4 monocytes are diminished, and antigen-processing dendritic cells disappear from lymph nodes.[27] *In vitro*

functional assays disclose a progressive failure of T4 lymphocytes to produce interleukin-2, natural killer cell defects, and loss of monocyte function.[19-22]

Taken together, the immunopathology of AIDS describes an inexorable depletion of T4 lymphocytes and antigen-processing cells accompanied by qualitative functional defects. These defects reflect temporal progression from a preactivated, proliferative state, through an intermediate stage of relative immunodeficiency and immune dysregulation, into a terminal hypoplastic state characterized by lymphoid atrophy and a chronic wasting illness. These phases are depicted graphically in Table 2.

Table 2 Stages of disease progression in AIDS

Proliferative	Intermediate	Hypoplastic
Clinical features		
Lymphadenopathy	Candidiasis	Severe opportunistic infections
Thrombocytopenia	Herpes zoster	
Skin disorders	Kaposi's sarcoma	Chronic wasting syndrome
Enteropathy	Lymphoma	
Diarrhea	Encephalopathy	
Fever	Neuropathy	
Weight loss	Myelopathy	
Fatigue	Oral hairy leukoplakia	
Immunologic features		
Follicular hyperplasia		Lymphoid atrophy
Hypergammaglobulinemia		Elevated T8
Immune complexes		Lowered T4
Acid-labile interferon		
Immunopathogenesis		
T4 Lymphocyte activation by LAV/HTLV-III		T4 and dendritic cell loss from auto-immune attack
B Cell hyperplasia (preactivation)		
Impaired regulatory circuits due to 'alloactivated' T4 lymphocytes		
Lymphokine production		

Determinants of progression

Since the discovery of a lymphocytopathic retrovirus associated with AIDS, it has been assumed that the loss and dysfunction of immunocytes can be traced directly to the effects of the virus. There are three possibilities to consider in understanding the causes of progressive illness: (1) an independent role of the virus; (2) the effects of host cofactors; or (3) a combination of the two.

So much has been learned about the biology of the AIDS virus since its

discovery, that space permits only a brief synopsis. The molecular anatomy of the virus is now well-characterized. There are three viral genes, *gag*, *pol*, and *env*, that code for core protein, polymerase (reverse transcriptase), and the envelope glycoprotein, respectively. The *env* gene varies considerably in different isolates, reflecting a high mutation rate.[28] Additional genes have been identified, one of which appears to function as an enhancer within the host genome. The *tat* gene, for transactivation of transcription, encodes an unusually potent protein that converts the cell into a virtual virus factory.[29]

The AIDS virus infects T4 lymphocytes (and other cells bearing this receptor) using the T4 molecule to gain entry into the cell.[30] Once infected, the viral reverse transcriptase helps encode the viral RNA into the DNA genome of the host cell. Activation of the *tat* gene results in rapid viral assembly and budding from the cell surface within days of infection. *In vitro* cytopathic effects are dramatic: infected cells fuse, undergo ballooning degeneration, and die. Occasional cells can remain productively infected and avoid the cytopathic effect. Other cells enter a non-productive latent phase, accompanied by disappearance of the T4 receptor. Latently infected cells can be reinduced into productive infection *in vitro* by a number of manipulations.[31,32]

Given these observations, one can infer several critical viral determinants in the outcome of a particular infection. First, there must be conformity of the virus envelope glycoprotein to the T4 receptor before infection can occur. Once infected, control of the *tat* gene expression appears to be an important step in productive infection.[29] Fusion of infected cells *in vitro* provides a mechanism of cell-to-cell infection without the release of infectious virus.[5] If this occurs *in vivo*, host-to-host infection by cells, as well as autoinfection between cells, can occur. The accumulation of unintegrated viral DNA may also contribute to cell death.[33] The degree and rapidity of the *env* gene variation provides an efficient mechanism to avert dectection by the immune response. Different viral 'strains' could then vary in pathogenicity.[28] Another possible pathogenic influence is the shedding of immunosuppressive viral products into the circulation.[34] Finally, the ability of the virus to enter a latent state that can be reactivated by many non-specific stimuli (e.g. repeated infections) suggests a major means of viral persistence in the host.[31,32] Reservoirs of latent infection could be macrophages or brain cells.

No pathogenic microbe produces clinical illness that is totally independent of the host response. Because AIDS is epidemiologically restricted to certain risk groups, cofactors that influence the outcome of infection must be invoked. Early cofactor theories proposed that the individuals at risk were already immunocompromised and therefore unusually susceptible. It was pointed out that all risk groups had in common, in addition to viral exposure, perturbations of the immune system induced by alloimmunization, repeated or chronic infections, immaturity, or malnutrition.[35] These perturbations

could influence both susceptibility to infection (by increasing the number and activation of target immunocytes) and reactivation of the latent state (by stimulating latently infected cells into a productive infection). Presumably, the progressive immune impairment in AIDS permits activation of latent, endogenous viruses such as cytomegalovirus, Epstein–Barr virus, and herpesviruses, which in turn worsen the immunodeficient state. Current theories on pathogenesis of AIDS are summarized in Figure 1.

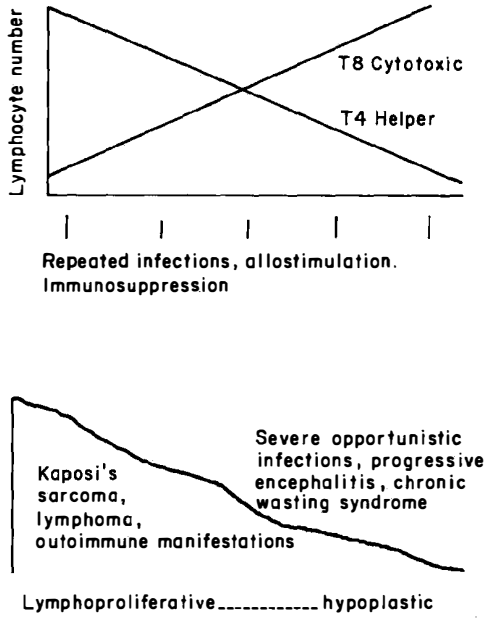

Fig. 1 Immune response to AIDS virus

A final consideration of the host's contribution to the pathogenesis of AIDS devolves on the immune response to the AIDS virus. The virus receptor is the T4 molecule whose ligand under normal circumstances is an invariant portion of the class II major histocompatibility antigen.[36] The T4-cells II interaction is critical to the discrimination of self in the initiation and induction of an immune response. It follows, then, that the AIDS virus is 'class II-like' in its configuration, and that the immune response to viral envelope might cross-react with class II antigen. This would result in antibodies and sensitized lymphocytes that attack class II bearing cells (B cells and antigen-processing cells). The anti-idiotypic regulatory response would produce antibodies and lymphocytes reactive with T4 bearing cells. The net

result would be a progressive, autodestructive process of the entire immune system (Figure 2). Many clinical manifestations of ARC and AIDS are autoimmune in nature, and lymphotropic antibodies to T4 lymphocytes have been found.[37] While an autoimmune pathogenesis of AIDS is speculative, there are important implications in vaccine development and treatment strategies.

SUMMARY AND FUTURE DIRECTIONS

The natural history of the AIDS virus infection is coming into focus as we learn more about the biology of the immune system and the behavior of the AIDS virus. Treatment considerations will depend on a better understanding of immunopathogenesis. The only sure method of containing the epidemic is to prevent infection in the first place. In the absence of a vaccine, which is many years away, education about risk of exposure, transmission from

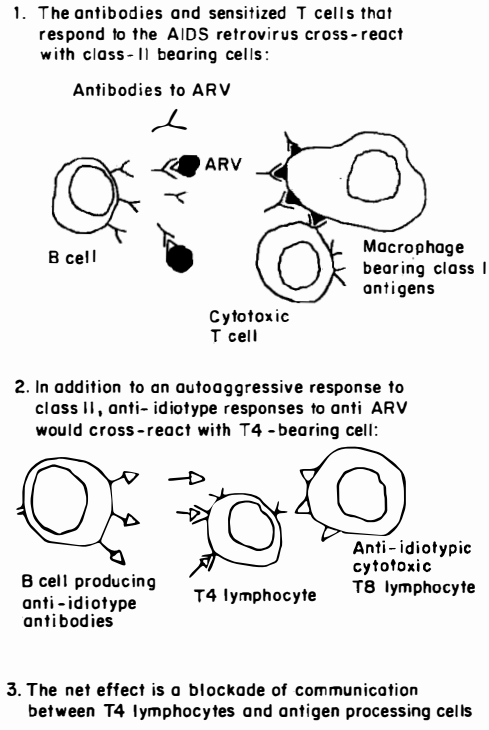

Fig. 2 Immuno pathogenesis of AIDS

infected persons, and protection of blood, blood products and tissue donations is paramount. Vaccine development must proceed at top speed. Antiviral drug trials will need to be tested to arrest or slow infection. Studies of determinants of progression may disclose other treatment strategies to reverse the progressive immune defects. Finally, the clinician is left to treat the many manifestions of AIDS which yield only temporarily to current therapy. AIDS is likely to remain a dominant spectre in medicine for many years to come.

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