THE RETINAL LESIONS OF THE ACQUIRED IMMUNE DEFICIENCY SYNDROME*

BY *Alan H. Friedman,* MD

INTRODUCTION

SINCE JUNE 1981, WHEN FIVE CASES OF *PNEUMOCYSTIS CARINII* PNEUMONIA IN YOUNG homosexual men were reported to the Centers for Disease Control (CDC),[1] the world health community has been examining new instances of opportunistic infections and Kaposi's sarcoma in young, previously healthy individuals. As of November 21, 1983, 2803 cases of opportunistic infections with or without Kaposi's sarcoma have been reported to date in the United States[2]; the common thread among all of these cases is a similar pattern of acquired immune deficiency.[3] The constellation of opportunistic infections and Kaposi's sarcoma has come to be known as the Acquired Immune Deficiency Syndrome (AIDS).

EPIDEMIOLOGY

AIDS is defined by the CDC as a reliably diagnosed disease that is at least moderately indicative of an underlying cellular immunodeficiency in a person who has no known cause of underlying cellular immunodeficiency or any other underlying reduced resistance reported to be associated with that disease.[4] The etiology of AIDS is postulated to be that of a transmissible blood borne agent.[3,5,6] As of September 1983, AIDS had been reported in 41 US states, the District of Columbia, and Puerto Rico (Table I). The syndrome has been described in at least 15 European countries (Table I), as well as in other nations around the world.[2,8] AIDS in these foreign countries resembles the disease described in the United States in nearly all respects.[9,10]

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TABLE I: GEOGRAPHIC DISTRIBUTION OF AIDS CASES

I. USA* (1676 cases)	
New York State	47.8%
California	20.6%
New Jersey	6.9%
Florida	6.7%
Remainder of US	18.0%
II. Europe« (267 cases)	
France	35.2%
Federal Republic of West Germany	15.7%
Belgium	14.2%
United Kingdom	9.0%
Switzerland	6.4%
Denmark	4.9%
Netherlands	4.5%
Remainder of Europe	10.1%

*College of American Pathologists AIDS Task Force—Skokie, Ill, 1983.

†World Health Organization: AIDS Weekly Epidemiologic Record 58:227-228, 1983.

The number of AIDS cases diagnosed each year has been climbing rapidly[11] (Table II). In the United States, during 1983, 1631 cases of AIDS were reported as of November 21; this is 58% of all cases reported as of that date in the United States.[7] The distribution of persons with AIDS in the United States reveals that most cases are clustered in port areas; 42% of all cases are in New York City, 11.1% in San Francisco, 7% in Los Angeles, and 5% in Miami[7] (Table I). Forty-one percent of persons with the disease have died, but the 2-year mortality rate is greater than 80%, with no spontaneous recovery of immune function once opportunistic infections have appeared.[12] Once opportunistic infections or Kaposi's sarcoma become obvious, most patients follow a hopelessly downhill course, and the actual case fatality rate in AIDS then approaches 100%.[11,13]

AIDS affects young, previously healthy persons. At least four groups have been found to be at a special risk (Table III): male homosex-

TABLE II: AIDS CASES DIAGNOSED PER YEAR IN THE UNITED STATES AND PUERTO RICO

YEAR	NO OF CASES
Before 1981	58
1981	231
1982	883
1983	1631 (by 11/21/83)

TABLE III: ACQUIRED IMMUNE DEFICIENCY SYNDROME (AIDS)

Population at risk*	
A.	1) Homosexual males (72%)
	2) IV drug abusers (17%)
	3) Normal Haitians (5%)
	4) Patients with hemophilia
	Type A - 19 patients
	Type B - 2 patients
	5) Children (mainly of IV drug abusers) (< 1%)
	6) Sex partners of AIDS patients (1%)
	7) No apparent risk group (3%)
B.	1) Males (93%)
	2) Females (7%)

*Analysis of 1566 cases, College of American Pathologists task force on AIDS.

uals,[5,6,14-24] intravenous (IV) drug abusers,[24,25] hemophiliacs,[26-32] and Haitians.[33,34] In addition, people not included in the above categories have had symptoms characteristic of AIDS.[35]

Seventy-two percent of persons with AIDS are homosexual or bisexual men (Table III), 17% are IV drug abusers (this group includes 51% of all women with AIDS), 5% are Haitian males, less than 1% are patients with hemophilia, 1% are sex partners of persons with AIDS or persons at high risk for AIDS, 1% have no recognizable risk factors, and epidemiologic information is absent or incomplete for 3%.[7,36] For women with AIDS, as a group, 51% are IV drug abusers, 9% are Haitian, and for the remaining 39%, the risk factors are unknown. Only 7% of all people with AIDS are female.

AIDS may be transmitted between male AIDS patients and female sex partners, ie, between heterosexual men and women, as well as from persons with AIDS to other individuals by blood transfusion (eg, hemophiliacs, infants).[26-32,37-41] In this way, the disease may spread from high risk to low risk populations. In addition, it has been found that a person

TABLE IV: AIDS: AGE DISTRIBUTION OF CASES (1676 CASES)

AGE DISTRIBUTION	%
< 20	0.5
20–29	22
30–39	47
40–49	21
> 50	7.5
Unknown	2
Total	100.0

TABLE V: AIDS: RACIAL DISTRIBUTION OF CASES (1676 CASES)

RACE	%
Caucasian	57
Black	26
Hispanic	14
Other or unknown	3
Total	100

may transmit AIDS before signs or symptoms of the disease develop in that person,[39,41] ie, "health AIDS carriers."

Only four cases of AIDS have been described in health care personnel not in AIDS risk groups.[42] These individuals had no history of caring for AIDS patients, and had no known contact with the blood of AIDS patients.[42] The CDC reports that there is no evidence for air borne spread, and no risk for casual contact with an AIDS patient.[36] The CDC found varying age clusters for the different groups at high risk of developing AIDS (Table IV). For homosexual or bisexual men with AIDS, 47% were 30 to 39 years old, 22% were 20 to 29 years old, and 21% were 40 to 49 years old (69% were 20 to 39 years old). Among IV drug abusers with AIDS, 81% were 20 to 39 years old and for Haitians with AIDS 41% were 20 to 29 years old. There was no age clustering for hemophiliacs with AIDS.[7]

AIDS affects all races (Table V). Fifty-seven percent of cases are Caucasian, 26% are black, 14% are Hispanic, and 3% are other or unknown.[7] Additionally, studies in Haiti have shown that AIDS strikes all socioeconomic groups.[43] These facts further illustrate that AIDS is not exclusively a disease of Caucasian homosexual men.[44] Patients are usually of diverse ethnic background.[5,16,17,45]

REASONS FOR RISKS

AIDS is thought to be caused by a transmissible blood borne agent. The chances of exposure to semen or a blood borne transmissible agent for sexually active homosexual men are increased with high frequencies of sexual activity with multiple partners.[3,5,6] The factors found to be associated with illness by the National Case Control Study of Kaposi's sarcoma and *Pneumocystis carinii* pneumonia in homosexual men were as follows: A larger number of male sex partners per year was the strongest associated variable. Cases were more likely than controls to have been exposed to feces during sex, to have had syphilis and hepatitis A or hepatitis non-A or non-B, to have been treated for enteric parasites, and to have used

various illicit substances.[46] In 1982, six persons with hemophilia were reported to the CDC to have AIDS, all with hemophilia A. By November 30, 1983, 21 cases of AIDS had been reported to the CDC, 19 with hemophilia A and 2 with hemophilia B. Seven cases of AIDS with hemophilia A also have been reported outside the United States.[47] Hemophiliacs with exposure to pooled concentrated clotting factor are at a special risk; the concentrate is the likely source of transmission, with each lot containing material pooled from 2500 to 22,500 individual donations. Cryoprecipitate and plasma factor concentrate are known to be associated with the transmission of cytomegalovirus, hepatitis B virus, and hepatitis non-A non-B.[47] A person with severe hemophilia using clotting factor concentrate is exposed to tens of thousands of donors per year, and a given donor may expose approximately 100 persons.[3,26-28,30]

The theory of a blood borne transmissible agent is further supported by the incidence of AIDS in IV drug abusers.[3,24,25] The factors predisposing Haitians to AIDS are unknown.[3,33,34,43,48,49] The clinical syndrome is consistent across all groups contracting AIDS.

The group in which AIDS is most difficult to define as a disease entity is infants.[50] The CDC reported on June 24, 1983, that there were 21 infants with opportunistic infections and unexplained cellular immunodeficiency.[36] Several authors claim that AIDS has appeared in infants by transmission of an infectious agent *in utero* or perinatally.[39-41,51,52] Intravenous drug abuse in the mothers is consistent.[40,41,51,52] Some of the cases are children of Haitian mothers.[41,53,54] In one case, an infant with Rhesus disease was given several blood transfusions. A transfusion given to an infant at 2 weeks of age was found to be from a donor who was healthy at the time of blood donation, but who later developed clinical AIDS and died 17 months after the donation. The infant developed signs and symptoms of AIDS at 6 months of age.[39-41] A second child who received blood from the same donor developed disseminated varicella and T-cell immunodeficiency.[41] Although one author claims that the immunodeficiency seen in Haitian infants may be due to malnutrition, this opinion has had little support.[53]

THE DISEASE

AIDS may have a long incubation period ranging from months to years.[3,39,48,55] One study found an incubation period with a mean of 14.6 months between presumptive discontinuation of intravenous drug use (due to imprisonment) and onset of various opportunistic infections.[25]

Patients with AIDS manifest a prodrome (Table VI) characterized by weight loss, diarrhea, fever, and lymphadenopathy.[5,14,19,22,45] This pro-

TABLE VI: CLINICAL MANIFESTATIONS OF AIDS

Malaise
Fever
Wasting
Dyspnea
Weight loss
Generalized lymphadenopathy
Diarrhea
Skin or mucosal lesions
Opportunistic infections—severe, life threatening, may be multiple or recurrent
Malignancies—may be multiple primary lesions

dromal period is more consistently present in patients with *Pneumocystis carinii* pneumonia (PCP), has a mean duration of over 6 months, and has a range of 1 to 30 months. Fever of unknown origin was present for more than 3 weeks in many of the patients studied.[5,17]

INFECTIOUS ORGANISMS AND NEOPLASIAS

Fifty-two percent of cases have PCP, 26% have a virulent and aggressive form of Kaposi's sarcoma (KS), 7% have both PCP and KS, and 15% manifest opportunistic infections without PCP or KS[7] (Table VII). This spectrum is similar across all groups with the exception of hemophiliacs, who do not develop KS. PCP is found in 95% of hemophiliacs with AIDS.[47] The various diseases and opportunistic infections affecting persons with AIDS are shown in Table VIII. These diseases range from infectious organisms including protozoa, fungi, bacteria, and viruses to neoplasias.[5,16,23,29,45,56,57]

Pneumocystis carinii is a protozoan about which little is known. It commonly causes pneumonia in patients with AIDS, but its mode of transmission is not known.[56] *Pneumocystis* pneumonia can present with a

TABLE VII: THE AIDS SPECTRUM

DISEASES* (1676 CASES)	%
PCP without KS	52
KS without PCP	26
Both KS and PCP	7
OOI without KS or PCP	15
Total	100

*KS, Kaposi's sarcoma; PCP, *Pneumocystis carinii* pneumonia; OOI, other opportunistic infection.

TABLE VIII: ACQUIRED IMMUNE DEFICIENCY SYNDROME (AIDS)

Diseases
- A. Kaposi's sarcoma (KS)
- B. *Pneumocystis carinii* pneumonia (PCP)
- C. Opportunistic infections
  - 1) Protozoa
    Pneumocystis carinii, Toxoplasma gondii, Cryptosporidium sp, *Entamoeba histolytica, Isospora belli,* and *Giardia lamblia*
  - 2) Fungi
    Candida sp, *Cryptococcus neoformans, Histoplasma capsulatum, Coccidioides immitis,* and *Aspergillus* sp
  - 3) Bacteria
    Mycobacterium avium-intracellulare, Mycobacterium tuberculosis, Nocardia asteroides, Klebsiella pneumonia, and *Legionella pneumophitus*
  - 4) Viruses
    Cytomegalovirus (CMV), *Herpes simplex* virus (HSV), Epstein-Barr virus (EBV), polyomaviruses, poxvirus, *Varicella-zoster* virus
- D. Lymphomas, squamous cell carcinoma, cloacogenic carcinoma

number of different roentgenographic findings depending on associated pathogens. *Pneumocystis* pneumonia should be suspected in any young male homosexual, hemophiliac, Haitian, or IV drug abuser with a febrile respiratory illness, pulmonary infiltrate on chest X-ray, and absence of leukocytosis. Such patients should be biopsied immediately for diagnosis and treatment. Mortality from the infection despite treatment is greater than 30%.[58]

Before 1979, PCP was seen only in immunosuppressed patients, patients with disseminated carcinoma, and high risk premature infants.[58] PCP in patients with AIDS is usually accompanied by a more severe prodrome and more opportunistic infections than those with KS alone. Both PCP and KS in AIDS patients are often associated with cytomegalovirus (CMV) infection.[5]

The link between KS and CMV is of interest. The CMV is often seen in patients with KS.[5,15,20,21] Until 1979, KS was a disease seen almost solely in older men (greater than 50 years of age) of Mediterranean descent, and the incidence was increased with immunosuppression. The disease was usually slowly progressive, involving the upper extremities and rarely the viscera. In homosexual males, KS is much more aggressive, more rapidly progressive, and widely disseminated.

TABLE IX: ACQUIRED IMMUNE DEFICIENCY SYNDROME (AIDS)

Immune Suppression	
A.	Defective cell-mediated immunity (CMI)
	1. T-cell lymphopenia (OKT 3+)
	2. Decreased ratio of helper/inducer (OKT 4+) to suppressor/cytotoxic (OKT 8+) T-lymphocytes due to decreased helper/inducer (OKT 4+) T-lymphocytes
	3. Decreased natural killer (NK) cells (OKM1)
	4. Cutaneous anergy
	5. Decreased response to proliferative mitogens: phytohemagglutinin, concanavalin A, and pokeweed mitogen
B.	Hyperactive B-cell activity and refractoriness to signals for T-cell-independent B-cell activation
C.	Normal neutrophil function, but may have pancytopenia
D.	Increased levels of immunoglobulins—especially IgA and IgG
E.	Normal C_3, C_4 and immune complexes
F.	Presence of acid labile alpha interferon
G.	Presence of HLA-DR5

Kaposi's sarcoma is actually most common in equatorial Africa and eastern Europe. In Africa it comprises 9% of all neoplasms among African blacks. The fascinating finding regarding KS in Africa is the fact that its distribution is similar to that of Burkitt's lymphoma, a tumor considered strongly related to the Epstein-Barr virus, a herpes virus. CMV may be related to KS as Epstein-Barr virus is related to Burkitt's lymphoma. CMV, also a member of the herpes virus family and tightly associated with KS, may act as this cancer's promoter, or may cause an immunodeficiency state such that this tumor and opportunistic pathogens may grow.[5,15,20,21,56] Bacteria have also been implicated in the pathogenesis of KS.[59]

Mycobacterium avium-intracellulare is one of the several opportunistic organisms affecting AIDS patients. It has recently been reported as causing bacteremia and disseminated infection. It has been found in lymph nodes, bone marrow, liver, spleen, lung, and the intestinal tract of persons with AIDS.[60,61] The elimination of intracellular mycobacteria by

TABLE X: OCULAR MANIFESTATIONS OF AIDS (41 CASES)

CMV retinitis	22
Cotton wool spots	17
Fungal retinitis	1
Toxoplasmosis	1
Total	41

TABLE XI: CYTOMEGALOVIRUS RETINITIS (22 CASES)

AIDS risk group	Homosexual (19) IV drug abuser (3)
Median age	33.3 years
Sex	20 Male; 2 female
Race	Black (13) Hispanic (4) Caucasians (5)
Retinitis	22/22 (bilateral in 20)
Optic neuritis	7/22
Vitritis	15/22
Response to treatment	None
Final outcome	18/22 died
Survival following diagnosis (6 cases)	6.7 months
PCP	18/22
KS	3/22

macrophages is impaired,[62,63] and there is often no granuloma formation or chronic inflammatory reaction at the site of infection in AIDS patients.[64,65] *M avium-intracellulare* and *M gordonae* have been found within KS tissues.[65] Some authors advocate routine bone marrow biopsies of AIDS patients to establish presence or absence of *M avium-intracellulare.*[64]

Cryptospodium enteritidis, an uncommon cause of diarrhea, has also recently been described in AIDS.[66,67] The infection in AIDS manifests as a persistent, unremitting high volume diarrhea and malabsorption syndrome (the "gay bowel" syndrome).[68-70] It may be diagnosed by intestinal biopsy and/or stool sample. Other causes of diarrhea in AIDS include *Isospora belli, Eschericia coli,* hookworm, *Entamoeba histolytica, Giardia lamblia,* and *Campylobacter.*[68]

Other unusual diseases recently described in AIDS include *Toxoplasma gondii* encephalitis,[71,72] a Burkitt's-like B-cell lymphoma[73] and maternal death due to *Listeria monocytogenes* bacteremia.[74]

The cause of death in AIDS is most commonly CMV viremia and its associated lung and adrenal infection, with death usually occurring through pneumonia and hypotension.[75,76]

LABORATORY STUDIES/IMMUNOLOGY

Laboratory data on patients with AIDS indicate a severe deficiency in cell-mediated immunity, as manifested by cutaneous anergy, lymphopenia, poor to absent response to mitogens and antigens, and decreased natural killer cell function (Table IX). There is an absolute lymphopenia in

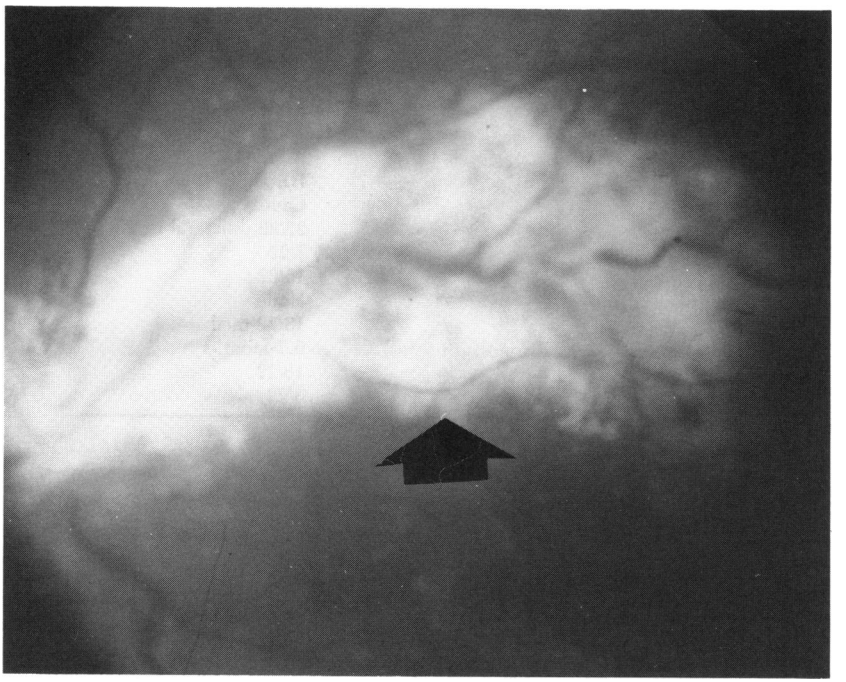

FIGURE 1
Clinica appearance of cytomegalovirus retinitis, left eye. Infection extends from disc into superotemporal quadrant and has typical granular white appearance.

AIDS, although there may be no leukocytopenia. The B to T cell ratio is normal, but absolute numbers of both B and T cells are decreased. Within the T-cell subsets, there is a decrease in helper/inducer cells (as assayed by OKT4 levels) and normal to increased suppressor cells, (as assayed by OKT8 levels) leading to an inverted and decreased helper to suppressor cell ratio, ie, decreased OKT4:OKT8.[14,17,19,22-34,56,57,97,98]

Inverted OKT4:OKT8 ratios have been found in 17% of healthy male homosexuals, as well as in patients with some viral infections (eg, infectious mononucleosis), following bone marrow transplant and in some healthy hemophiliacs; however, the inversion of the ratio in these cases is due to an increase in suppressor T-cells (OKT8), whereas in AIDS the ratio is inverted due to a decrease in helper T-cells (OKT4).[97,99-102] The fact remains, though, that an increase in suppressor T-cells may precede AIDS.[102] T-lymphocytes taken from lymph nodes, as opposed to peripheral blood samples, show a similar pattern of OKT4:OKT8 inversion. In

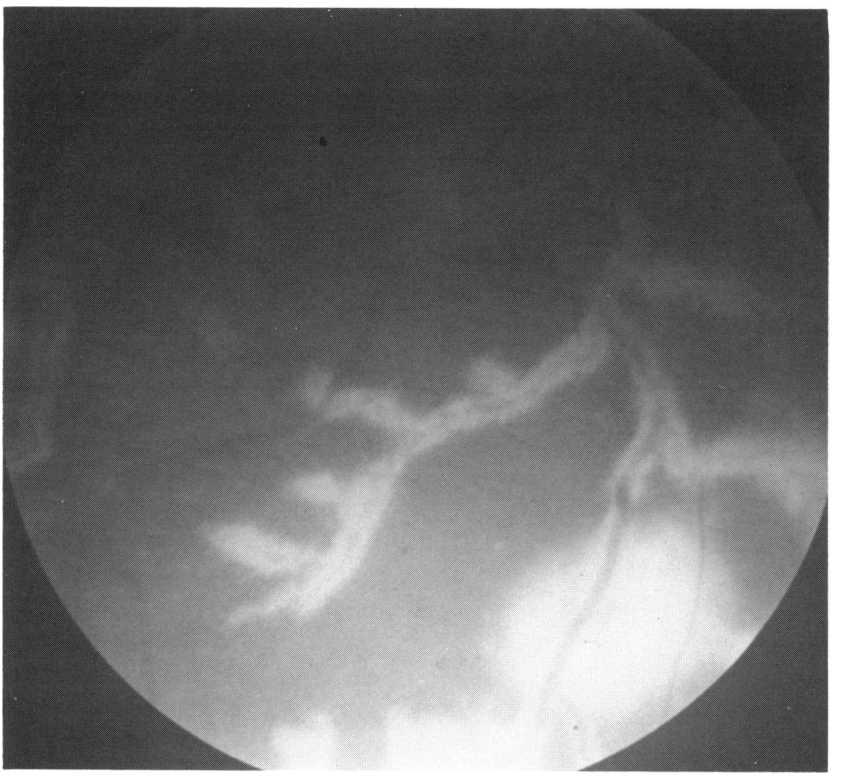

FIGURE 2
Clinical photograph of periphlebitis in a patient with cytomegalovirus (CMV) retinitis, right eye. Vasculitis extends inferiorly into a large area of CMV retinitis.

addition, lymph nodes in AIDS patients show an abundance of suppressor T-cells in the follicular center and mantle areas where these cells are normally uncommon.

A syndrome of lymphadenopathy (LAS) has been described in homosexual men which shows similar immunologic signs, including OKT4: OKT8 inversion. This is postulated to be a mild or early form of AIDS. Several persons with LAS have gone on to develop AIDS.[103,104] Pancytopenia has also been reported in AIDS.[105] There often remains normal B-cell function; however, there may be hyperactive spontaneous B-cell activity, as well as refractoriness to signals for T-cell independent B-cell activation. Polyclonal activation of B-cells may be responsible for the B-cell hyperactivity (eg, hypergammaglobulinemia). The scope of the immune dysfunction in AIDS extends to B-cells as well as T-cells.[106,107]

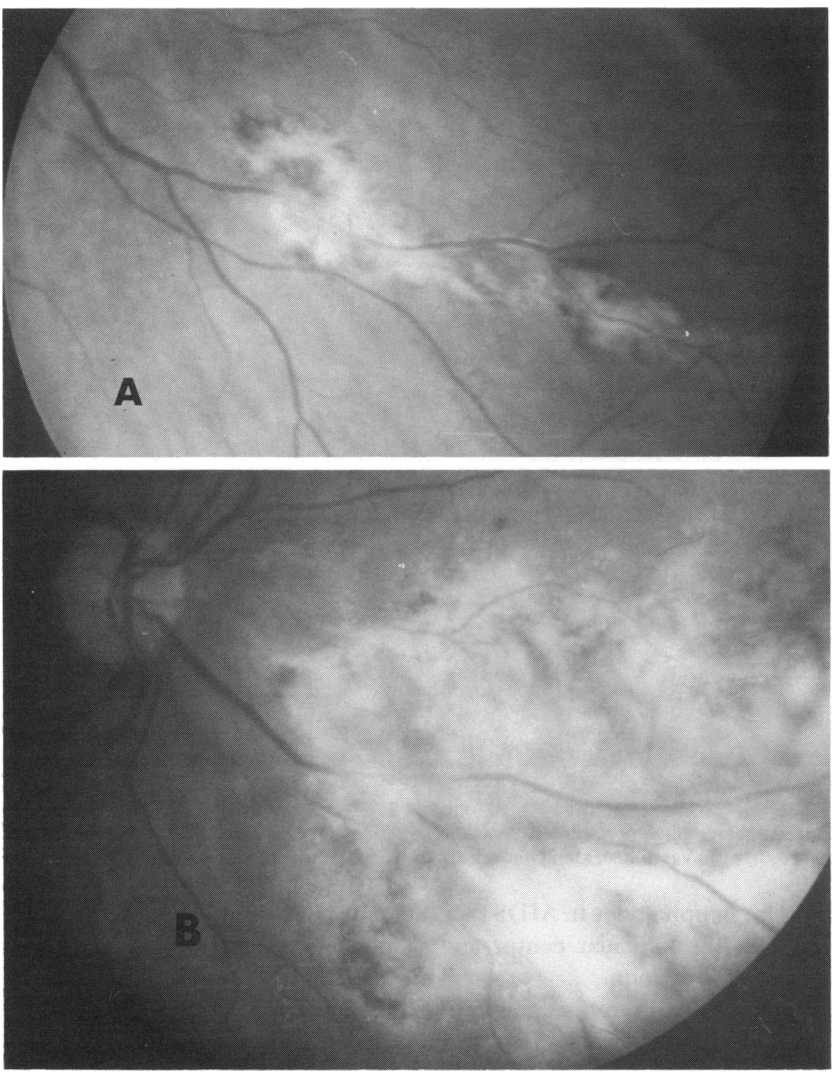

FIGURE 3
A and B: A shows and area of CMV retinitis in inferonasal quadrant, right eye. In B same area 6 weeks later. Lesion has only tripled in size. Note clarity of media.

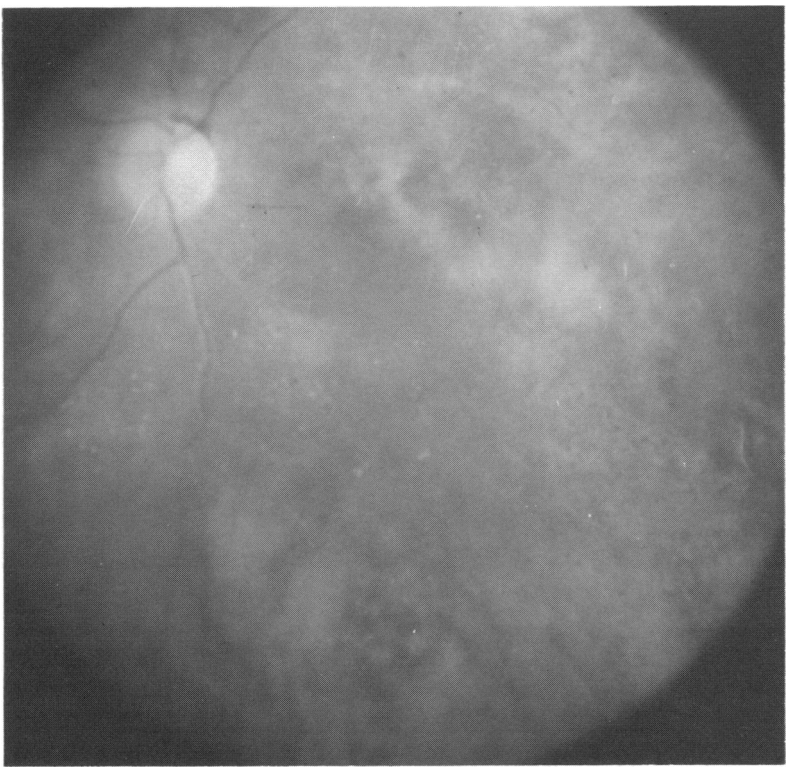

FIGURE 4
Photograph shows an area of atrophy and pigment dispersion in a location that previously had an active CMV retinitis. Note optic atrophy.

The immunoglobulins are normal or increased, with IgG and IgA the most consistently increased immunoglobulin; the increased immunoglobulins may be polyclonal.[14,17,19,22-34,56,57,99,108] Immune complexes and C_3, C_4 components of complement are normal.

Skin anergy[108] is reportedly an unreliable marker of decreased cell-mediated immunity in AIDS, since hypersensitivity may disappear well into the course of the disease. *In vitro* mitogen-induced lymphocyte transformations are reduced when lymphocytes are exposed to mitogen such as phytohemagglutinin. Interferon production is limited. The immune defect may be such that clonal losses are gradual and memory T cells are last to be lost.[109]

Acid labile alpha interferon is present in 8% of healthy homosexual men, 29% of homosexual men with LAS, and 63% of homosexual men

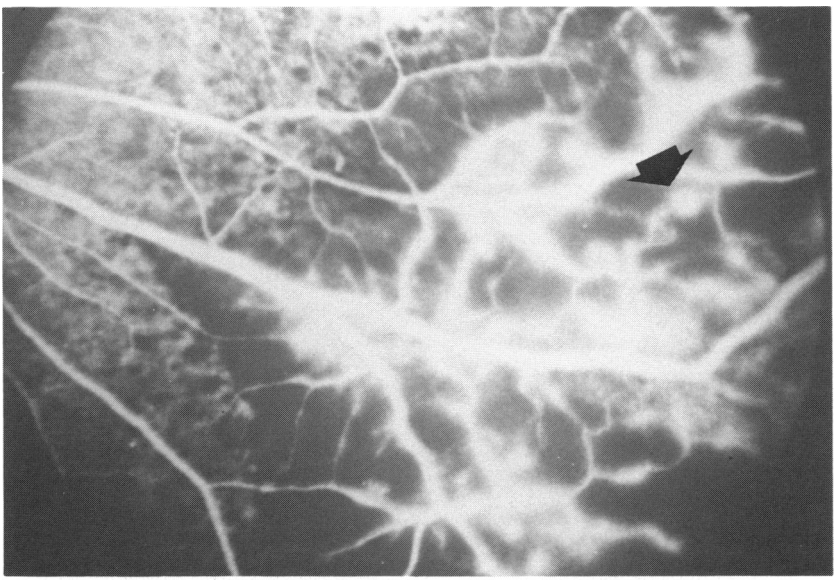

FIGURE 5
An intravenous fluorescein angiogram in a case of cytomegalovirus retinitis demonstrates areas of nonperfusion and marked leakage of dye. Note microaneurysms (*arrow*) on small vessels.

with KS and AIDS. These high interferon levels may be predictive of development of opportunistic infections or KS associated with AIDS, and may serve as a marker to identify asymptomatic numbers of high risk groups before development of clinical disease.[8,110,111]

There is an increase in human leukocyte antigen DRS in homosexual or bisexual men with KS and AIDS, as well as in LAS. There is no significant difference between the frequency of human leukocyte antigen DRS in persons with KS with AIDS and those with LAS. It is suggested that human leukocyte antigen DRS may afford a genetic susceptibility to the development of immunodeficiency in AIDS.[17,104,112]

The immunologic and clinical findings are suprisingly consistent across the groups contracting AIDS; that is, across male homosexuals and bisexuals, IV drug abusers, Haitians, and hemophiliacs. This fact, along with the sudden appearance of the syndrome, the geographic distribution and the fact that no cases of AIDS were diagnosed prior to 1979 speak for a single new epidemic of acquired immunodeficiency caused by a blood borne transmissible agent.[3,5,26,28-30,33,45,112] The epidemiologic trends

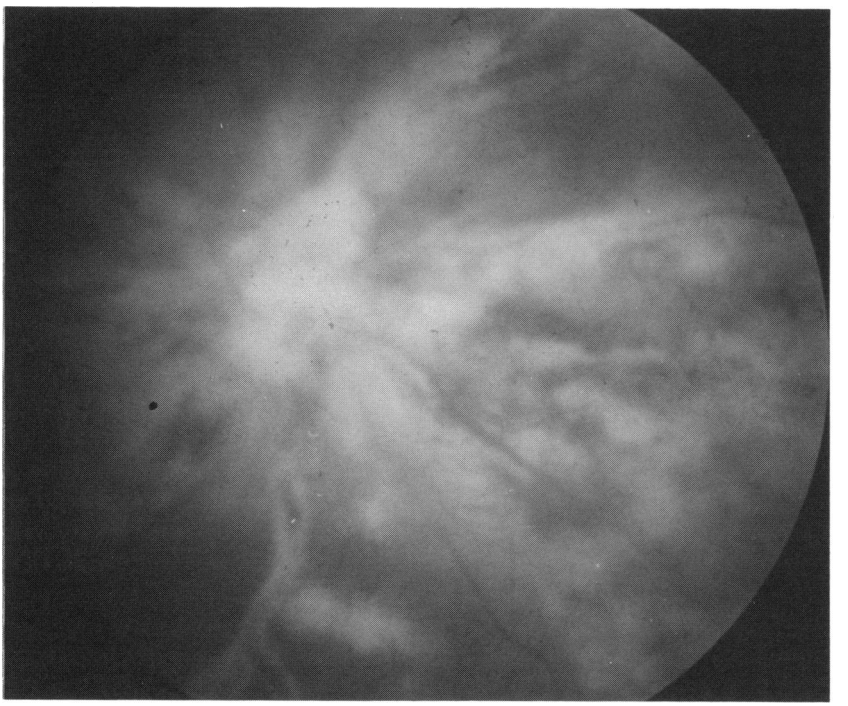

FIGURE 6
Clinical photograph of optic neuritis, right eye. Note presence of hemorrhages and periphlebitis.

indicate the gradual extension of an infectious agent into new populations.[113]

ETIOLOGY

Several possible etiologies for the syndrome have been proposed and rejected, such as amyl nitrite or butyl nitrite inhalant induced immunosuppression,[28,45,114-116] immunosuppression from semen or sperm,[117] and antigen overload.[112] These theories do not explain all cases. Additional proposed theories include the following: AIDS may be due to a lack of natural immunity secondary to the overuse of antibiotics,[118] AIDS may be due to a failure of the immune system to control viruses, which then result in neoplasia.[119] It has been suggested that a lymphotrophic agent (probably a virus) causes AIDS through destruction of certain populations of lymphoid cells.[120] Another theory states that since leukocytes in semen

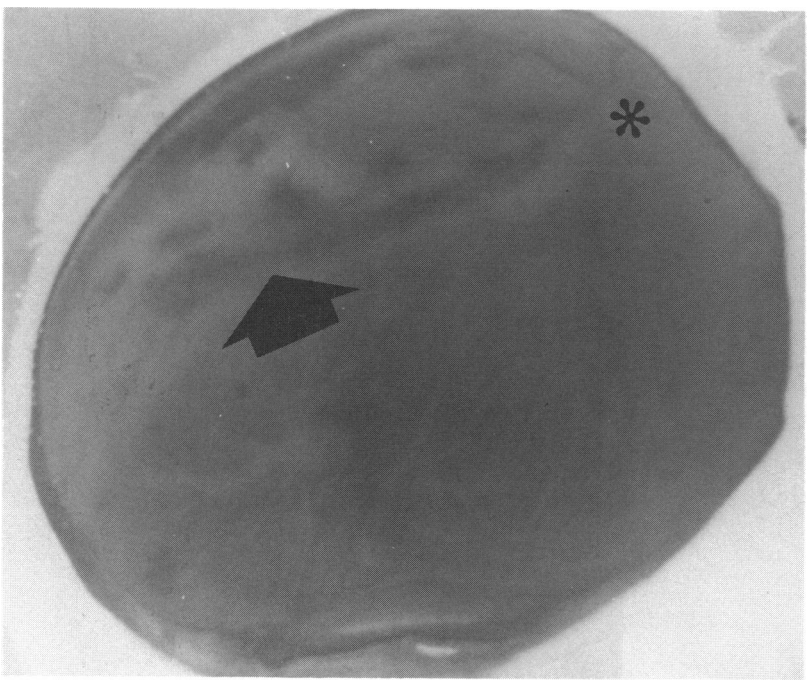

FIGURE 7
Gross photograph of a postmortem eye with cytomegalovirus retinitis. Involvement extends from disc (*asterisk*) to periphery (*arrow*).

have been shown to efficiently infect lymphoid tissue in the rectal mucosa of a partner, a common virus carried in these infecting leukocytes could cause AIDS in the partner through the unusual route of transmission.[121] Still another hypothesis related to the thymic dysplasia seen in AIDS, which is comparable to the thymic dysplasia in genetically determined severe combined immunodeficiency,[122] and similar to that in graft versus host disease. The theory states that the induction of thymic dysplasia through injury to the thymic endothelium may be the critical event in relation to the immunologic abnormalities seen in AIDS.[123]

Human T-cell leukemia virus (HTLV) has been reported in connection with AIDS. HTLV is a retrovirus, and antibody to HTLV may be detected in approximately 25% of persons with AIDS or LAS.[121,125] While the T-cell is the target of HTLV, the virus appears to be common in persons with AIDS.[126,127] Although the T-cell shows the greatest level of dysfunction of all cells in AIDS,[126,127] it is not likely that HTLV is the cause of

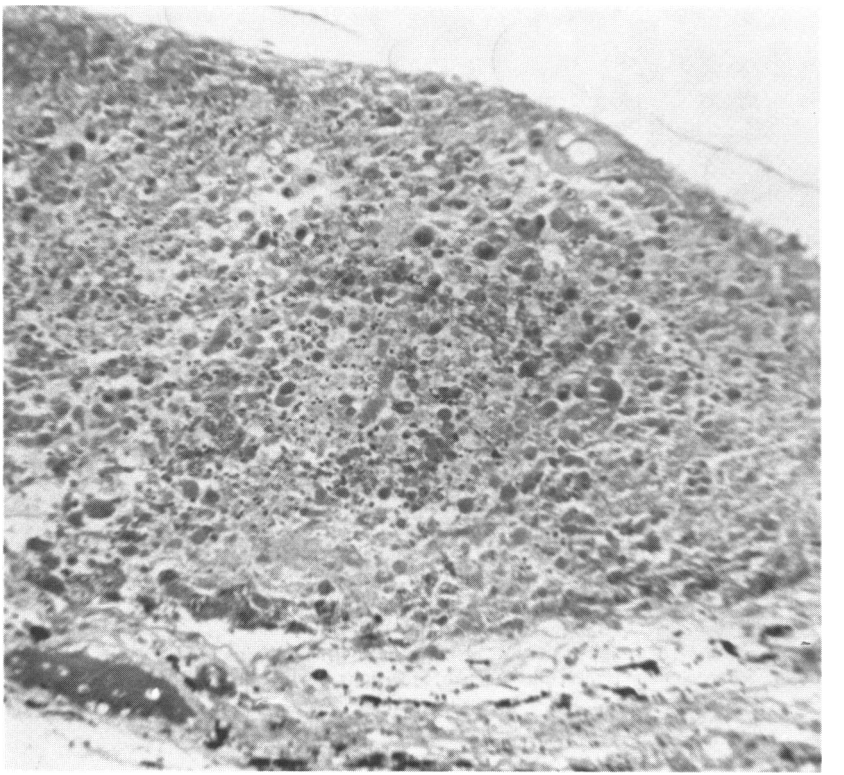

FIGURE 8
Photomicrograph shows an area of full-thickness retinal and retinal pigment epithelial necrosis in a case of cytomegalovirus retinitis (hematoxylin and eosin, × 150).

AIDS.[125,128] HTLV is not cytopathogenic; rather HTLV immobilizes helper T-cells. The HTLV retrovirus infects the T-cell, the thymus is destroyed (this may relate to the thymic dysplasia), and a lymphoma of T-cells is formed. In AIDS, however, B-cell tumors are generally formed. The prevalence of antibody to HTLV in AIDS patients may reflect the generally increased antibody to many infectious agents in AIDS.[125] HTLV may act as a cofactor in AIDS, AIDS may be related to HTLV with antigenic cross reactivity, or most likely, HTLV may be another opportunistic agent affecting persons with AIDS.[128]

Cytomegalovirus has received a great deal of consideration as a possible cause of AIDS. It is known that infection with CMV causes a transient immunosuppression in the acute and convalescent stages, with a reversal

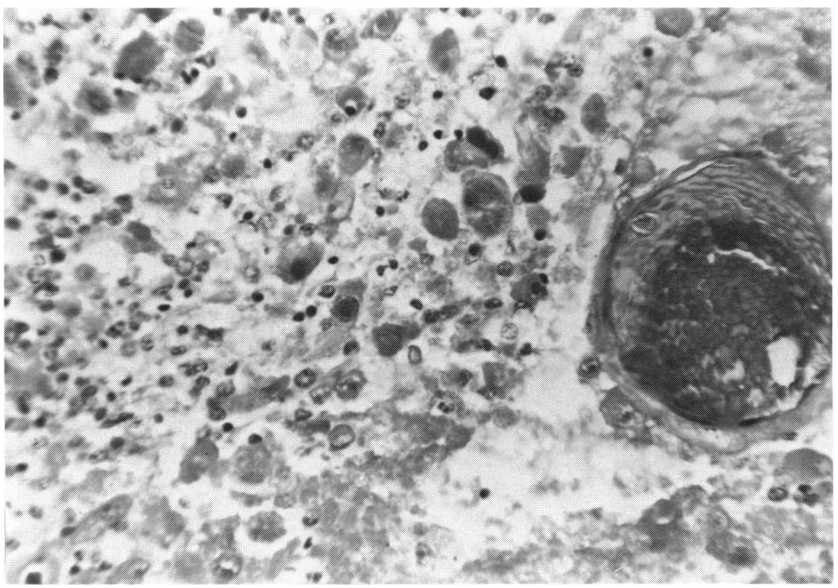

FIGURE 9
High-power view of retina in a case of cytomegalovirus retinitis. Many large cells are present. Some contain typical intranuclear inclusions (owl's eye cells) (hematoxylin and eosin, ×250).

of the helper:suppressor T-cell ratio; however, over 90% of homosexuals have positive antibody titers for CMV, making the role of CMV in AIDS unclear. Almost all patients with AIDS have proven CMV. One theory states that CMV is causative for AIDS. Homosexuals are constantly exposed to CMV, and CMV can be transmitted by blood transfusions.[6,15-21,29,45,129] Furthermore, in renal transplant patients, the highest incidence of CMV infection is in immunocompromised hosts, and is most frequently manifest as asymptomatic shedding of the virus.[129]

Chronic CMV exposure and infection may act to cause a severe AIDS[6,15-21,29,45,129]; it may act to permit infection by *Pneumocystis carinii*[18]; or it may act as a cancer promoter for KS, as on oncogenic human virus.[20] CMV may act to cause immunosuppression particularly in those people with human leukocyte antigen-DR5; these people may be genetically predisposed to immunosuppression by any means, and are more likely to develop KS.[17,104,112]

There are several other theories regarding the etiology of AIDS. A new virus could be causative,[45] possibly resembling hepatitis B virus in its

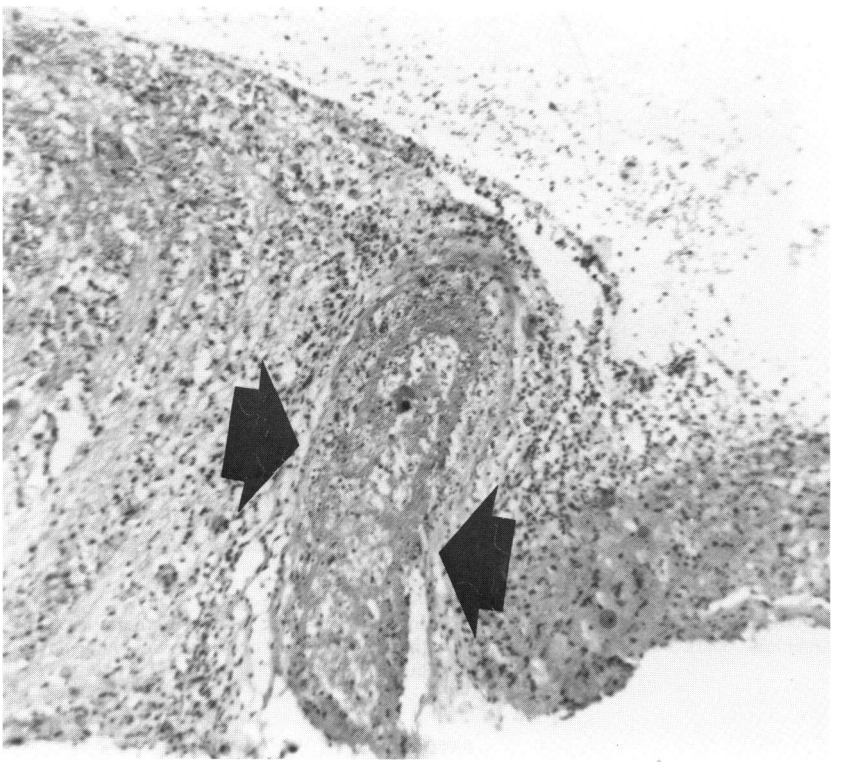

FIGURE 10
Photomicrograph shows an occlusion of central retinal artery in optic nerve head (*arrow*) (hematoxylin and eosin, ×150).

biologic behavior and epidemiology.[130] Indeed, the transmission of AIDS resembles that of hepatitis B virus.[112] Epstein-Barr virus, *herpes simplex* or hepatitis B virus may be causative.[14,131] Sexual promiscuity may increase the risk of acquiring the disease.[132] Healthy people may act as vectors for the disease.[24] There may be a latent broad based cellular immune deficiency in homosexual men manifest with exposure to certain pathogens in particular combinations.[14] Lastly, malnutrition, especially a zinc deficiency, may play a role in increasing the immune deficit, but correcting the nutritional status does not have much affect on the disease.[14]

The hypothesis with the most support currently suggests that a still unidentified virus causes AIDS.[16] It is most likely, however, that multiple factors, rather than a novel virus alone, induce AIDS.[133]

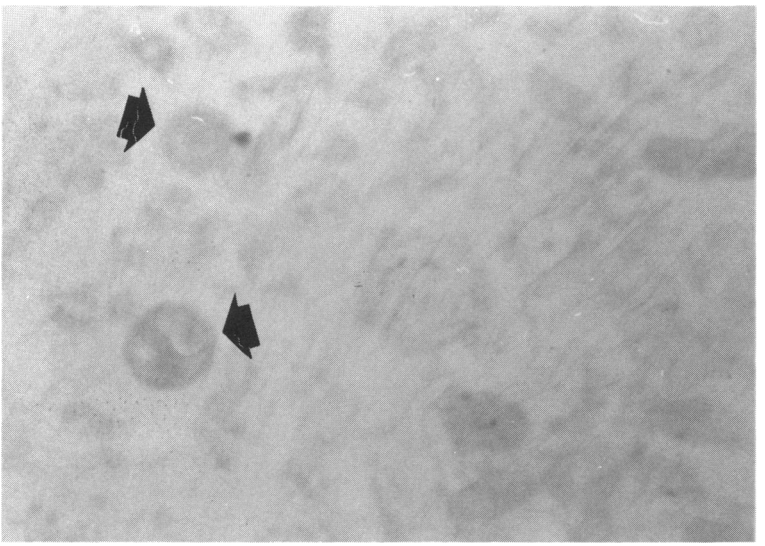

FIGURE 11
Photomicrograph of sections stained for cytomegalovirus using indirect immunoperoxidase technique. Dark areas on cell surface and within cells indicate presence of cytomegalovirus (methylene blue counterstain, ×625).

PATHOLOGY

AIDS patients may manifest unusual lymph node pathology. There are two different morphological patterns seen on lymph node biopsy. Patients with follicular and paracortical hyperplasia show no clinical deterioration, whereas those patients with AIDS with an abnormal pattern of lymphoid proliferation show rapid development of non-Hodgkin's lymphoma and/or opportunistic infections.[77] Thus lymph node morphological findings may be a predictor of outcome in AIDS.[77]

At the ultrastructural level, tubuloreticular structures and test tube and ring shaped forms have been described as cytoplasmic structures in AIDS lymph nodes.[78-83] Tubuloreticular structures occur in 80% to 95% of AIDS patients studied; test tube and ring shaped forms occur in 39%, and are never present in the absence of tubuloreticular structures. Tubuloreticular structures are seen in systemic lupus erythematosis and other collagen vascular and autoimmune diseases, viral infections, and some diseases of obscure etiology. Tubuloreticular structures can be induced by alpha and beta interferon but not gamma interferon. AIDS patients have acid labile alpha interferon in their serum.[82] Test tube and ring

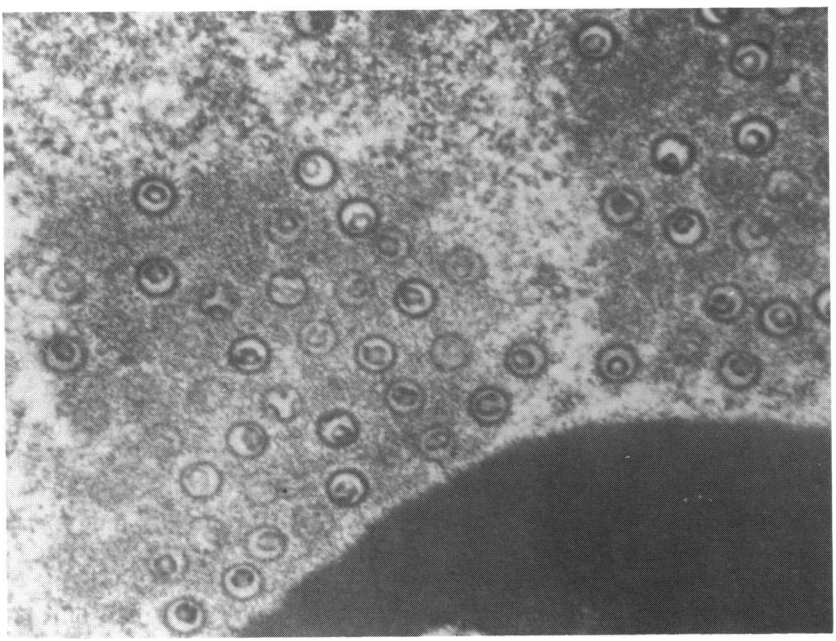

FIGURE 12
Electron micrograph of nucleus of an infected retinal cell in a case of cytomegalovirus retinitis demonstrating viral particles consistent with a herpes family virus. Note typical hexagonally shaped capsomers (×60,000).

shaped forms have been described before in HTLV,[81] *Herpes simplex* virus and CMV. Test tube and ring shaped forms have been induced in chimpanzees with non-A non-B hepatitis virus serum, but the test tube and ring shaped forms are seen only during the incubation period.[83] Tubuloreticular structures and test tube and ring shaped forms are relatively uncommon, and may function as a marker for AIDS.

OCULAR INVOLVEMENT

The ocular manifestations of AIDS are for the most part due to the opportunistic infections and neoplasias seen in the syndrome. Infections of CMV, *Pneumocystis carinii*, toxoplasmosis, *Candida albicans*, *Cryptococcus* sp, and *M avium-intracellulare* have been reported.[76,84-95] Conjunctival KS has been noted as well.[94]

Ocular findings were observed in 41 of 71 (57.8%) of AIDS patients examined during the period from April 1981 to December 1983 (Table X,

Appendix I). The majority (55 cases) were seen on referral from the medical service subdivisions of Clinical Immunology and Infectious Diseases. The remainder (16 cases) were seen as consultations from referring ophthalmologists. Some of the patients were examined only once while the remainder were followed for months usually until the patient's death. The presence of certain lesions like cotton wool spots which are evanescent may reflect the fact that they were present at the time of a particular examination. The lesions of CMV on the other hand, once present, do not abate and are present until the eventual death of the patient.

CYTOMEGALOVIRUS RETINITIS

Cytomegalovirus retinitis was the most common intraocular lesion observed in the group of 41 patients with retinal manifestations (Table XI). Retinal involvement by CMV was observed in 22 patients of whom 19 were homosexual males and 3 were IV drug abusers (2 females and 1 male). Their median age was 33.3 years (Table XI). During the past year, the median age of patients with CMV retinitis has gradually crept upward mirroring the rise in age of AIDS patients seen in the past year. PCP was present, at some time, in 18 of 22 patients with CMV retinitis while 3 of 22 patients with CMV retinitis had lesions of KS (Table X). The outcome in 18 of these 22 patients was fatal, reflecting the generally hopeless prognosis for AIDS patients with extraocular CMV infections. This is not surprising as no form of antiviral therapy alone or in combination with interferon has proven effective in halting the progression of the disease. Macher and co-workers[75] recently emphasized this point by demonstrating in an autopsy study, the presence of disseminated CMV in 14 of 15 AIDS cases.

The retinal manifestations of CMV in the AIDS patient produces such a characteristic picture that on several occasions the ocular diagnosis preceded viral isolation from various bodily fluids such as urine (Fig 1). Although the presence of serum antibody titers to CMV is the usual observation, in four of the cases either negligible or absent titers were reported. The retinal lesions are white and granular (resembling the classic description "crumbled cheese") in appearance and often associated with hemorrhage (Fig 1). Foci of CMV infection nearly always commence in the posterior pole although isolated cases may be seen in the periphery. In the posterior fundus, CMV involvement usually follows a vascular distribution in producing either large necrotic areas or smaller perivascular infiltrates (Fig 2). Lesions of all sizes progress so slowly that they may double or triple in dimension in 1 month's time (Fig 3A and B). As the areas of retinal and eventually retinal pigment epithelial necrosis resolve,

TABLE XII: COTTON WOOL SPOTS (17 CASES)

AIDS risk group	Homosexual (14) IV drug abuser (3)
Median age	31.7
Sex	6 Male; 1 female
Race	Caucasian (12) Black (5)
Bilaterality of retinal lesions	14/17
PCP	15/17
KS	4/17

large zones of atrophy appear, often accompanied by foci of pigment dispersion (Fig 4). Fluorescein angiography has been helpful in studying the retinal infection. One nearly always sees occlusion of retinal vessels with concomitant nonperfusion of large areas of retina (Fig 5). The retinal vaso-occlusion seen in the AIDS patient with CMV retinitis is similar to that seen in other opportunistic infections such as *Herpes simplex* retinitis and mucormycosis involvement of the optic nerve and adjacent retina. The retinal involvement is also similar to the vascular occlusions seen in the acute retinal necrosis syndrome. Acute retinal necrosis syndrome begins in the periphery, progresses rapidly, and is unassociated with systemic disease of any sort, to date. Although poor perfusion appears mainly as a retinal problem, background choroidal fluorescence is diminished suggesting the process extends to this level. Histopathological studies though have only shown choroidal infiltration with inflammatory cells producing a nongranulomatous inflammation without the presence of CMV. Microaneurysms, can be observed along dilated vessels in areas of necrosis (Fig 5). Angiograms routinely show extensive leakage in the necrotic zones.

In 7 of the 22 patients with CMV retinitis, an optic neuritis was present (Fig 6). Involvement of the optic nerve always produces a precipitous decrease in visual acuity compared to the remarkably excellent preservation of vision in patients with widespread areas of CMV retinitis with necrosis. The disc is elevated and the margins blurred, at first, and then becomes engulfed by a yellow-white mass with hemorrhage. Retrobulbar cases of optic neuritis have been seen in which the loss of vision is accompanied by the appearance of optic atrophy.

A minimal vitritis may be present in face of massive degrees of retinal necrosis. In no patient did the vitritis progress to a point which precluded a clear view of the fundus. Indeed in the majority of patients who exhibited significant degrees of retinal necrosis, the vitreous was only minimally involved. CMV was isolated from the vitreous antemortem, in two

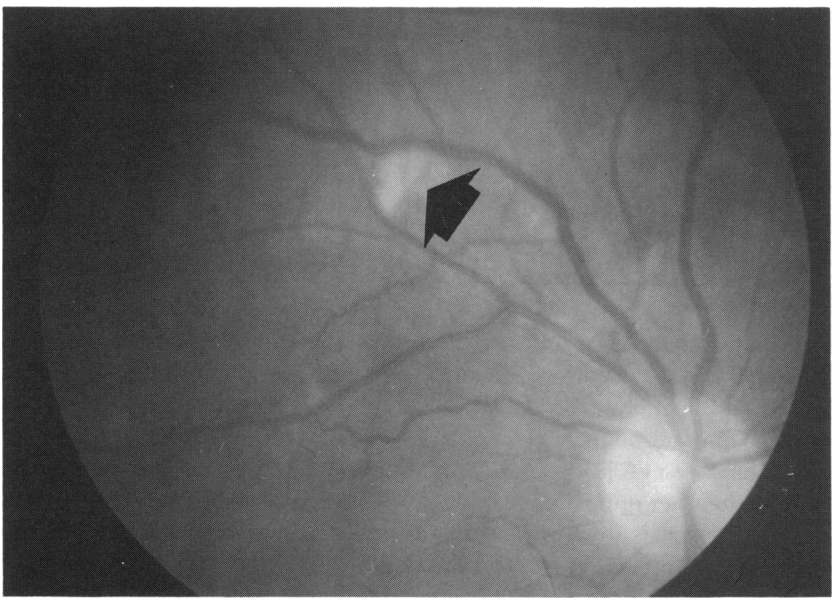

FIGURE 13
Clinical photograph demonstrates typical cotton wool spots, right eye. Patient had a concomitant *Pneumocystis carinii* pneumonia.

patients by simple aspiration through the pars plana, and postmortem in one patient. Anterior uveitis although often present in patients with CMV retinitis was invariably negligible.

Six pairs of eyes obtained as part of a complete autopsy were studied by histopathological examination. Studies of the gross specimens revealed extensive areas of necrosis often extending from the posterior pole to the periphery (Fig 7). Histological sections showed extensive areas of full-thickness retinal and retinal pigment epithelial necrosis (Fig 8). Affected areas of retina contained typical intranuclear and intracytoplasmic inclusions in cytomegalic cells (Fig 9). Some of these cells demonstrated the typical owl's eye appearance characteristic of CMV infection. In a few instances a neutrophile response rather than the typical lymphocyte response was seen. The presence of the neutrophile responses may reflect the depth of mononuclear cell depression present in the AIDS patient in general. Occluded vessels of all calibers were observed in involved areas of the retina and optic nerve (Fig 10). A nongranulomatous inflammatory response was present in areas of choroid subjacent to involved retinal areas. CMV was demonstrated in the retina by indirect immunoperoxi-

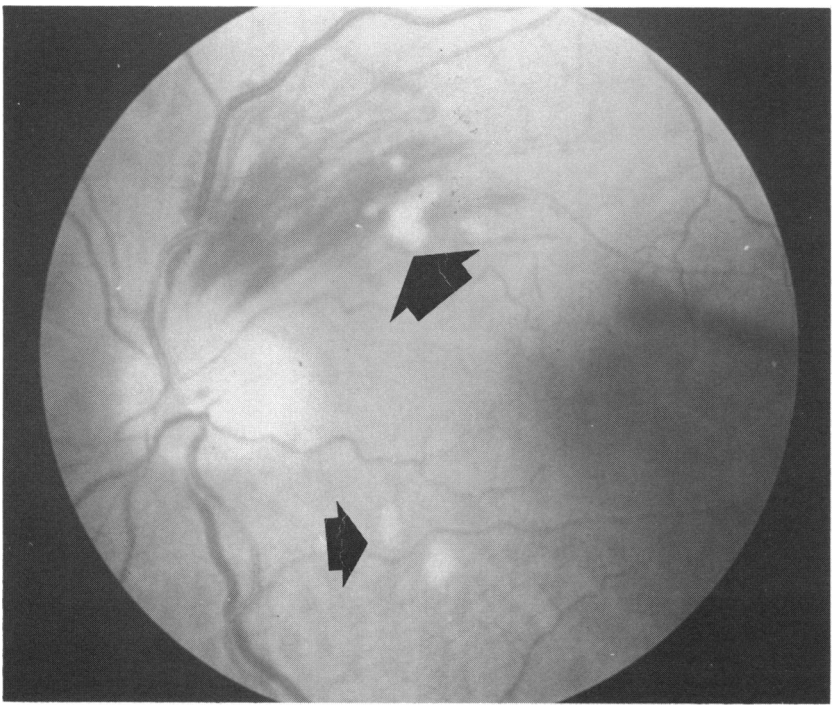

FIGURE 14
Hemorrhages accompany cotton wool spots lying in superotemporal arcade (*large arrow*).

dase stains prepared specifically against CMV (Fig 11). Electron micrographs showed typical CMV as one of the typical herpes virus family. The hexagonal capsomers of CMV were present in retina and in retinal pigment epithelium (Fig 12). Incomplete virions were seen, as well (Fig 12).

The development of CMV retinitis in an AIDS patient is a poor prognostic sign. The lesions have not responded to treatment with antiviral agents such as acyclovir or vidarabine either alone or in combination with interferon. Bone marrow transplantation has been equally unsuccessful. Eighteen of the 22 patients with CMV retinitis have died usually within 6 months from the time of first observation of the retinal involvement. In one patient (patient 9, Appendix I), the diagnosis of CMV retinitis and AIDS was not made by the referring ophthalmologist. Inadvertant treatment with high doses of systemic corticosteroids had produced an atypically rapid progression of the retinal lesions. The rapid progression was

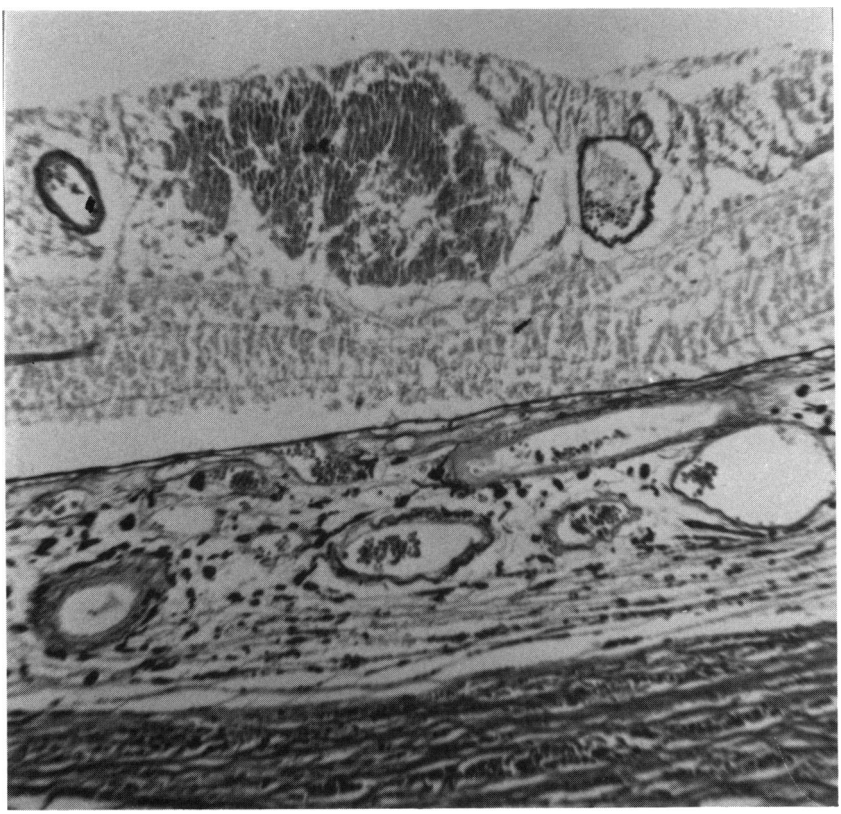

FIGURE 15
Photomicrograph of eye shows a cytoid body in superficial retina (hematoxylin and eosin, ×60).

halted by the termination of the corticosteroid therapy, but this did not affect the eventual outcome.

COTTON WOOL SPOTS

Cotton wool spots were the second most common retinal finding in this group of 41 AIDS patients and were seen in 17 individuals (Table XII, Appendix I). Fourteen patients of the group were homosexual males while 3 were IV drug abusers. Fifteen of the 17 patients had PCP at the time the cotton wool spots were observed. Several of the patients had infections with other opportunistic agents such as *Candida* sp, CMV, and *Herpes simplex* virus at that time. In five patients of the group, no other

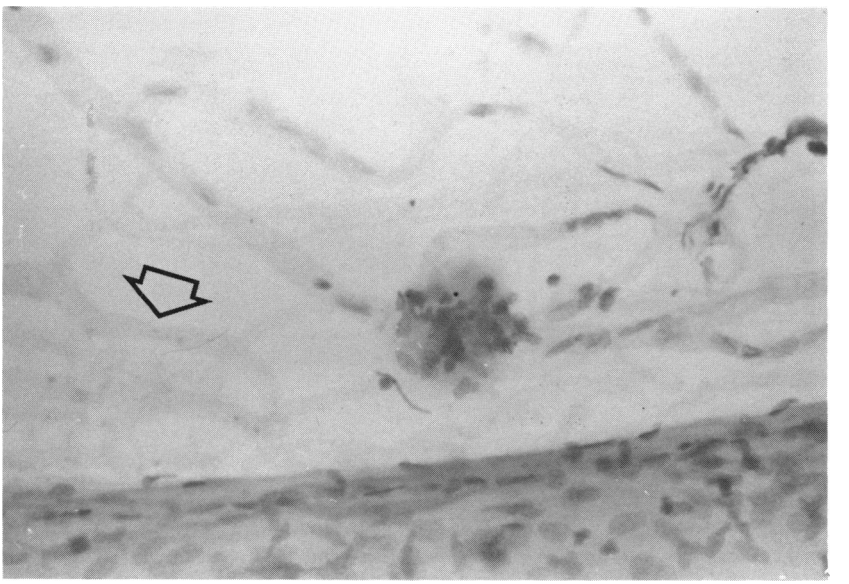

FIGURE 16
Photograph of a trypsin-pepsin digest of retina demonstrates a zone of microvascular damage (*arrow*) manifested by loss of endothelial cells and pericytes. A microaneurysm is present at center of photograph (periodic acid-Schiff reagent with hematoxylin, ×625).

opportunistic organism was demonstrable at the time the cotton wool spots were seen. Four of the patients had nonocular KS. Of the four patients with KS, one was an IV drug abuser and three were homosexuals.

The cotton wool spots were bilateral in 14 of 17 cases and were quite similar in appearance to those seen in diseases associated with the presence of circulating immune complexes or microvascular occlusive disease (Fig 13). Thus, in none of the patients were conditions such as diabetes mellitus, collagen-vascular disease, untreated hypertension, or severe anemia present. Circulating immune complexes have been demonstrated in patients with PCP.

The cotton wool spots are white and fluffy, present at the posterior pole and are superficial in the retina. They resolve in 4 to 6 weeks leaving no clinical trace. New lesions may develop as older ones resolve. In only 1 case of the 14, were flame-shaped hemorrhages present, as well (Fig 14). Fluorescein angiography revealed foci of retinal capillary nonperfusion.

Histopathologic studies of autopsy eyes demonstrated typical cytoid bodies in the nerve fiber layer (Fig 15). Retinal digests using the trypsin-

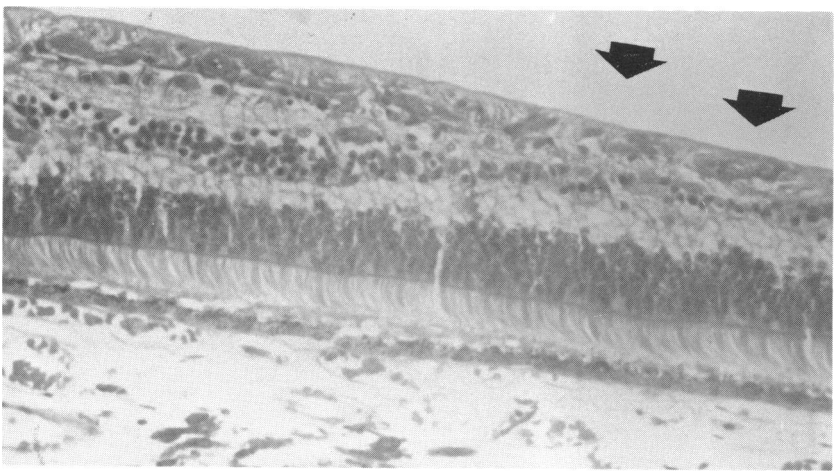

FIGURE 17
Photomicrograph shows a healed area where a cotton wool spot had been present clinically and a cytoid body histopathologically. Inner retina is focally atrophic (*arrows*) (hematoxylin and eosin, ×100).

pepsin technique showed evidence of microvascular damage as manifested by loss of pericytes, degenerating endothelial cells, nonperfused areas and occasional microaneurysms (Fig 16). Healed areas of retina where a cotton wool spot had existed clinically revealed typical thinning of the superficial retina (Fig 17).

Both electron microscopic studies and special silver stains of light microscopic sections failed to reveal *Pneumocystis carinii* organisms in or near cystoid bodies in the retina. Control preparations taken from the infected lungs of patients with PCP and cotton wool spots in the retina easily demonstrated the organisms in the lung only, with silver stains (Fig 18). No other opportunistic organisms were demonstrable in the retinas of these patients.

FUNGAL RETINITIS

Unilateral fungal retinitis was observed in a male, Hispanic, IV drug abuser who had AIDS (Table XIII, Appendix I). He was a confirmed heroin addict who had been using drugs up until the time of admission to the hospital. The retinitis was due to *Candida albicans* and was associated with *Candida* sepsis and widespread dissemination. The retinal lesion in this case was revealed as a white, intraretinal discrete, creamy focus. In time, satellite lesions developed with eventual spread to the vitreous (Fig

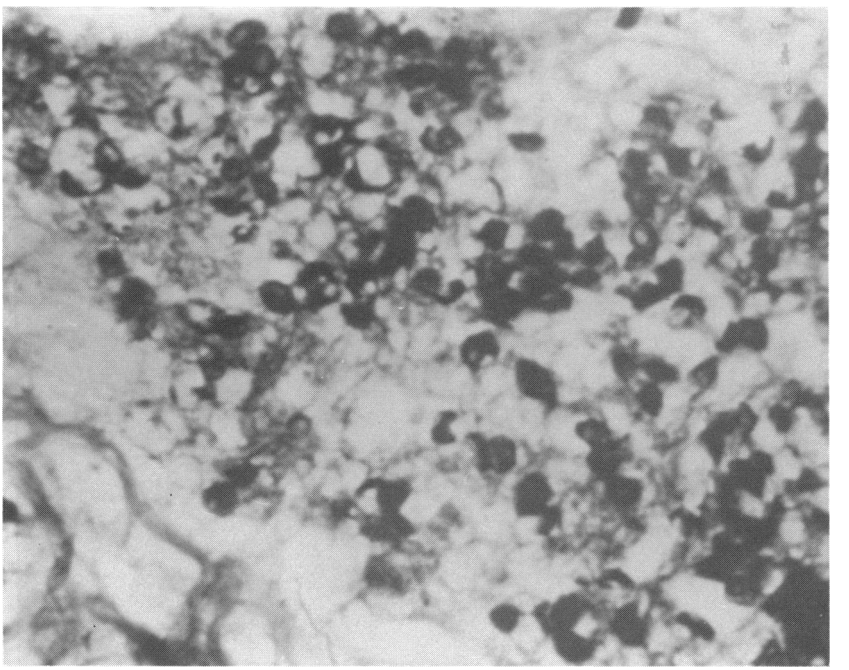

FIGURE 18
Silver stain of lung tissue of a patient who had cotton wool spots in retina and *Pneumocystis carinii* pneumonia. Numerous *P carinii* organisms are present in lung. None were demonstrated in eye (Gomori methenamine silver [modified], ×625).

19). Histopathologic studies of the eye revealed large areas of retinal necrosis. Fungi were present in the retina (Fig 20A and B). No other opportunistic organisms were demonstrable in the eye.

Although this patient had unequivocal AIDS by the usually accepted

TABLE XIII: FUNGAL RETINITIS (1 CASE)

AIDS risk group	IV drug abuser (1)
Median age	27
Sex	1 Male
Race	Hispanic (10)
Retinitis	1 (unilateral)
Vitritis	1
Response to treatment	0
Pathogen	*Candida albicans*
Final outcome	Died
PCP	1
KS	0

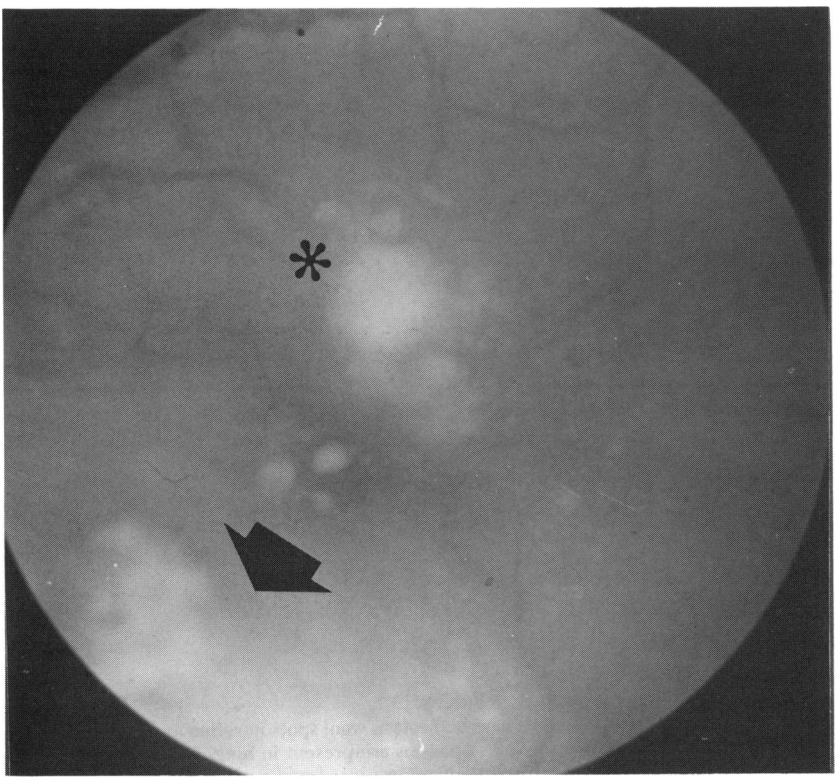

FIGURE 19
Clinical photograph of *Candida albicans* retinitis in an IV drug abuser with AIDS. Primary focus of infection is designated by *asterisk* and satellite lesions by *arrow*.

criteria, it must be borne in mind that introduction of the organisms may have been by the intravenous route, possibly in association with contaminated heroin. Mucocutaneous candidiasis is quite common in AIDS patients, *Candida* sepsis is not.

TOXOPLASMOSIS RETINOCHOROIDITIS

In the course of examining the 71 AIDS patients, 1 was noted to have ophthalmoscopic evidence of toxoplasmosis retinochoroiditis (Table XIV, Appendix I). The case occurred in a homosexual male who had been seen at another institution 5 months previously with bilateral cotton wool spots. When seen on this occasion, the patient was known to have toxoplasmosis of the central nervous system manifested by a frontal abscess. Serological studies revealed a positive toxoplasmosis titer by the indirect

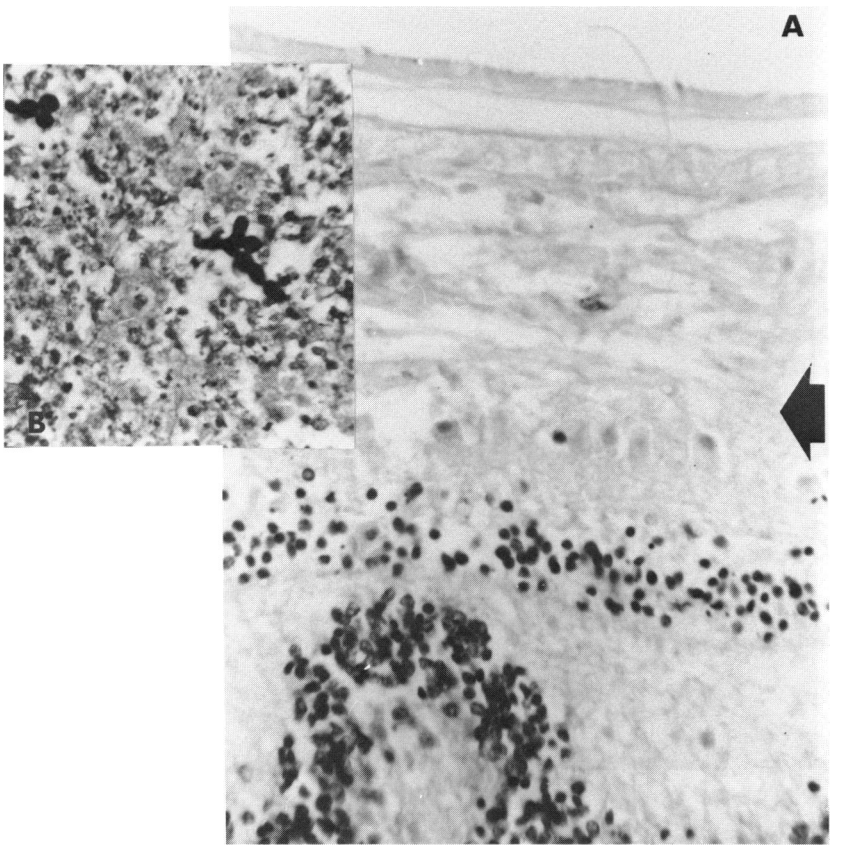

FIGURE 20
A and B: Photomicrograph in A shows an area of superficial retinal necrosis at edge of one of the satellite lesions depicted in Fig 19 (hematoxylin and eosin, ×625). B: High-power view demonstrates *Candida* organisms in lesion (Gomori methenamine silver, ×1000).

fluorescence antibody technique at 1:128. Ophthalmoscopy demonstrated mild vitreous haze overlying a yellow-white slightly raised intraretinal lesion with irregular borders (Fig 21). No fundus scars consistent with previous infection were present. An examination 6 weeks later revealed the lesion had doubled in size. Enlargement was unimpeded by treatment with clindamycin, pyrimethamine, and triple-sulfas. The patient expired and gross examination revealed a large necrotic mass in the posterior pole. Histopathologic examination demonstrated a necrotizing retinitis with total obliteration of the retinal architecture (Fig 22). There was a paucity of inflammatory cell reaction in and around the necrotic

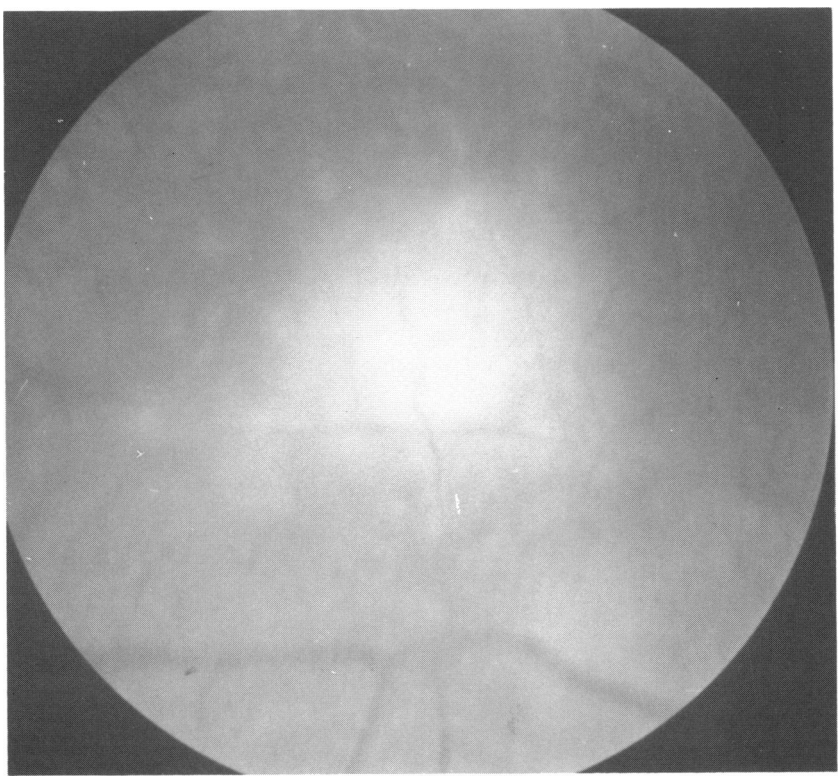

FIGURE 21
Clinical photograph shows a focus of toxoplasmosis retinochoroiditis in an AIDS patient.

TABLE XIV: TOXOPLASMOSIS (1 CASE)

AIDS risk group	Homosexual (1)
Median age	35
Sex	1 Male
Race	Caucasian (1)
Retinochoroiditis	1 (unilateral)
Vitritis	1
Response to treatment	0
Final outcome	Died from toxoplasmosis brain abscess
PCP	1
KS	0

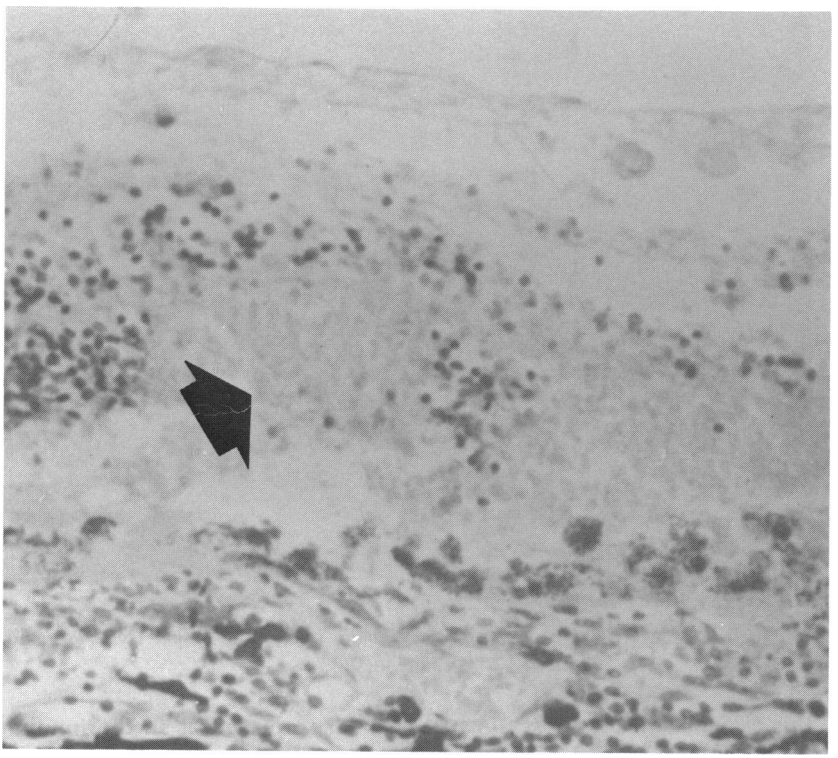

FIGURE 22
Photomicrograph demonstrates an area of full-thickness retinal necrosis in a case of toxoplasmosis retinochoroiditis (hematoxylin and eosin, ×150).

focus. Cysts of *Toxoplasma gondii* were easily observed in the necrotic area and the environs (Fig 23). The cysts measured about 20 to 30 μm in diameter and contained basophilic organisms within. The choroid contained an inflammatory infiltrate containing lymphocytes and neutrophiles.

Toxoplasmosis is the most common cause of posterior uveitis in humans.[96] Less than 1% of patients who acquire toxoplasmosis in adult life develop ocular lesions. Consequently, the majority are acquired congenitally. Most cases of ocular toxoplasmosis retinochoroiditis encountered in clinical practice occur in apparently healthy individuals. Although toxoplasmosis is known to cause central nervous system, visceral, and lymph node infection in immunosuppressed individuals, ocular toxoplasmosis in

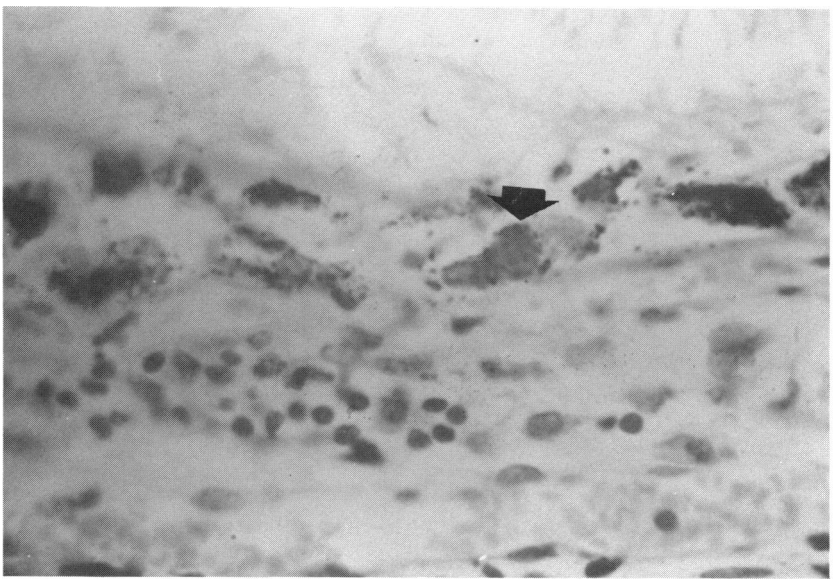

FIGURE High-power view shows *Toxoplasma gondii* in necrotic tissue. Cysts are readily identified (*arrow*).

this circumstance is most unusual.[134-137] Toxoplasmosis in the immunocompromised host is an aggressive and often fulminant disorder.

TREATMENT

The mortality rate in AIDS following the development of opportunistic infection of KS approaches 100%.[11,13] Among the treatment modalities tested in AIDS patients are interleuken-2, beta interferon, and bone marrow allografting.[138-140] Highly purified interleuken-2 has been shown to potentiate the depressed cytotoxic activity of peripheral blood lymphocytes from homosexual men with AIDS *in vitro*.[138,139] Beta interferon has no effect on the cytotoxic function of peripheral blood lymphocytes of this same group of AIDS patients *in vitro*.[138] Bone marrow allografting late in the course of AIDS is ineffective in restoring immune function to normal. It is not known what the effect of bone marrow grafting would be earlier in the course of the disease.[140]

PREVENTION

The recommended precautions to prevent spread of AIDS are consistent

with those for the prevention of hepatitis B.[48,55] The recommendations include elimination of sexual contact with AIDS or suspected-AIDS cases, reduction in the number of sexual partners and elimination of intravenous drug abuse.[141] Persons in established risk groups should not donate blood. Sexually active homosexuals continue to be at highest risk due to the concentration of the disease in that community and their large number of risk factors.[3,17]

SUMMARY

AIDS is a reliably diagnosed disease that is indicative of an underlying cellular immunodeficiency with no other cause for the disorder. To date over 2000 cases have been reported in North America and Europe and the number is rising. Patients fulfilling the definition for AIDS have included male homosexuals, IV drug abusers of both sexes, people from Haiti, heterosexual partners of AIDS patients, hemophiliacs, and some patients who fit no particular pattern. The etiology has been attributed to factors acting singly or in synergy namely that repeated exposure to CMV, semen, or other antigens results in progressive cellular immunodeficiency, or alternatively, a novel virus has an etiologic role.

The epidemiology of the syndrome suggests a horizontally transmissible agent. The spectrum of opportunistic infections observed in AIDS patients is well documented. A higher incidence of KS as well as squamous carcinoma of the oral cavity, cloacogenic carcinoma of the rectum, primary lymphomas of the brain, and systemic Burkitt's-like lymphoma has been noted.

Seventy-one patients with AIDS were examined and followed during the course of their disease. Forty-one patients had definite retinal lesions at the time of examination. The most common intraretinal finding was CMV retinitis which displayed the typical white, crumbly areas of retinal necrosis and hemorrhage. Optic nerve involvement was quite common. The development of retinitis was a harbinger of eventual death as it was a progressive and a nontreatable disorder, lasting about 6 months. The second most common retinal finding was cotton wool spots, the lesions were usually present during the course of PCP and were due to microvascular damage in the retina from circulating immune complexes. No organisms were demonstrated in the retina. One AIDS patient who had been an IV drug abuser developed fungal retinitis due to *Candida albicans*. The patient eventually died from *Candida* sepsis. One patient had acquired toxoplasmosis retinochoroiditis. Examination revealed a large ac-

tive intraretinal focus of infection. No other retinal lesion was noted. The patient, a homosexual, died from a toxoplasmosis brain abscess.

The patient with AIDS is in a continuing struggle for survival against a myriad assortment of opportunistic infectious agents. Careful initial ophthalmological examination and long-term follow-up are mandatory.

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APPENDIX I: AIDS PATIENTS

PATIENT	AGE	SEX	HOMO-SEXUAL	IV DRUG ABUSE	PCP	KS	OOI	OCULAR DIAGNOSIS
1	38	M	+	−	+	−	CMV, *Candida*, HSV, cryptosporidiosis	CMV retinitis both eyes, optic neuritis, vitritis
2	35	M	+	−	+	−	CMV, *Candida*, HSV, *M avium-intracellulare*	CMV retinitis both eyes, optic neuritis, vitritis
3	31	M	+	−	+	−	CMV, *Candida*	CMV retinitis both eyes, optic neuritis, vitritis
4	30	M	+	−	+	−	CMV, HSV	CMV retinitis both eyes, optic neuritis, vitritis
5	29	M	+	−	+	−	CMV, HSV	CMV retinitis both eyes, cotton wool spots
6	27	M	+	−	+	−	CMV only	CMV retinitis both eyes, optic neuritis, vitritis
7	43	M	?	−	+	−	CMV only	CMV retinitis right eye only
8	24	M	−	−	+	−	CMV; *Candida*	CMV retinitis both eyes, vitritis
9	32	M	+	−	−	−	CMV	CMV retinitis both eyes, optic neuritis, vitritis
10	31	M	?	−	−	−	CMV, HSV	CMV retinitis both eyes, optic neuritis, vitritis
11	34	M	−	+	+	−	CMV only	CMV retinitis both eyes, vitritis

12	36	M	+	−	+	+	CMV, *M avium*	CMV retinitis both eyes, vitritis
13	37	M	+	−	+	−	CMV, HSV	CMV retinitis both eyes
14	27	F	−	+	−	−	CMV, *Candida*	CMV retinitis both eyes, vitritis
15	44	M	+	−	+	−	CMV, *Candida*	CMV retinitis both eyes, vitritis
16	47	M	+	−	+	−	CMV, HSV, cryptococcus	CMV retinitis both eyes
17	29	F	−	+	+	−	CMV, *Candida*, HSV, cryptococcus	CMV retinitis both eyes, optic neuritis, vitritis
18	39	M	+	−	+	−	CMV only	CMV retinitis right eye only
19	28	M	+	−	+	−	CMV, HSV	CMV retinitis both eyes, vitritis
20	34	M	+	−	−	−	CMV only	CMV retinitis both eyes, vitritis
21	32	M	+	−	+	−	CMV, *Candida*	CMV retinitis both eyes
22	26	M	+	−	+	−	CMV, *Candida*, HSV	CMV retinitis both eyes
23	33	M	+	−	+	+	*Candida*	Cotton wool spots both eyes
24	37	M	+	−	+	−	CMV	Cotton wool spots right eye
25	35	M	+	−	+	−	CMV	Cotton wool spots both eyes
26	26	M	−	+	−	+	None	Cotton wool spots both eyes
27	24	F	+	−	+	−	None	Cotton wool spots both eyes
28	27	M	+	−	+	−	HSV, *Candida*	Cotton wool spots left eye

29	28	M	−	+	+	−	CMV, *Candida*, *M avium*	Cotton wool spots both eyes
30	36	M	+	−	+	−	None	Cotton wool spots both eyes
31	24	M	+	−	−	−	None	Cotton wool spots right eye
32	45	M	+	−	+	+	*Candida*	Cotton wool spots right eye
33	25	M	−	−	+	−	CMV only	Cotton wool spots right eye
34	43	M	+	−	+	−	CMV, HSV	Cotton wool spots right eye
35	31	M	+	−	+	−	*Candida*, cryptospo ridium	Cottom wool spots right eye
36	33	M	+	−	+	−	HSV	Cotton wool spots right eye
37	32	M	−	−	+	−	None	Cotton wool spots right eye
38	29	M	+	−	+	−	CMV, HSV	Cotton wool spots both eyes
39	27	M	+	−	+	+	CMV, HSV, *M avium*	Cotton wool spots both eyes
40	27	M	−	+	+	−	*Candida*	*Candida*, retinitis right eye
41	35	M	+	−	+	−	HSV, CMV, *Candida*	Toxoplasmosis retino-choroiditis right eye, past history CWS both eyes

p, *Pneumocystis carinii* pneumonia; KS, Kaposi's sarcoma; OOI, other opportunistic infection; CMV, cytomegalovirus; HSV, *Herpes simplex* virus; *M avium*, *Mycobacterium avium-intracellulare*.