The Acquired Immunodeficiency Syndrome: Current Status

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A recently recognized syndrome of acquired immunodeficiency (Acquired Immunodeficiency Syndrome—AIDS) has arisen since June 1981. It has received international attention. The clinical spectrum consists of repeated opportunistic infections, rare malignancies, and autoimmune phenomena, occurring in previously healthy adults with no history of an immunologic disorder. The population subset at risk for this syndrome appears to be predominantly homosexual American males and intravenous drug abusers with rare cases being reported in heterosexuals, hemophiliacs, and foreign patients, especially Haitians. The immunologic aberrancy in all patients described appears limited to T-lymphocyte hyporesponsiveness and imbalance of T-helper and suppressor cells. This disordered immunoregulation is a consistent finding in all reported cases and appears to predispose to the opportunistic infections and malignancies which have been associated with a 40 percent mortality. The underlying factor responsible for the immunoregulatory defect is unknown but possible etiologies include a transmissable infectious agent, drug use, chronic antigen stimulation, and spermatozoa exposure. Treatment of the associated infections and malignancies has been a frustrating endeavor as many patients respond incompletely or relapse soon after successful treatment course. Preventive measures, including patient education, physician awareness, and immunomodulating agents, are discussed.

INTRODUCTION

The clinical syndrome of acquired immunodeficiency is one that has received national and international attention since its original description in June 1981. This widespread attention is of no surprise as the syndrome is not only of medical interest with respect to immunology, infectious disease, and oncology, but has devastating epidemiologic and social implications. Despite preliminary research and mounting clues, the etiology of the syndrome is still not defined. Hence, the purpose of this review is to describe what is the current status of the epidemiologic, oncologic, and immunologic concepts of this syndrome, evaluate some possible etiologic agents, and touch on the implications of therapy and prevention.

EPIDEMIOLOGY

The history of the syndrome dates to June 1981 when the CDC reported the unprecedented occurrence of pneumocystis carinii pneumonia (PCP) in five previously healthy homosexual men—all five of whom had documented cytomegalovirus (CMV) infections and reported use of inhalant drugs [1]. Soon thereafter, numerous reports began to appear of the alarming occurrence of PCP as well as other oppor-

tunistic infections, in addition to Kaposi's sarcoma (a previously rarely reported neoplasm of elderly men, equatorial Africans, and immunosuppressed patients) in previously healthy homosexual males [1-6].

Over the ensuing year, increasing numbers of recognized cases have been reported to CDC with two new patterns emerging:

First, the disease spectrum has expanded to include (aside from PCP and Kaposi's sarcoma) virtually every known opportunistic infection (including disseminated candida, cryptococcus, mycobacteria and herpes virus [7]), other rare malignancies (including squamous cell CA of tongue and diffuse undifferentiated lymphoma [8]), autoimmune phenomena (including ITP and autoimmune hemolytic anemia [9]), as well as a poorly defined "prodromal syndrome" consisting of chronic fever, fatigue, and generalized lymphadenopathy (which often preceded development of malignancies and/or opportunistic infections [10]).

Second, the population at risk is not limited to homosexual men, but has expanded to include heterosexual men and women (most of whom were intravenous drug abusers) [11], Haitian immigrants recently entering the U.S.A. [12], and most recently three hemophiliacs [13].

Most alarming, perhaps, are the increasing numbers of cases being reported (approximately three cases per day to CDC) and a devastating 40 percent mortality (a rate that exceeds 60 percent for those patients diagnosed over a year ago — see Fig. 1) [7]. Indeed, this newly recognized syndrome has accounted for more deaths than the combined total attributed to toxic shock syndrome and the Philadelphia outbreak of Legionnaire's disease [2].

The current tabulated figures as of November 1982 are as follows [14]:

Total cases: 691
Location: 639 USA, 52 foreign (Haiti, Canada, Europe, Argentina, and Japan)
Patient characteristics: 75 percent homosexual or bisexual males
12 percent intravenous (IV) drug abusers
6 percent Haitian immigrants
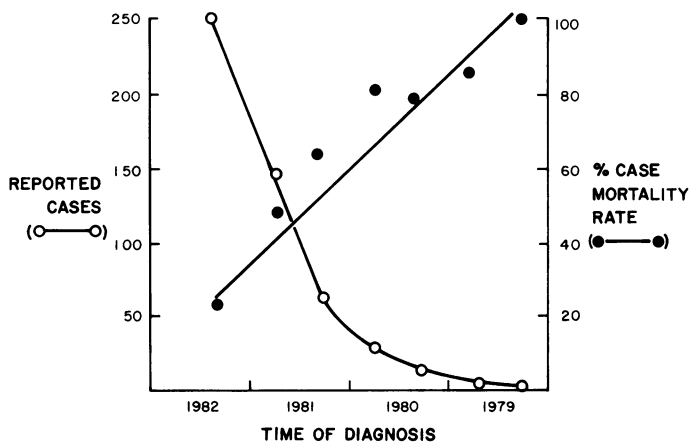6 percent other (i.e., hemophiliacs, heterosexuals)
Total deaths: 278

FIG. 1. Reported cases and mortality rates by time of diagnosis (adapted from [7]).

IMMUNOLOGIC PATTERNS

Upon examination of the clinical syndromes with which these patients were presenting (i.e., opportunistic infections, rare malignancies), it became clear that the common link among all of them was a profound disorder of immunoregulation — and this disorder appeared confined to the cellular arm of the immune response.

In order to interpret more clearly the implications of the observed immune status that has been described in these patients, let us briefly review what is the current conceptual model of the character and function of human T cells (see Fig. 2) [15].

Precursor prothymocytes migrate from the bone marrow to the thymus where they are processed in three stages (as manifest by changes in cell surface antigens), become functionally competent, and are exported to the peripheral lymphoid compartment. Stage I (10 percent of the thymocyte population) represents the earliest lymphoid cells bearing immature antigens shared by bone marrow cells of several lineages. With further maturation, cells enter Stage II (70 percent of thymocytes) where they develop thymocyte distinct antigens (i.e., T_4, T_5, and T_8 as defined by monoclonal antibody techniques). Upon entrance into Stage III (20 percent of population), immunologic competence is acquired, and cells segregate antigenically into T_4^+ and T_5^+/T_8^+ subsets which are mutually exclusive [15–18].

Functional studies of isolated subpopulations of peripheral T cells have demonstrated that this expression of a particular cell surface antigen is linked to specific cell function. That is, the T_4^+ population has been shown to exclusively possess an assigned inducer role in T-T, T-B, and T-macrophage interactions, whereas the T_5^+/T_8^+ subset demonstrates only cytotoxic/suppressor function (refer to Table 1) [18]. Furthermore, surface antigen differentiation appears even more complex as further studies have demonstrated functional heterogeneity within the T_4^+ subset (i.e., a population which induces help, and a population which induces suppression — see Fig. 3) [18]. Thus, one should be cautioned that measurement of T_4^+/T_8^+ subset ratios *in vitro* (as has been done in patients with AIDS) is a convenient assay, yet crude representation of *in vivo* immune status.

Given this background, what are the recognized immune defects in patients with AIDS? With repeated investigations, clinicians and scientists alike have observed a consistent pattern. *In vivo*, patients were noted to be profoundly lymphopenic, as well as anergic to a multitude of skin test antigens (e.g., candida, PPD). More interestingly, *in vitro*, patients' lymphocytes were found to demonstrate T-cell depletion, diminished proliferative response to mitogens (i.e., ConA, PHA), and a much publicized imbalance of T_4^+ (helper)/T_8^+ (suppressor) ratio in favor of suppression (humoral responses appear normal or increased) (refer to Table 2) [19–22].
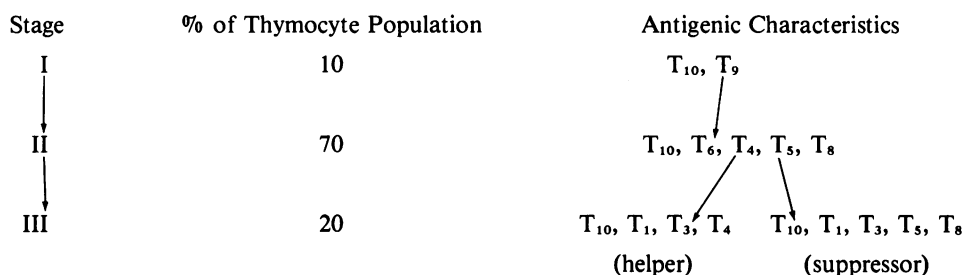
Stage	% of Thymocyte Population	Antigenic Characteristics
I	10	T_{10}, T_9
II	70	T_{10}, T_6, T_4, T_5, T_8
III	20	T_{10}, T_1, T_3, T_4 (helper) T_{10}, T_1, T_3, T_5, T_8 (suppressor)

FIG. 2. Stages of human T-cell differentiation (adapted from [15]).

TABLE 1
Functional Characteristics of T-Cell Subsets*

Function	T Inducer (T₁, T₃, T₄)	T Cytotoxic/Suppressor (T₁, T₃, T₅, T₈)
Proliferative Response		
MLC	+	+
Con A	+	+
Regulatory Events		
Helper (inducer)		
T-T	+	−
T-B	+	−
T-macrophage	+	−
Suppression		
T-T	−	+
T-B	−	+

*Adapted from [18]

This pattern of immune deficiency has been demonstrated repeatedly in the cases reported over the past year to CDC. However, ongoing investigation has revealed some new and interesting observations regarding the immune dysfunction in these patients. First, the T-helper/T-suppressor imbalance seen in patients with AIDS appears also to be present in healthy homosexual controls as well (albeit to a lesser degree). In a recent study of 81 healthy homosexual males in New York City, 80 percent showed altered distribution of T-cell subsets [23]. The implication of this is that we may just have encountered "the tip of the iceberg" and the number of persons at risk for serious illness may be much larger than is indicated by the reported cases. Second, there appears to be a gradation of ratio imbalance among the various clinical subsets of AIDS with the patients developing opportunistic infections demonstrating the most severe imbalance (refer to Table 3). Furthermore, on follow up of these patients (three to six months), ratios have remained unchanged despite effective treatment of opportunistic infections or KS [24]. Third, some immunologic features of patients with KS or unexplained lymphadenopathy resemble those found in patients with autoimmune disorders—including abnormal T-cell subsets, polyclonal hyperglobulinemia, circulating immune complexes, and an unusual acid labile from of human leukocyte interferon (HuIFN-α) in their serum (seen in many patients with SLE) [25]. Finally, investigators from New York University have demonstrated
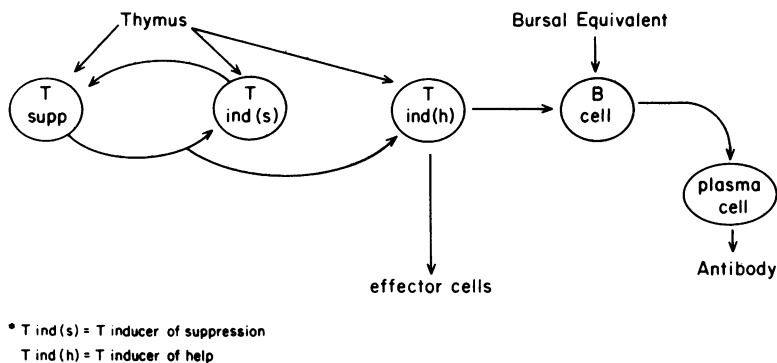

* T ind(s) = T inducer of suppression
  T ind(h) = T inducer of help

FIG. 3. The human T-cell scheme (adapted from [18]).

TABLE 2
In Vitro Characteristics of Four Patients with AIDS*

	Mean WBC Count	Mean Lymphocyte Count	Mean % E Rosette Formation	Mean T Helper/Suppressor Ratio
Patients	3186	418	52	0.06
Normal range	4800–10,800	1440–3040	59–74	0.86–2.34

*Adapted from [21]

an increased frequency of HLA DR5 haplotypes in homosexual as well as non-homosexual males with KS. This observation suggests that specific immune response genes in linkage dysequilibrium with DR5 may genetically predispose a patient to this opportunistic malignancy [26].

In summary, depending on the genetic substrate of the host and the severity of the underlying immune defect, a given patient may develop KS, opportunistic infection, autoimmune disease, or a combination of all.

ETIOLOGIC AGENTS

With respect to potential etiologies three key questions arise. Does this represent a new virus or other infectious agent which is first becoming manifest in the homosexual community due to the high exposure potential within this group? Do recreational drugs have a direct causative role or merely represent an epiphenomenon? Does the immunosuppression relate to chronic, repeated antigen exposure?

The possibility that an infectious agent represents the ultimate underlying cause stems from three epidemiologic observations. One is the geographic clustering of cases in major cities (New York, Los Angeles, and San Francisco), suggesting common sources of possible primary infectious factors [27,28]. Second, the host pattern emerging (i.e., homosexuals, hemophiliacs, IV drug abusers) represents the distribution of disease by common transmissable agents (e.g., hepatitis B virus). Third, homosexual men with multiple sexual partners are at increased risk of acquiring sexually transmitted disease—including traditional VD (GC, syphilis), viral hepatitis, CMV, and multiple enteric pathogens (including giardia, shigella, amebiasis) collectively referred to as the "gay bowel syndrome" [29-31].

Considering the innumerable transmissable infectious agents, CMV has received most attention, and there are several reasons for this. One is that evidence of previous or current CMV infection is a unifying presence in all the CDC case reports

TABLE 3
Ratio Imbalance by Various Clinical Subsets*

	OK T4/T8 Ratio
Control	1.75
Heterosexual with KS	1.79
Healthy homosexual male	1.1
Homosexual male with prodrome	0.7
Homosexual male with KS	0.48
Homosexual male with opportunistic infections	0.17

KS—Kaposi's sarcoma
*Adapted from [24]

(though the CMV isolated does not appear to represent a new, more virulent strain). Indeed, previous studies have shown that homosexual males are at greater risk for developing CMV infections than heterosexual males (i.e., approximately 95 percent have positive antibody titers to CMV and 10 percent have active viruria), felt to be primarily due to exposure to infected semen in which CMV persists for up to 18 months [32-33]. Second, acute CMV infection has been shown to be associated with a similar pattern of T-cell imbalance as seen in patients with AIDS—namely, an increased number of cytotoxic/suppressor (T_8^+) cells and a decreased number of helper cells (T_4^+) associated with lymphocyte hyporesponsiveness to mitogens (ConA). Furthermore, this T-cell imbalance has been documented to last for up to ten months [34-37]. In addition, CMV has been shown in clinical studies of renal transplant recipients to be associated with a high rate of superinfection, especially PCP. Although this clearly could be related to the underlying immunosuppressed state of these patients, CMV has been shown to directly depress alveolar macrophage function in the murine model [38], and thus may predispose at a local level, along with systemic T-cell imbalance, to superinfecting pneumonia. Finally, increasing evidence has supported the association of CMV and Kaposi's sarcoma, an association proposed by Giraldo in 1972 when a CMV strain was isolated from a KS tissue biopsy in culture. Since then, he and several other investigators have demonstrated an increased incidence of CMV antibodies in European and American KS patients as well as CMV DNA and RNA sequences detected recently from tumor biopsies of ten KS patients [39-43].

The hypothesis that CMV is the ultimate underlying etiology for AIDS suffers from two major flaws. One is that patients who are immunosuppressed for other reasons (e.g., steroids) also have a high incidence of CMV infection; thus the immunosuppression seen in these patients may have another etiology which secondarily allows for CMV reactivation. A second flaw is that CMV is not a new infectious agent and homosexuality as a lifestyle has been around for centuries, so this hypothesis does not explain why AIDS is apparently new.

Hence, the search has continued for a new epidemiologic factor and has led investigators to suspect the recent popularity of drug use as a possible etiologic factor.

Support for the "drug hypothesis" dates back to the original five cases reported in June 1981, and stems from the facts that recreational drugs are widely used in large cities and that the majority of non-homosexual AIDS patients reported were drug users. Of all the potential candidate drugs, amyl nitrite has been a leading possibility for the homosexual community with AIDS, as it is commonly used to intensify orgasm [44]. It is currently unclear from available data whether nitrite use has a direct effect on T-cell function or whether it represents a certain lifestyle that may predispose to transmission of an infectious agent.

For example, in a study of 150 homosexual men, it was found that users of amyl nitrite had a higher incidence of multiple sexual partners, group sex, and venereal disease [44]. Conversely, ongoing studies of KS patients at New York University have revealed that, using multivariate analysis, both multiple sexual partners (> 10 per year) and amyl nitrite use were independent risk factors for KS development [43,45]. Thus, until more data are collected, the role of amyl nitrite as a direct causative factor remains unclear.

Assuming that CMV and amyl nitrite use may be potential candidate etiologies for the homosexual community, how do we explain the emergence of this syndrome in the IV opiate user? Actually, immunologic abnormalities in IV opiate addicts have been clinically observed for over a decade (e.g., hypergammaglobulinemia, false ⊕

VDRL), but it was not until recently that the immune dysfunction has been better characterized. In a study of 38 heroin addicts [46], *in vitro* lymphocyte responsiveness to mitogen stimulation was impaired compared to controls. The authors hypothesized that chronic antigen stimulation can lead to a "hyperimmunized state" wherein hypergammaglobulinemia and aberrant antibody formation could occur (e.g., ⊕ VDRL), with serum factors emerging that could temporarily affect lymphocyte function. This concept is further supported by more recent studies demonstrating evidence for opiate receptors on lymphocytes *in vitro*, as well as depression of T-cell number and function *in vivo* opiate addicts (refer to Table 4) [47]. In this same study, these effects were reversed by naloxone (an opiate antagonist), thus supporting the hypothesis of a direct opiate effect on lymphocytes. In addition to the potential immunologic effects of chronic antigen stimulation (i.e., via injection of particulate matter) and a potential transmissable agent, IV opiate abusers may develop immune dysfunction as a result of a direct opiate-lymphocyte interaction.

Perhaps the most exciting potential candidate etiology (with respect to homosexual patients at least) is that of spermatozoa exposure. Indeed, there has been interest in germ cell-induced immunosuppression prior to the recognition of AIDS. Much of the work has been done at NIH where investigators have demonstrated that the injection of sperm (syngeneic or allogeneic) into the bloodstream of mice induced an increased suppressor cell activation, and profound suppression of cell-mediated functions. It was postulated that germ cells expressing embryonic antigens enter the circulation and generate an immunologic suppressor reaction to protect the host from an autoimmune response [48–50]. Interest in this hypothesis as a mechanism for immunosuppression in AIDS has been sparked recently by New York University investigators who have detected antisperm antibody that cross-reacted with T cells in the circulation of twelve KS patients, all of whom were azospermic on testicular biopsy [24]. Therefore, in homosexual males, sperm may reach the bloodstream via intestinal mucosal lesions (perhaps enhanced by nitrite-induced vasodilation) and lead to immunosuppression independently (via antisperm antibody coating of T cells enhancing their destruction in RE system), or as a carrier of viruses.

In conclusion, it is likely that the immunosuppression seen in patients with AIDS is multifactorial with different etiologic possibilities acting alone or synergistically in different populations, with the clinically observable syndrome dependent on host susceptibility.

TREATMENT

Treatment of this complex syndrome which presents with a variety of clinical manifestations, has been a frustrating endeavor for all clinicians. Opportunistic infections must be treated individually but this often is a fruitless battle, as patients

TABLE 4
Mean White Blood Cell and T Lymphocyte Numbers
in IV Addicts and Controls*

	Controls	Addicts
Patients	28	44
Mean WBC	7210	7287
% B cells	17.8	16.3
% T cells	69.1	27.5

*Adapted from [47]

TABLE 5
Kaposi's Sarcoma in AIDS—Therapeutic Experience*

	No. of Patients	Complete Remission	Partial Remission	No Remission
Chemotherapy (NYU Data)				
VP$_{16}$	19	4 (2 relapsed)	13	2
ABV^a	20	4 (3 relapsed)	14	2
Immunotherapy (Sloan-Kettering)				
Interferon	12	1	7	4

^{a}ABV = adriamycin, bleomycin, and Velban
*Adapted from [24]

frequently relapse with multiple opportunistic infections. Initial chemotherapy trials for KS in AIDS patients have revealed similar though somewhat more encouraging results with approximately 20 percent of patients achieving a complete remission (Table 5) [24]. Of the potential immunotherapeutic agents, interferon appears most promising, as it possesses antiviral, antiproliferative, and immunomodulating properties. Other immunologic modalities have met with minimal success and have included thymosin (no response in three patients), bone marrow transplantation (unsuccessful in one patient), as well as transfer factor and plasmapheresis [24].

Potential oral agents of use, both as adjunctive and possibly preventive as well, include isoprinosine, an agent available only in Europe which has been shown to improve lymphocyte activity as well as to increase the relative number of T-helper cells. In the U.S.A., cimetidine has been proposed as a potentially effective agent based on the fact that histamine, in a reversible dose-response fashion, inhibits cell-mediated immunity. Indeed, there has been one published report [51] of its use in four patients with chronic mucocutaneous candidiasis with encouraging results as an immunomodulator, but its use in AIDS patients is as yet unproven.

PREVENTION

Preventing expansion of this devastating epidemic can be approached from four potential fronts. First is physician awareness of the problem and the routine mandatory taking of sexual histories (especially in patients presenting with pneumonia, skin nodules, prolonged fever, or generalized unexplained lymphadenopathy). Second, to prevent in-hospital spread of a potentially infective agent, it appears prudent for physicians to observe the same precautions for AIDS patients as for patients with hepatitis B virus infection [52]. Third, prophylactic antibiotic therapy (i.e., trimethoprim-sulfamethoxazole), as used in other high-risk populations for PCP, is likely to be useful in these patients but fraught with danger as most patients at risk are already profoundly leukopenic. Thus further bone marrow suppression (seen commonly in these patients treated with this agent) may preclude its benefit as a prophylactic agent.

Finally, perhaps the most important role for physicians lies in patient education. At present, with the available data regarding potential risk factors, one should probably recommend decreased drug use and decreased numbers of sexual partners to homosexual patients. However, one should stress that this is purely a medical recommendation as its emotional, social, and ethical implications may be as devastating as the illness one is trying to prevent.

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