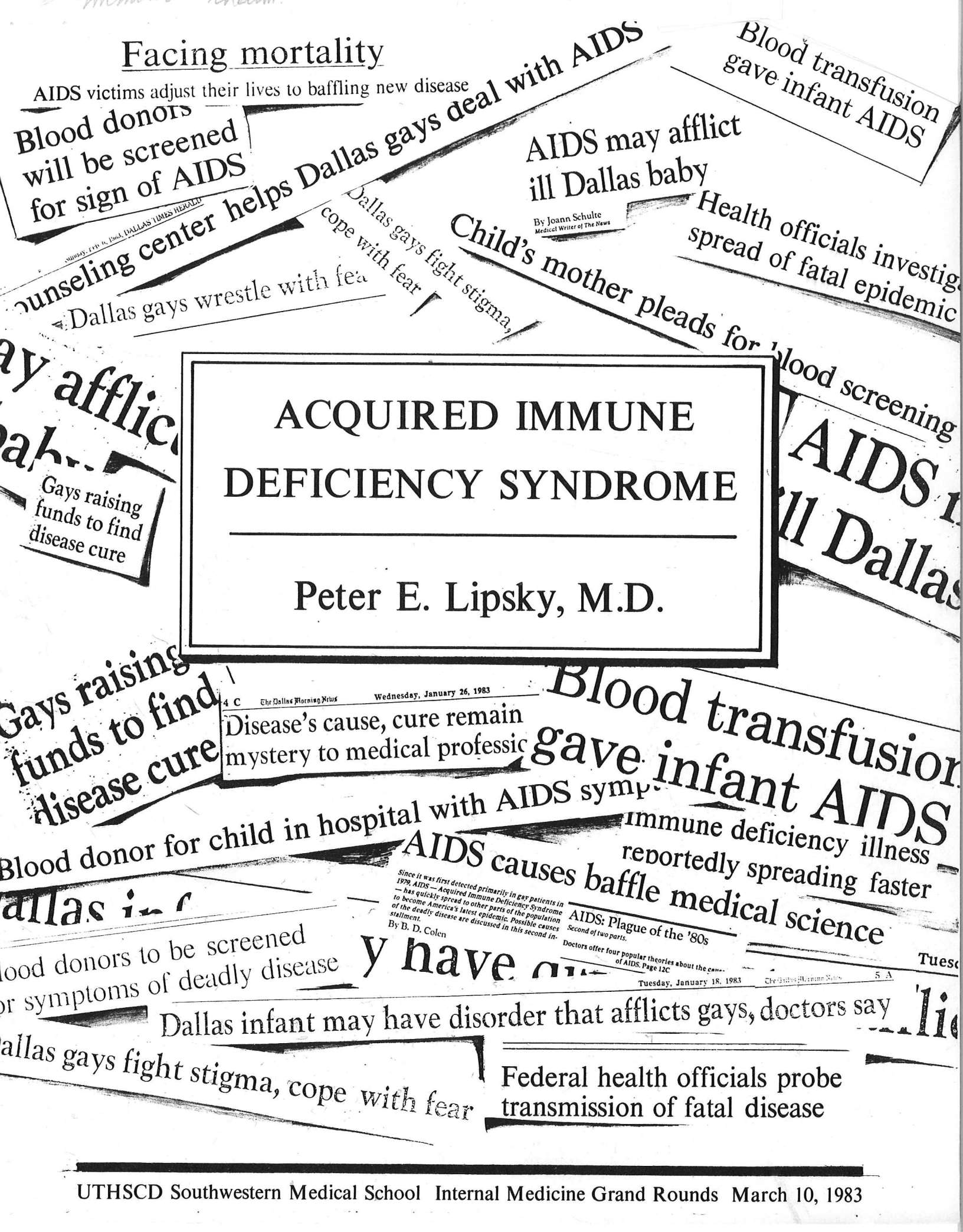

UTHSCD Southwestern Medical School Internal Medicine Grand Rounds March 10, 1983

Introduction

In June of 1981, the Center for Disease Control reported that five young male homosexuals had been treated for biopsy-confirmed Pneumocystis carinii pneumonia at three separate hospitals in Los Angeles, California between October, 1980 and May, 1981 (1). Two of the patients died. All five had laboratory-confirmed previous or concurrent cytomegalovirus infection and mucosal candidiasis. Four of five of the patients had serological evidence of previous hepatitis B infection, while each was negative for hepatitis B surface antigen. Three of the five individuals' immunological testing revealed depressed cell-mediated immunity. Since Pneumocystis carinii pneumonia is almost unheard of in adults without a known underlying condition resulting in immunosuppression, this cluster of cases caused the CDC tentatively to suggest that there might be "an association between some aspect of a homosexual lifestyle or disease acquired through sexual contact and Pneumocystis pneumonia". During the next month, the CDC reported ten additional cases of Pneumocystis pneumonia occurring in homosexual men from Los Angeles and San Francisco.

In July of 1981, the CDC reported that since January of 1979, Kaposi's sarcoma, an uncommonly reported malignancy in the United States, had been diagnosed in 26 homosexual men (2). Twenty of these were from New York City and 6 from California. Eight of these patients died within 24 months of the diagnosis. Seven subsequently developed serious opportunistic infections, including four with Pneumocystis carinii pneumonia and one with necrotising toxoplasmosis of the central nervous system. Of twelve patients studied, all had evidence of past or present cytomegalovirus infection and in three who were studied, cytomegalovirus was isolated from blood, urine and/or lung. This outbreak of cases caused the CDC to recommend that physicians "be alert for Kaposi's sarcoma with immunosuppression in homosexual men". The CDC also reported that four homosexual men in New York City developed severe progressive perianal Herpes simplex infections and had evidence of cellular immunodeficiency. Three of these patients died. One had a cytomegalovirus infection.

The report of these cases signalled the beginning of an epidemic of a disease characterized by profound immunosuppression, opportunistic infections, and neoplastic malignancies which has come to be known as acquired immune deficiency syndrome (AIDS). Within two months of the original report, the CDC was able to collect 111 cases of Kaposi's sarcoma, Pneumocystis carinii pneumonia, or both (3). Data from 108 of these patients are displayed in Table I. The age of these patients varied from 15 to 52. More than 95% of them were men aged 25 to 49 years; 94% were homosexuals while 79% were white. The majority of cases occurred in New York City and in California. The disease carried with it the staggering mortality rate of 40%.

By June of 1982, the CDC had collected 355 cases of AIDS. At that time, the disease was tentatively defined as an illness in a person who 1) had biopsy proven Kaposi's sarcoma or biopsy or culture-proven life-threatening opportunistic infection; 2) was under the age of 60; and 3) had no history of either immunosuppressive underlying disease or immunosuppressive therapy. Of the 355 cases reported in June of 1982, 79% occurred in homosexual or bisexual males. The incidence of the illness in heterosexuals had increased such that they made up 16% of all cases, including 41 (12%) heterosexual males and 13 (4%) heterosexual females. Eighty-six percent of the cases

TABLE I

Cases of Kaposi's Sarcoma (KS) and Pneumocystis carinii Pneumonia (PCP) reported to CDC with dates of onset between January, 1976 and July, 1981 (MMWR 30:409, 1981)

Characteristic of Patients	Diagnosis KS (n = 47)	PCP (n = 54)	KS + PCP (n = 7)	Total (n = 108)
Sex				
Male	47	53	7	107
Female	0	1	0	1
Race of men				
White	41	33	5	79
Black	3	9	0	12
Hispanic	3	7	1	11
Unknown	0	4	1	5
Sexual Preference of Men				
Homosexual or bisexual	44	44	7	95
Heterosexual	1	5	0	6
Unknown	2	4	0	6
Mortality rate (%)	17	59	43	40

occurred in California, Florida, New Jersey, New York City and Texas. The remainder of the cases occurred in 15 other states. The mean age of onset of symptoms for homosexual males was 36 years, for heterosexual males 31.5 years, and for women 29 years. The epidemic nature of the disease was suggested by the finding that the disease appeared to have spread to a number of other locations and that the number of reported cases continued to increase. For example, 69% of all reported cases had their onset after January 1, 1981 (Figure 1).

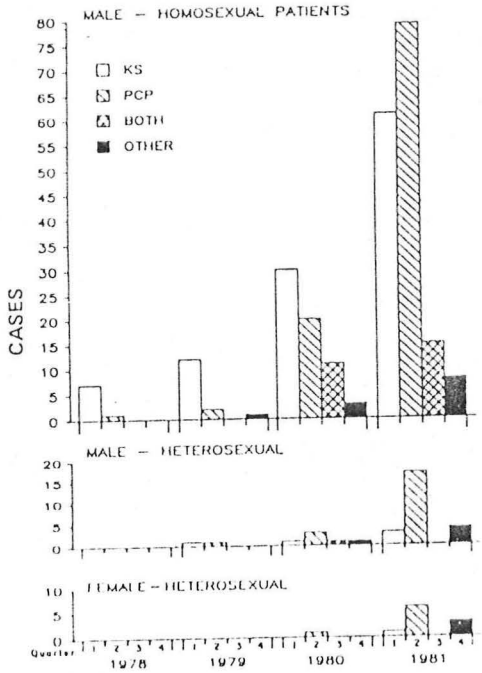

Figure 1: Cases of AIDS per year in the United States. Reprinted from MMWR 31:294, 1982.

By the end of 1981, the CDC was receiving new case reports at the rate of 7 per week. By the latter part of 1982, this had increased to 20 per week and in December, 1982, the CDC received reports on 92 new cases. While the disease remained predominantly one of white homosexual males (Table II), increased numbers of heterosexual patients, especially those who used intravenous drugs, was observed.

TABLE II

Cases of Pneumocystis carinii pneumonia in previously healthy persons, June 1 1981-May 28, 1982
(MMWR 31:294, 1982)

Patient Group	Total	Race			Mortality Rate (%)	Intravenous Drug Use (%)
		White	Black	Hispanic		
Homosexual men	118	80	22	15	51	14
Heterosexual men	26	8	11	6	35	65
Heterosexual women	8	1	4	2	50	57

It soon became apparent, however, that the disease was not limited to homosexual men and intravenous drug users as a similar disease was reported among 34 Haitians who had recently immigrated to the United States (4). Subsequently the disease was reported in female partners of intravenous drug users (5), hemophiliacs (6,7), infants of possibly-affected mothers (8) and individuals receiving blood transfusions (9). Through January 20, 1983, 979 cases have been reported to the CDC. The overall mortality rate is 38%. While the majority of cases remain confined to New York City and California, cases have now been reported in 33 states and the District of Columbia (Table III).

While the disease predominantly effects homosexual males (Table IV), nearly 8% of affected individuals are heterosexual males and females with no history of IV drug abuse. To date, AIDS has caused the death of more individuals than toxic shock syndrome (84 deaths, 1978-1980) and the Legionaire's disease epidemic of 1976 (34 deaths) combined. It is therefore appropriate to review the currently available information concerning this syndrome at this time. Since knowledge of the disease is rapidly evolving and much of it remains unavailable, there are major gaps in our understanding of this syndrome. Nevertheless, it is worth considering not only because of the enormous amount of human suffering that it has caused, but also because of the knowledge we can learn about the role of certain elements of the immune system in host defense.

TABLE III

Acquired Immune Deficiency Syndrome in the U.S.
(Through January 20, 1983)

State	Total	Alive	Dead	% Mortality
Alabama	1	1	0	0
Arizona	2	1	1	50
California	202	143	59	29
Colorado	7	4	3	43
Connecticut	11	4	7	64
Florida	61	34	27	44
Georgia	14	7	7	50
Hawaii	3	2	1	33
Illinois	22	10	12	55
Kansas	2	2	0	0
Kentucky	1	1	0	0
Louisiana	5	3	2	40
Maryland	2	0	2	100
Massachusetts	13	10	3	23
Michigan	3	2	1	33
Minnesota	3	2	1	33
Missouri	2	0	2	100
Nevada	1	1	0	0
New Jersey	60	33	27	45
New Mexico	1	0	1	100
New York	471	287	184	39
North Carolina	2	2	0	0
Ohio	8	3	5	63
Oregon	2	2	0	0
Pennsylvania	17	11	6	35
South Carolina	3	1	2	67
Tennessee	1	1	0	0
Texas	21	12	9	43
Dallas	4	3	1	25
Houston	16	8	8	50
San Antonio	1	1	0	0
Vermont	1	1	0	0
Virginia	4	4	4	0
Washington	2	2	2	0
Washington, D.C.	9	6	3	33
Wisconsin	1	1	0	0
Total	979	605	374	38

TABLE IV

Acquired Immune Deficiency Syndrome: Sexual Orientation
and Intravenous Drug Use, June 1, 1981 - Sept. 15, 1982
(MMWR 31:507, 1982)

Sex	Orientation	AIDS Number	AIDS % of Total	Intravenous Drugs Yes	Intravenous Drugs No	Intravenous Drugs Unknown	% Using I.V. Drugs*
Male	Homosexual or bisexual	445	75.0	42	300	103	12.3
	Heterosexual	84	14.2	49	33	2	59.8
	Unknown	30	5.1	11	11	8	50.0
Female	Heterosexual	34	5.7	20	12	2	62.5
TOTAL:		593	100.0	122	356	115	25.5

* Excluding individuals with unknown history of intravenous drugs

Definition of the Syndrome

Currently there does not exist a reliable, widely-available test for the diagnosis of AIDS. Therefore, the current definition is only a working one which is used for epidemiological purposes. As a better understanding of the full scope this syndrome develops, the definition of the condition may well change. Currently, the CDC (10) considers AIDS to be "a disease at least moderately predictive of a defect in cell-mediated immunity occurring in a person with no known cause for diminished resistance to that disease". Manifestations of the disease include a) Kaposi's sarcoma, b) Pneumocystis carinii pneumonia, and c) other opportunistic infections. These latter infections include 1) pneumonia, meningitis or encephalitis caused by aspergillosis, candidiasis, cryptococcosis, cytomegalovirus, nocardiosis, strongyloidosis, toxoplasmosis, zygomycosis, atypical mycobacteriosis (other than tuberculosis or the lepra bacillus); 2) esophagitis caused by candidiasis, cytomegalovirus or herpes simplex virus; 3) progressive multifocal leukoencephalopathy; 4) chronic enterocolitis of longer than 4 weeks caused by cryptosporidiosis; and 5) extensive mucocutaneous Herpes simplex infection of more than 5 weeks duration. The diagnosis must be based on sufficiently reliable methods which should include either biopsy or culture.

The definition is a fairly rigorous one which appears to include only the most severe forms of AIDS. As newer information is collected, however, this condition seems to include a wider spectrum of abnormalities in immune competence ranging from an absence of all symptoms despite subtle laboratory evidence of immunodeficiency (11-15), through a variety of non-specific symptoms including weight loss, fever, and generalized persistent lymphadenopathy with immunodeficiency (16,17) and finally a syndrome of cellular immune deficiency with autoimmune thrombocytopenic purpura (18,19). Moreover, the definition excludes individuals with specific diseases that are not sufficiently predictive of cellular immunodeficiency such as tuberculosis, oral candidiasis, or more routine infections with Herpes zoster, Toxoplasma and cytomegalovirus, all of which occur in increased frequencies in the population at risk for AIDS. In addition, the presence of certain malignant neoplasms such as Burkitt's lymphoma which have been reported in AIDS patients (20,21), is not currently viewed as a criterion for the diagnosis. Conversely, some cases may be included even though the nature of the underlying immune defect is not entirely clear. For example, individuals with cryptococcosis may not actually be immunodeficient and thus may be inappropriately included as part of the current epidemic. Until there is a definitive way to diagnose the syndrome, only working definitions will be tenable. This should be borne in mind whenever one is entertaining the diagnosis of AIDS in an individual with subtle but not necessarily compelling abnormalities.

Patients Affected

1) Homosexual Males. The vast majority of cases of AIDS continues to be reported in young homosexual males. A number of risk factors have been identified for this group of patients. A study by Marmor et al (22) has identified certain risk factors for Kaposi's sarcoma in homosexual men compared to age and race matched symptom-free homosexual males. The first is the use of a number of drugs (Table V).

TABLE V

Risk Ratios for "Recreational" Drug Use in Patients With Kaposi's Sarcoma and Matched Controls (Marmor et al, Lancet 1:1083, 1982)

Drugs Used	% reporting history of drug use: Patients (n = 20)	Controls (n = 40)	Risk ratio*	p value
Cocaine	90	43	20:0	0:001
Amphetamines	80	29	11:5	0:0005
Methaqualone	70	35	8:0	0:003
Phencyclidine	55	20	5:7	0:005
Amyl nitrite	100	68	4:9	0:01
Ethyl chloride	55	23	4:2	0:01
Marijuana	95	88	2:5	NS
Butyl nitrite	55	37	1:9	NS

NS = not significant

* Risk ratios and one-tailed p values calculated from matched-triplets analysis except for amyl nitrite, where a lack of discordant triplets necessitated using an age-stratified analysis and incrementing each cell frequency by 0-5.

Users of cocaine, amphetamines, methaqualone, phencyclidine, amyl nitrite, and ethyl chloride had a significantly increased risk of contracting AIDS with Kaposi's sarcoma. When dose response relationships were examined (Table VI), it was found that patients compared to controls had a much greater incidence of high lifetime exposure levels to amphetamines, amyl nitrite, cocaine and ethyl chloride.

TABLE VI

Exposure to Various Drugs Among Homosexual Patients With Kaposi's Sarcoma and Controls (Marmor et al, Lancet 1:1083, 1982)

Risk factor	Group	Reported lifetime exposure† Low	Medium	High	χ^2 trend (p)
Amphetamines	Patients	7 (35%)	3 (15%)	10 (50%)	
	Controls	30 (75%)	6 (15%)	4 (10%)	13.6 (0.0001)
Amyl nitrite	Patients	4 (20%)	4 (20%)	12 (60%)	
	Controls	25 (63%)	9 (22%)	6 (15%)	12.7 (0.0002)
Cocaine	Patients	7 (35%)	7 (35%)	6 (30%)	
	Controls	24 (60%)	12 (30%)	4 (10%)	4.6 (0.02)
Ethyl chloride	Patients	13 (65%)	4 (20%)	3 (15%)	
	Controls	34 (85%)	4 (10%)	2 (5%)	3.0 (0.04)
Phencyclidine	Patients	14 (70%)	4 (20%)	2 (10%)	
	Controls	33 (83%)	7 (18%)	0 (0%)	2.6 (NS)
Methaqualone	Patients	12 (60%)	5 (25%)	3 (15%)	
	Controls	29 (72%)	10 (25%)	1 (3%)	1.9 (NS)

NS = Not significant

† Exposure levels for all drugs except amyl nitrite are 0-9 (low), 10-99 (medium), and ≥ 100 (high) lifetime uses; for amyl nitrite 0-99 (low), 100-499 (medium) and ≥ 500 (high) lifetime uses.

Sexual activity in the year before onset of the disease also appeared to be a risk factor. Thus, 50% of the patients reported having sex with 10 or more different partners during an average month in the year before onset of Kaposi's sarcoma, compared with 17% of controls. Patients also were found to have a greater incidence of sexually-transmitted diseases including Giardia lamblia infection, amebiasis, condylomata accuminata, syphilis, gonorrhoea, and Herpes simplex, but these incidences were not statistically different from the control group (Table VII).

TABLE VII

Risk Ratios for Sexually Transmitted and Other Infectious Diseases in Kaposi's Sarcoma Patients and Controls
(Marmor et al, Lancet 1:1083, 1982)

Disease	% reporting history of disease		Risk ratio	p value
	Patients (n = 20)	Controls (n = 40)		
Mononucleosis	30	8	7.0	0.01
Giardia lamblia infection	25	10	3.0	NS
Amebiasis	70	42	2.8	NS
Condylomata accuminata	55	38	2.7	NS
Syphilis	60	35	2.4	NS
Gonorrhoea	85	72	2.2	NS
Herpes simplex	30	23	1.6	NS
Hepatitis	65	65	1.0	NS

NS = not significant

Both groups had a very high incidence of hepatitis B infection. The incidence of mononucleosis was significantly greater in the patients than in the control group.

A second major analysis of homosexual men with AIDS is currently being carried out by a CDC task force. This unpublished study has compared a number of characteristics in 50 AIDS patients with those of 120 controls. Preliminary results suggest significant differences between patients and controls in the number of sex partners per year, the use of amyl nitrite, and butyl nitrite and in the incidence of other sexually transmitted diseases such as syphilis (Task Force on Acquired Immune Deficiency Syndrome, unpublished observation).

A number of other factors have also been suggested to play a potential role in the development of AIDS in homosexual males. One of these is the cytomegalovirus (CMV). As noted above, sexually transmitted infections, including CMV are very prevalent in the male homosexual community. In one recent study, 94 percent of exclusively homosexual men had serologic evidence of CMV infection as compared with 54 percent of heterosexual men attending the same venereal disease clinic and 43% of male blood donors (23). The shedding of CMV for prolonged periods of time in many secretions, including

semen may facilitate sexual transmission (24). However, there is no convincing evidence homosexual men with AIDS differ from asymptomatic homosexual males in their incidence or severity of CMV infection. Because CMV is so prevalent in homosexual males it will be extremely difficult to establish whether it plays any role in the development of AIDS.

2) Heterosexual Males. AIDS has been reported in at least 84 heterosexual men of whom 59.8% were users of intravenous drugs. This group includes 12 men under the age of 60, who were not homosexual, intravenous drug users, Haitians or hemophiliacs. No further detailed information is available concerning these persons.

3) Haitians. Between April, 1980 and July, 1982, acquired immune deficiency syndrome has been reported in 34 Haitians living in the United States (4,25). Only one of these cases appeared to have the onset of the illness before arrival in the United States. The remainder, as shown in Table VIII, had the onset of the illness anywhere from one month to eight years after immigrating to the United States.

TABLE VIII

Acquired Immune Deficiency Syndrome in Haitians Living in the United States

	Miami (n = 20)	Brooklyn (n = 10)	Other (n = 4)	Total (n = 34)
Onset	4/80 → 6/82	1/81 → 7/82	→ 7/82	
Males: Females	17:3	10:0	3:1	30:4
Mean age (years)	28.4 (22→43)	29.3 (24→39)	?	
Time in U.S. (Months)	20.5 (1 mo.→7 yrs)	32.4 (3 mo.→8 yrs)	?	
Sexual persuasion	Heterosexual (12/12)	Heterosexual (8/8)	Heterosexual (3/3)	Heterosexual (23/23)
Intravenous drug use	0/14	0/9	0/3	0/26
Kaposi's sarcoma	1	0	1	2
Opportunistic infections				
P. carinii pneumonia	6	4	1	11
Intracerebral T. gondii	7	4	0	11
Cryptococcus	4	1	0	5
Candida esophagitis	7	3	1	11
Tuberculosis	8	6	0	14
Misceilaneous	11	0	0	11
Multiple	14	7	?	21
Deaths	10	6	?	16/30

There are a number of important differences between the Haitians who contracted AIDS and the remainder of the AIDS patients. First, the disease is seen primarily in heterosexual males; 88% of all cases have occurred in males, all of whom were heterosexual. Secondly, the disease does not appear to be related to intravenous drug use since none of 26 patients questioned admitted to the abuse of intravenous drugs. Third, the incidence of Kaposi's sarcoma appears to be much lower in this patient group, with only 2 of 34 patients reported from the United States developing evidence of this malignant neoplasm.

Finally, there appear to be some differences in the spectrum of opportunistic infections that these patients acquire. Although they have a high incidence of Pneumocystis carinii pneumonia, and a variety of other opportunistic infections, they also have been observed to have a very high frequency of intracerebral Toxoplasma gondii infection. It has not been established whether the cases of toxoplasmosis represent reactivation of old lesions acquired in Haiti, or whether they are progressive primary infections acquired in the United States. Two serum specimens obtained from patients in Miami were tested by the CDC for IgM antibody to Toxoplasma and found to be negative (4). This result suggests that the infection in these two patients was not recently acquired. In addition, the Haitian patients had a very high frequency of infection with Mycobacterium tuberculosis. This may reflect the fact that this disease is endemic among Haitian immigrants with a prevalence in the 24 to 39-year old age group of 8 per 1,000 population (26). The death rate among all Haitian AIDS patients was extremely high with 16 of the 30 patients dead at the time they were reported, and at least 2 of the other patients in Brooklyn ill at the time of follow-up at 6 months. It should be noted tht 11 cases of disseminated Kaposi's sarcoma have been diagnosed by dermatologists in Port a Prince Haiti (27). Details of these cases, however, are currently unavailable for inspection.

The explanation for the development of AIDS in Haitians is unknown. The epidemiologic features common to most of the cases in homosexuals and drug abusers, including multiple sexually-transmitted infections and frequent use of prescription or recreational drugs were absent in the Haitians. In general, these patients did not have an increased prevalence of CMV infection. Only one of ten of the patients seen in Brooklyn and 3 of 19 seen in Miami had evidence of active CMV infection. However, Haitians apparently do have a very high incidence of hepatitis B infection with 86% reported to have one or more serologic markers of this infection (quoted in 25).

4) Women. Between June, 1981 and January, 1983 the CDC received reports of 43 previously healthy females who had developed Pneumocystis carinii pneumonia or other opportunistic infections typical of AIDS (5). Of these 43 patients, 13 were neither Haitians nor IV drug abusers. Five were reported to be steady sexual partners of male IV drug abusers. One of these male IV drug users contracted acquired immune deficiency syndrome three months before the patient. Four other of the male IV drug users had no overt illness suggesting AIDS although one had some abnormalities of in vitro lymphocyte responsiveness suggestive of those characteristic of early AIDS patients. One additional patient was a steady sexual partner of a bisexual male who was not a drug abuser but who contracted evidence of AIDS eight months before the onset of the patient's own illness. Details of five of the female patients (4 of whom were drug users) including 3 who were heavy users of intravenous drugs are presented in Table IX. Characteristics of these patients are fairly typical of those of male homosexual patients with AIDS. It should, however, be pointed out that Kaposi's sarcoma appears to be extremely rare in female patients with acquired immune deficiency syndrome.

TABLE IX

Clinical Features of Five Female Patients With
Acquired Immune Deficiency Syndrome in the
Metropolitan New York Area, April, 1981 → April, 1982
(Masur et al, Ann. Int. Med. 97:533, 1982)

Clinical Feature	Patient				
	1	2	3	4	5
Age, yrs	31	25	26	37	27
Race	Black	Hispanic	Hispanic	Hispanic	White
Sexual preference	Bisexual	Heterosexual	Heterosexual	Heterosexual	Heterosexual
Drugs used	Cocaine, mescaline	None (sexual partner is heroin addict)	Heroin, cocaine	Heroin, cocaine	Heroin, cocaine
Initial opportunistic infection	P. carinii pneumonia	P. carinii pneumonia	P. carinii pneumonia	Esophageal candidiasis	Perianal Herpes simplex
Duration of symptoms before diagnosis	2.5 months	3 weeks	34 months	2 weeks	3 months
Initial opportunistic infection	November 1981	October 1981	August 1981	November 1981	April 1981
Outcome of initial infection	Survived	Survived	Survived	Died	Survived
Other opportunistic infections	Oral candidiasis	Oral candidiasis	Candida esophagitis, perirectal Herpes simplex, disseminated Mycobacterium avium-intracellulare	P. carinii pneumonia	Disseminated M. avium-intracellulare infection, disseminated cytomegalovirus infection, P. carinii pneumonia, pulmonary aspergillosis, Pseudomonas bacteremia
Follow-up	6 months	7 months	9 months	1 month	7 months
Current status	Alive	Alive	Dead	Dead	Dead

5) Hemophiliacs. Through December 10, 1982, the CDC reported that eight patients with hemophilia A had developed features of acquired immune deficiency syndrome (6,7). Characteristics of these individuals are reported in Table X.

TABLE X

Acquired Immune Deficiency Syndrome
in Patients with Hemophilia A

State	Age	Status of Hemophilia	Treatment	Onset	Initial Symptoms	First Infection	Other Infections	Outcome
New York	62	Severe	VIII conc.	2/81	weight loss abdominal pain	Pneumocystis carinii pneumonia	--	dead
Colorado	59	Severe	VIII conc.	10/80	weight loss lymphadenopathy aphthous stomatitis	oropharyngeal candidasis	Pneumocystis carinii and cytomegolovirus pneumonia	dead
Ohio	27	Severe	VIII conc.	7/81	fever, lassitude	Pneumocystis carinii pneumonia	Candidiasis, Mycobacterium avium-intracellulare	alive
Alabama	55	Severe	VIII conc.	9/81	weight loss, anorexia	Herpes zoster	Pneumocystis carinii pneumonia	alive
Pennsylvania	10	Severe	VIII conc.	9/81	fever, vomiting lymphadenoapthy	Pneumocystis carinii and Cryptococcus neoformans pneumonia	--	alive
Ohio	49	Mild	VIII conc.	6/82	weight loss, dysphagia	Pneumocystis carinii pneumonia	--	dead
Missouri	52	Severe	VIII conc.	4/82	fever, lymphadenopathy	Histoplasma capsulatum	Candidiasis	dead
California	7	Severe	VIII conc.	9/81	lymphadenopathy	Herpes zoster, Candidiasis	--	alive

All of the patients were heterosexual males with no history of intravenous drug use. In addition, detailed histories gave no suggestion that the disease could have been acquired through contact with each other, with homosexuals, with illicit drug users, or with Haitians. Moreover, no known medications, occupations, habits, types of pets or antecedent history of personal or family illness with immunological relevance was found in these individuals. Most often these patients represented the first AIDS cases in their cities, states or regions. In general, the clinical characteristics of hemophiliac patients who contracted AIDS are very similar to those of the other AIDS patient groups. Two hemophiliac children with this syndrome have been reported, however, while the remainder of the patients are of a somewhat older age than the other AIDS patients. In addition, no hemophiliac patient with Kaposi's sarcoma has been reported. The overall death rate from AIDS in the hemophiliac population is 50%.

All of the hemophiliacs with AIDS were receiving lyophilized factor VIII concentrate. None was treated with cryoprecipitate. Seven of the eight patients had severe hemophilia which required the administration of large amounts of factor VIII concentrate. There was no indication from the available data that any of these patients had used a common lot of factor VIII concentrate. The available data supports the view that this disease may have been contracted from the factor VIII concentrate, each lot of which is prepared from pooled plasma obtained from 2,000-5,000 individual donors. The average patient requires about 40,000 units of factor VIII yearly. One unit is equivalent to the factor VIII activity found in 1 ml of normal

TABLE XI

Acquired Immune Deficiency Syndrome
in Infants

Characteristic	Patient 1	2	3	4
Race	Black/Hispanic	Haitian	Haitian	White
Sex	Male	Male	Male	Female
Location	NYC	Brooklyn	Newark	San Francisco
Birth	12/80	1/81	1/81	4/82
Age at onset	3 months	2 weeks	5 months	2 months
First infection	candidiasis	diarrhea	P. carinii pneumonia	candidiasis
Age at subsequent infection	17 months	5 months	-	6 months
Second infection	M. avium-intracellulare	P. carinii C. neoformans and CMV pneumonia	-	P. carinii pneumonia
Outcome	alive	dead-6 months	dead-6 months	dead-7 months
Mother:				
Personal habits	Intravenous drugs	Unknown	Unknown	Intravenous drugs; prostitution
Evidence of immunodeficiency	P. carinii pneumonia	-	-	Oral candidiasis lymphopenia

plasma (29). Thus, the exposure to blood products by these patients is enormous. Another risk factor may be the high incidence of hepatitis B infection in hemophiliacs (30).

6) Infants. By December 17, 1982, the CDC had received reports of unexplained immunodeficiency and opportunistic infections in a number of infants (8). Details of four of these patients are presented in Table XI. None of the infants had received blood or blood products before the development of their immunodeficiency syndrome. All of the infants were offspring of women who were at risk to develop acquired immune deficiency syndrome, in that they were either Haitian or intravenous drug users. The first patient's mother was an intravenous drug user who was in apparently good health at the time of the infant's birth. Ten months later she developed dyspnea, fever and oral candidiasis. Eleven months after the birth of her child, she was hospitalized and died of biopsy proven Pneumocystis carinii pneumonia. The mother of case 4 was a known intravenous drug user with a history of oral candidiasis and mild lymphopenia. She had had two other female children by different fathers. Each of these children had unexplained cellular immunodeficiency. One of them had died of Pneumocystis carinii pneumonia. The children had not lived together.

Besides the four patients presented in Table XI, six additional young children with opportunistic infections have been reported to the CDC (8). Five of these had Pneumocystis carinii pneumonia and one had disseminated infection with Mycobacterium avium-intracellulare. Three of the six children are males. All six are dead. In addition to these cases, twelve young children with immunodeficiency syndromes have been seen in New York City, Newark, New Jersey, and California (8). However, these children have not had life-threatening opportunistic infections. All of the children are currently alive. Their ages range from one to four years. Eight of the twelve are male. Clinical features of these twelve infants include failure to thrive (83%), oral candidiasis (50%), hepatosplenomegaly (92%), generalized lymphadenopathy (92%), and chronic pneumonitis without a demonstrable infection in 83%. Of the nine mothers on whom information is available, seven are reported to be intravenous drug users. None is Haitian. The possibility that these twelve children have an incomplete form of acquired immune deficiency syndrome is currently under active investigation.

It is quite likely that the four children described in the table, and perhaps some of the others, have acquired immune deficiency syndrome. The early onset of immunodeficiency in these children suggests the possibility that the acquisition of this defect occurred either in utero or shortly after birth.

7) Recipients of Blood Transfusions. On December 10, 1982, the CDC reported on a 20-month old white male infant from San Francisco who developed unexplained cellular immunodeficiency and opportunistic infection (9). This occurred after multiple transfusions necessitated by erythroblastosis fetalis. Included among the blood products received by the infant were platelets derived from the blood of a male subject subsequently found to have acquired immune deficiency syndrome. The patient developed his first evidence of infection at 7 months of age when he developed severe otitis media followed by oral candidiasis. Hepatosplenomegaly had been noted three months earlier. Non-A non-B hepatitis was contracted at age 9 months. At 14 months of age,

the infant developed neutropenia, autoimmune hemolytic anemia and thrombocytopenia. He was begun on systemic corticosteroid therapy and three months later was noted to have bone marrow cultures positive for Mycobacteria avium-intracellulare. There was no evidence of infection with cytomegalovirus. The parents and brother of the infant are in good health. The parents are normal heterosexual whites with no history of intravenous drug use. One of the 19 donors of the blood products the infant received during his first month of life was subsequently reported to have developed acquired immune deficiency syndrome. The donor, a 48 year old white male resident of San Francisco, was in good health when he donated the blood. Eight months later he developed fatigue, decreased appetite, and lymphadenopathy. One month later he was diagnosed as having Pneumocystis carinii pneumonia. Although he initially improved, subsequent immunological studies revealed severe cellular immune deficiency characteristic of AIDS. He subsequently developed fever, oral candidiasis and weight loss. Nine months after the initial onset of his illness, he died with a combination of Salmonella sepsis, perianal Herpes simplex virus infection, encephalitis of unknown etiology, and disseminated cytomegalovirus infection.

Of the 788 definitive AIDS cases among adults reported to the CDC through December 10, 1982, 42 (5.3%) belong to the "no known risk" group. That is, they are not known to be homosexually-active men, intravenous drug users, Haitians, or hemophiliacs. Two of these cases received blood products within two years of the onset of their illnesses and are currently being investigated as possibly having acquired their immune deficiency syndrome from contaminated blood or blood products. In addition, four other possible cases of blood borne transmission of AIDS are currently being investigated by the CDC.

The Clinical Spectrum of Acquired Immune Deficiency Syndrome

1) Kaposi's sarcoma and/or opportunistic infections. Currently the CDC defines a case of AIDS as a disease at least moderately predictive of a defect in cell-mediated immunity occurring in a person with no known cause for diminished resistance to that infection. Such diseases include Kaposi's sarcoma, Pneumocystis carinii pneumonia, and serious opportunistic infection. These infections include 1) pneumonia, meningitis or encephalitis caused by one or more of the following: aspergillosis, candidiasis, cryptococcosis, cytomegalovirus, nocardiosis, strongyloidosis, toxoplasmosis, zygomycosis, or atypical mycobacteriosis, especially Mycobacterium avium-intracellulare; 2) esophagitis due to candidiasis, cytomegalovirus or herpes simplex virus; 3) progressive multifocal leukoencephalopathy; 4) chronic enterocolitis (more than 4 weeks) due to cryptosporidiosis; or 5) unusually extensive mucocutaneous Herpes simplex of more than 5 weeks duration. The underlying deficiency in these individuals appears to be a profound defect in cell-mediated immunity. While treatment of the opportunistic infection may result in a cure of that particular infection, there is no indication that the underlying immune defect is reversible. As a result, the current overall survival in this entity is approximately 38% (Table III) whereas the two-year survival (survival of all patients diagnosed during 1980 or before) is less than 20% (Table XII).

TABLE XII

Acquired Immune Deficiency Syndrome:
Case Mortality Rates by Year of Diagnosis
(MMWR 31:507, 1982)

Year of Diagnosis	Cases	Deaths	Case Mortality Rate (%)
1979	7	6	86
1980	43	35	81
1981	207	124	60
1982 (Jan. → June)	249	67	27
TOTAL:	506	233	46

Patients may present with opportunistic infections, Kaposi's sarcoma or both. Among patients with both Kaposi's sarcoma and P. carinii pneumonia, Kaposi's sarcoma was diagnosed first in 40%, P. carinii pneumonia was diagnosed first in 40% and the diagnoses were made during the same month in the remaining 20% (31). Both groups of patients often present with a prolonged prodrome of fever, weight loss and lymphadenopathy. A considerable delay occurred between the initial onset of symptoms and diagnosis in both the Kaposi's sarcoma and P. carinii pneumonia groups. For the Kaposi's sarcoma group, the time from the onset of symptoms to diagnosis ranged from one to thirty months (median, 5.5 months); for P. carinii pneumonia, the range was one to eighteen months (median, 3.5 months). Two pieces of evidence suggest that those individuals who have Kaposi's sarcoma may have a milder illness than those who develop P. carinii pneumonia. First, those with Kaposi's sarcoma alone are significantly less likely to develop additional opportunistic infections than are patients who present with P. carinii pneumonia (31). In addition, the case mortality rate for those with Kaposi's sarcoma alone appears to be much less than for those in the P. carinii pneumonia group (Table XIII).

TABLE XIII

Acquired Immune Deficiency Syndrome:
Case Mortality Rate, June 1, 1981 → Sept. 15, 1982
(MMWR 31:507, 1982)

Presenting Feature	Number of Cases	Percentage of Total	Case Mortality Rate (%)
Pneumocystis carinii pneumonia*	302	51	47
Kaposi's sarcoma*	178	30	21
PCP + KS*	42	7	68
Other opportunistic infection	71	12	48
TOTAL:	593		41

* With or without other opportunistic infections

The patients who presented with both Kaposi's sarcoma and P. carinii pneumonia appear to have the worst prognosis, independent of the presence of an additional opportunistic infection. This may reflect the more profound nature of the immune deficiency observed in the patients with opportunistic infections (vide infra).

Kaposi's sarcoma was the initial malignant neoplasm found in association with acquired immune deficiency syndrome. The nature of the Kaposi's sarcoma found in these individuals is somewhat unusual. The generalized distribution of skin lesions, the presence of lesions on the head and neck, and the absence of predominantly lower extremity involvement is atypical of the form of Kaposi's sarcoma usually encountered in North America and Europe. The generalized lymphadenopathy and visceral involvement that is observed is also unusual, as is the aggressive nature of the tumor. The rapid clinical course closely resembles that of the lymphadenopathic form of Kaposi's sarcoma found in young adults in equatorial Africa (32-35). A similar form of Kaposi's sarcoma has been reported to develop in renal transplant patients and other individuals receiving immunosuppressive therapy (36-43). In these cases, the lesions of Kaposi's sarcoma often regress when immunosuppressive therapy is discontinued.

Preliminary evidence from New York City has suggested that the incidence of Kaposi's sarcoma in both homosexual males with the lymphadenopathic disease and in non-homosexuals with classic Kaposi's sarcoma is associated to a significant degree with the occurrence of the histocompatibility antigen HLA-DR 5 (Table XIV).

TABLE XIV

HLA-DR Antigen Frequencies in Patients
With Kaposi's Sarcoma
(Friedman-Kien et al, Ann. Int. Med. 96:693, 1982)

DR Antigen	Homosexuals with Kaposi's Sarcoma (n = 19)	Non-Homosexuals with Classic Kaposi's Sarcoma (n = 13)	Control A* (n = 26)	Control B† (n = 231)
		(percent)		
1	16.6	31	8	10
2	16.6	31	35	25.1
3	5.4	8	12	20.3
4	22.2	8	23	23.4
5	63.0 ($p < .005$)	62 ($p < .005$)	23	23.4
6	27.6	8	23	14.7
7	11.0	8	23	20
8	0	0	0	3.5

* Control A = randomly selected homosexual men from New York City

† Control B = normal white population from New York City

No association with any histocompatibility gene product has been observed for any of the other manifestations of acquired immune deficiency syndrome.

The association of cytomegalovirus infection with Kaposi's sarcoma is an intriguing one. Serologic studies have shown an extremely high rate of seropositivity in patients with Kaposi's sarcoma (44). Moreover, Herpes virus-like particles have been observed in cell lines derived from Kaposi's sarcoma tumors (45). Finally, studies utilizing DNA-DNA association kinetics have suggested the presence of CMV DNA and early antigens in Kaposi's sarcoma cells (46).

More recent reports have suggested that other malignant neoplasms may also be found in patients with acquired immune deficiency syndrome. Four cases of diffuse, undifferentiated, non-Hodgkins lymphoma, a malignancy of B cell origin, have recently been reported in homosexual males living in San Francisco (20). Each of these individuals had had one or more infections such as hepatitis B, anal warts, gonorrhea or syphilis. All patients had generalized lymphadenopathy and three had splenomegaly of uncertain duration. In addition, a 25 year old white male homosexual from Arizona has been reported to develop Burkitt's lymphoma (21). In New York City, two additional homosexual males have also been found to have Burkitt's lymphoma (44), a 33 year old homosexual male with known Kaposi's sarcoma has been reported to develop a second lymphoblastic neoplasm (47) and two homosexual men have developed primary lymphomas of the central nervous system (48).

2) Idiopathic Thrombocytopenic Purpura. Thirteen homosexual males have been reported who developed idiopathic thrombocytopenic purpura (18). Although these patients had no evidence of opportunistic infection, they did have immunological deficits characteristic of acquired immune deficiency syndrome. Each of these patients responded to corticosteroid therapy and three patients had splenectomy with excellent responses. In addition, two patients with Kaposi's sarcoma and thrombocytopenia have been observed in New York, but no details concerning these patients are currently available. Five patients with hemophilia who had received repeated transfusions with lyophilized factor VIII concentrate also have been reported to develop idiopathic thrombocytopenic purpura (19). Immunological evaluations of these patients also suggested abnormalities characteristic of acquired immune deficiency syndrome, although none of the patients had opportunistic infections. Four responded at least somewhat to therapy with corticosteroids. Splenectomy was performed in one, which was followed by a remission of thrombocytopenia. Each of the patients tolerated these therapeutic maneuvers without developing opportunistic infections.

3) Persistent Generalized Lymphadenopathy. Since October, 1981, the CDC has followed 57 homosexual men with diffuse lymphadenopathy (16). The cases all met the following criteria: 1) lymphadenopathy of at least three months duration involving two or more extra-inguinal sites and confirmed on physical examination by the patient's physician; 2) absence of any current illness or drug use known to cause lymphadenopathy; and 3) presence of reactive hyperplasia in a lymph node if a biopsy was performed. The 57 patients had a mean age of 33 years and all were homosexual or bisexual. Median duration of lymphadenopathy was 11 months. Forty-three of the patients had lymph node biopsies which showed reactive hyperplasia. Seventy percent of the patients had constitutional symptoms, including fatigue in 70%, fever in 49%, night sweats in 44%, and weight loss of greater than 5 pounds in

28%. Hepatomegaly and/or splenomegaly were found in 26% of the patients. Many of these patients had a history of sexually transmitted infections including gonorrhea in 58%, syphilis in 47%, and amebiasis in 42%. Of the patients tested, many had immunological abnormalities characteristic of patients with acquired immune deficiency syndrome. Between October, 1981 and May, 1982, one of the 57 patients with lymphadenopathy developed Kaposi's sarcoma. None has developed significant opportunistic infections. Causes for the persistent lymphadenopathy in these patients could not be identified.

The relationship of the syndrome of persistent lymphadenopathy to acquired immune deficiency remains obscure, especially in view of the relatively low incidence of progression of this syndrome into the complete syndrome of acquired immune deficiency. However, a number of features suggest that it might be part of the spectrum of AIDS. Epidemiological characteristics including age, racial composition, city of residence of the homosexual patients with lymphadenopathy are similar to those of the homosexual patients with acquired immune deficiency and Kaposi's sarcoma and/or opportunistic infection. Moreover, 32 of 73 Kaposi's sarcoma patients (44%) and 14 of 61 Pneumocystis carinii pneumonia patients (23%) reported to the CDC in the period from June, 1981 to January, 1982, had a history of lymphadenopathy before diagnosis, suggesting the possibility of a relationship between the syndrome of persistent lymphadenopathy and AIDS (16).

More recently, two white male hemophiliacs treated with factor VIII concentrate have also developed diffuse persistent lymphadenopathy (17). These patients also had immunological abnormalities characteristic of AIDS. Biopsies showed benign non-specific hyperplasia.

Finally, a 23 year old Hispanic female has been reported to have generalized persistent lymphadenopathy, elevated immunoglobulin levels, and lymphopenia (5). The lymphadenopathy has persisted for nearly a year and no etiology has been found. Although she denies IV drug use, her only sexual partner was a bisexual male who developed malaise, weight loss, lymphadenopathy, oral candidiasis, Pneumocystis carinii pneumonia, and Kaposi's sarcoma.

4) Asymptomatic Individuals. Immunological evaluation of asymptomatic homosexual males and hemophiliacs receiving factor VIII concentrate have revealed immunological abnormalities that may be part of the spectrum of acquired immunodeficiency syndrome (11-15). At this time, however, there is no convincing evidence that these individuals are at increased risk to develop the more full-blown syndrome of acquired immune deficiency.

Immunological Abnormalities in Acquired Immune Deficiency Syndrome

Acquired immune deficiency syndrome is characterized by a profound deficit in the cellular immune system. This has been found to be a uniform characteristic in all patients meeting the CDC criteria of AIDS. The deficiency in cell-mediated immunity appears to predispose both to the opportunistic infections characteristic of this syndrome and to the development of Kaposi's sarcoma and a variety of other malignant neoplasms. In general these patients exhibit severe peripheral lymphopenia and cutaneous anergy. In addition, they tend to have markedly deficient in vitro lymphocyte responses when stimulated with non-specific phytomitogens, antigens or with allogeneic or

autologous lymphocytes in the allogeneic or autologous mixed lymphocyte reaction respectively. The predominant abnormality appears to be a deficiency of T lymphocytes.

Through the use of hybridoma technology, monoclonal antibodies have been developed which recognize non-overlapping sub-populations of human T lymphocytes (49). Two of these antibodies T4 and T8 were initially thought to be differentiation antigens that identify functionally distinct sub-populations of human T cells, the helper/ inducer subset and the cytotoxic/suppressor subset respectively (Figure 2). More recent evidence indicates however, that T cells within each of these subpopulations have a variety of different additional functions. Thus, for example, the T4+ population contains cytotoxic lymphocytes which specifically identify Class II histocompatibility antigens (50) as well as a suppressor population of T cells (51), while the T8 population contains some helper cells (52) as well as a subset of the natural killer cell population (53). Nonetheless, these monoclonal antibodies have been widely used to evaluate T lymphocyte subpopulations in a variety of clinical conditions.

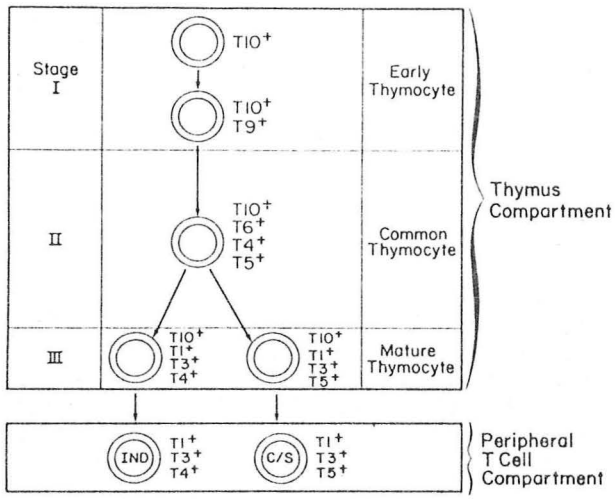

Figure 2: Stages of T-Cell Differentiation in Human Beings. Three discrete stages of thymic differentiation can be defined on the basis of reactivity with monoclonal antibodies. The most mature thymocyte population (Stage III) gives rise to the peripheral T-cell helper induced (IND) and cytotoxic/suppressor (C/S) subsets. The cell-surface antigens expressed during T-cell ontogeny are shown. The T5+ population is equivalent to the T8+ population. Reprinted from Reinherz and Schlossman, N. Engl. J. Med. 303:370, 1980.

It has become clear that the most profound abnormality in the AIDS patients is a decrease in the number of T4(+) cells. There may also be either a decrease, increase or no change in the T8(+) population with a resultant decline in the so-called "helper" to "suppressor" (T4/T8) ratio.

In contrast to the decrease in cell-mediated immunity, humoral immunity appears to be intact in AIDS patients. The number of circulating B lymphocytes is usually normal. In vitro testing of B cell function appears to be normal. Moreover, these patients are able to make normal antibody responses to a

variety of in vivo immunization procedures and often have hypergammaglobulinemia. Finally, as mentioned above, a number of patients have been reported who developed autoimmune thrombocytopenic purpura.

Patients with acquired immunodeficiency syndrome and opportunistic infections have profound evidence of deficiency in a cellular immunity (54-57). As seen in Tables XV→XX, AIDS patients with opportunistic infections manifested cutaneous anergy, severe peripheral lymphopenia, and depressed in vitro responses to non-specific phytomitogens, antigens and allogeneic lymphocytes or autologous non-T cells. Although the lymphopenia most profoundly affected the population of T cells identified by the monoclonal antibody T4, depressed absolute numbers of T lymphocytes identified by the monoclonal antibody T8 were also frequently seen. This deficiency is usually not as marked as that seen in the T4 positive population. In fact, an increase in the percentage of T8 positive cells may actually be seen although the absolute number of these cells is usually diminished. The net result of these abnormalities is a marked diminution in the so-called "helper to suppressor cell ratio", (T4 positive cells divided by T8 positive cells).

TABLE XV

Immunologic Abnormalities in Male Homosexual Patients with AIDS and Opportunistic Infections
(Gottlieb et al, N. Engl. J. Med. 305:1426, 1981)

Immunologic Tests	Patients 1	2	3	4	Controls
Delayed-type skin response	Absent	Absent	Absent	Absent	Present
Leukocyte count (cells/mm^3)	4300	2700	1950	4400	4800 - 10,800
Lymphocyte count (cells/mm^3)	411	402	585	132	1440 - 3040
T lymphocytes (%)	50	55	56	44	59 - 74
Absolute number	210	221	328	58	849 - 2249
T4 + (%)	0	0	10	2	46.0 ± 12.0
T8 + (%)	57	52	57	47	28.0 ± 8.0
T4+/T8+	0	0	0.18	0.04	1.6 ± 0.74
B lymphocytes (%)	3	10	12	10	5 - 10
Absolute number	12	40	70	13	72 - 304
PHA response (Δcpm)	27,000	81,186	5,000	6,142	155,383 ± 53,552

TABLE XVI

Immunologic Abnormalities in Male Homosexual Patients
with AIDS and Opportunistic Infections
(Masur et al, N. Engl. J. Med. 305:1431, 1981)

Patient	Total Lymphocytes/mm³	T Lymphocytes (per mm³)	B Lymphocytes (per mm³)	Delayed-Type Skin Responses	Antibody Responses to Immunization*
1	835	463	217	Absent	Present
2	398	163	196	Absent	Present
3	825	454	388	Absent	Present
4	2065	1507	620	Absent	Present
5	510	92	418	Absent	Present
6	987	548	156	Absent	Present
7	555	314	214	Absent	Present
8	588	129	-	Absent	Present
9	735	74	-	Absent	Present
10	824	602	147	Absent	Present
11	82	9	73	Absent	Present
Control	1500 - 4000	1080 - 2880	150 - 960	Present	Present

* Tetanus toxoid, diphtheria, pneumococcal polysaccharide

TABLE XVII

Immunologic Abnormalities in Male Homosexual Patients
with AIDS and Opportunistic Infections
(Siegal et al, N. Engl. J. Med. 305:1439, 1981)

Immunologic Test	Patients 1	2	3	4	Controls
Delayed-type skin response	Absent	Absent	Absent	Absent	Present
Lymphocyte count (cells/mm³)	657	435	316	360	1000 - 4800
T lymphocytes (%)	70	69	28	62	80 ± 7
B lymphocytes (%)	0	-	8	8	6 ± 2
PHA responsiveness (Δcpm)	11,852	1,509	1,313	23,100	29,000 ± 4,400
Natural killer activity	+	+	+	+	Present
Serum immunoglobulins - IgG (mg/dl)	864-1394	2360	1660	1370-1710	500-1,500
- IgA	322-375	445	435	420-1431	40-30
- IgM	133-300	90	230	55-275	40-200

TABLE XVIII

Immunologic Abnormalities in Male Homosexual Patients
with AIDS and Opportunistic Infections
(Mildvan et al, Ann. Int. Med. 96:700, 1982)

Immunologic Test	Patient 1	Patient 4	Control
Total leukocytes per mm^3	2250	1867	4900 - 8600
Total lymphocytes per mm^3	333	556	1567 - 2507
Total T lymphocytes per mm^3	308	339	1488 - 2382
T4 + per mm^3	27	39	1050 - 1680
T8 + per mm^3	251	299	558 - 945
T4+/T8+	0.14	0.14	1.0 - 3.0

TABLE XIX

Immunologic Abnormalities in Female AIDS Patients
with Opportunistic Infections
(Masur et al, Ann. Int. Med. 97:533, 1982)

Immunologic Test		Patient 1	2	3	4	5	Controls
Delayed-type skin response		Absent	Absent	Absent	Absent	Absent	Present
PMN/mm^3		3773	3431	14,365	7332	4264	3000-5000
Lymphocytes/mm^3		245	752	893	20	884	1500-4000
B lymphocytes (%)		8	ND	44	18	35	11.4 ± 4.5
T lymphocytes (%)		36	ND	20	68	58	85.0 ± 6
Serum immunoglobulins							
(mg/dl)	IgG	689	1630	1067	1500	ND	616 - 1647
	IgA	160	732	871	460	ND	59 - 371
	IgM	164	111	182	60	ND	57 - 343
In vitro Lymphocyte Responses							
PHA (Δcpm)		6584	8822	6789	24,499	11,311	> 20,000
MLR (Δcpm)		287	492	934	ND	ND	> 7,500

TABLE XX

Immunologic Abnormalities in Haitian Men with AIDS
and Opportunistic Infections
(Vieira et al, N. Engl. J. Med. 308:125, 1983)

Immunologic Test	Patients 3	5	10	Control
Leukocytes/mm³	2,200	4,200	5,800	4,800-10,600
Lymphocytes/mm³	352	378	638	1,200-3,000
B lymphocytes/mm³	19	53	26	64-475
(%)	(5)	(15)	(4)	(6-21)
T lymphocytes/mm³	185	127	523	867-1897
(%)	(49)	(36)	(82)	(53-81)
T4+/mm³	8	7	19	468-1433
(%)	(3)	(2)	(3)	(30-56)
T8+/mm³	189	99	453	192-726
(%)	(50)	(28)	(71)	(15-32)
T4/T8	0.04	0.07	0.04	1.2-2.5
In vitro lymphocyte stimulation				
PHA (%)	< 1	< 1	< 1	100
Antigen	↓↓	↓↓	↓↓	

In contrast to the severe deficiencies in cellular immunity seen in patients with AIDS and opportunistic infections, humoral immune responses are usually intact or augmented. In general, in vivo antibody responses to immunization with tetanus toxoid, diptheria toxoid, or pneumococcal polysaccharide are intact in these individuals. This is observed despite the fact that some individuals showed decreased numbers of circulating B lymphocytes. In addition, hypergammaglobulinemia is a common feature.

TABLE XXI

Immunologic Findings in Homosexual Men with Kaposi's Sarcoma
(Friedman-Kien et al, Ann. Int. Med. 96:693, 1982)

Immunologic Test	Kaposi's Sarcoma (n = 17)	Normal Controls
Delayed-type skin response	Negative (16/19)	Positive
Leukocyte count (cells/ml³)	5035 ± 1674	6800 ± 3200
Lymphocyte count (cells/mm³)	1955 (680-3976)	2100 (500-4700)
B lymphocytes (%)	8 (3-16)	9 (1-14)
T lymphocytes (%)	56 (37-70)	60 (38-75)
T4 + (%)	20 (1-43)*	48 (35-59)
T8 + (%)	54 (34-71)*	27 (19-39)
T4+/T8+	0.4 (0.03-1.1)*	1.9 (1.0-3.3)
Mitogen-induced lymphocyte responses (Δcpm)		
Phytohemagglutinin	43,345 (4717-102,691)*	87,190 (40,150-169,460)
Pokeweed mitogen	9,669 (1134-43,845)*	43,253 (17,444-114,881)
Reactivity in mixed lymphocyte culture (% of control)		
As responders	42 ± 39*	100
As stimulators	84 ± 55*	100

* $p < 0.01$

The patients with acquired immune deficiency syndrome and Kaposi's sarcoma without opportunistic infections likewise have abnormalities in cellular immunity (33). However, as shown in Table XXI, these abnormalities tend to be somewhat less marked than those noted in the patients with AIDS and opportunistic infections. The vast majority of these patients display anergy (16 of 19) to a variety of non-specific skin test antigens. However, they do not show circulating lymphopenia. While the T4 positive population is diminished, the magnitude of this depression in terms of the absolute number of circulating T4+ cells is less marked than in patients with AIDS and opportunistic infection. Moreover, the T8 positive population is usually increased not only relatively but also in terms of the absolute number of circulating cells identified by this monoclonal antibody. The net result of this abnormality is a decrease in the T4+ to T8+ ratio. In general, the so-called helper to suppressor ratio is less abnormal in patients with Kaposi's sarcoma without opportunistic infections than in those with AIDS and opportunistic infections. Humoral immunity tends to be intact in these patients. Moreover, evidence of elevated concentrations of at least one class of immunoglobulin is routinely observed (Figure 3).

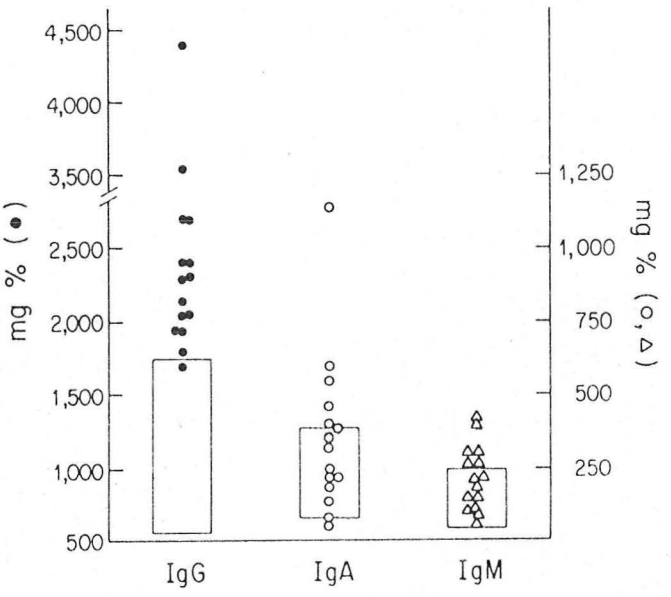

Figure 3: Serum immunoglobulin levels in patients with Kaposi's sarcoma. The boxes denote levels of these proteins in the serum of normal persons. Reprinted from Friedman-Kien et al. Ann. Int. Med. 96:693, 1982.

Patients with autoimmune thrombocytopenia also tend to have less marked immunological abnormalities than those patients with acquired immune deficiency syndrome and opportunistic infections (18,19). As shown in Tables XXII and XXIII, both homosexual men with this syndrome and hemophiliacs tend to have normal or only marginally depressed numbers of circulating lymphocytes. While the T4 to T8 ratio is diminished somewhat, this is not a uniform finding. The vast majority of the patients have increased numbers of OKT8

positive cells and most have diminished numbers of OKT4 positive cells. The majority of these patients also have elevated levels of circulating immunoglobulins, especially IgG.

TABLE XXII

Immunologic Abnormalities in Homosexual Men with Autoimmune Thrombocytopenic Purpura (Morris et al, Ann. Int. Med. 96:714, 1982)

Immunologic Test	ITP (n = 13)	Controls
Lymphocytes per mm^3	1632 ± 178 (5 of 9 lymphopenic)	1632 ± 178 (1500-3040)
T4/T8	0.54 ± 0.15 (3/5 ↓ OKT4) (5/5 ↑ OKT8)	1.0 - 3.3
Gamma globulin (gm/dl)	1.78 (6/9 ↑)	0.70 - 1.40

TABLE XXIII

Immunologic Abnormalities in Hemophiliacs with Idiopathic Thrombocytopenic Purpura (Ratnoff et al, N. Engl. J. Med. 308:439, 1983)

Immunologic Test	Patients 1	3	4	5	Controls
Lymphocytes per mm^3	2400	1287	1120	1104	1519 ± 379
T4 +	607	279	426	475	684 - 760
T8 +	962	731	426	276	380 - 410
T4+/T8+	0.63	0.38	1.0	1.72	1.8 - 2.0

Patients with diffuse lymphadenopathy also tend to have immunological abnormalities, but again these are less marked than those noted in the patients with acquired immune deficiency syndrome and opportunistic infection (16,17). The hemophiliacs tend to be more abnormal than the homosexual men with diffuse lymphadenopathy (Tables XXIV and XXV). The homosexual men tend to have very marginally decreased numbers of T4 positive cells and increased or normal numbers of T8 positive cells while the depression in the T4 positive population is more marked in the hemophiliac patients, and the T8 positive cells tend to be normal in these individuals. As a result, in both groups the T4+ to T8+ ratio is marginally abnormal. Of 21 additional homosexual males with lymphadenopathy followed by the CDC, 8 exhibited abnormally low T4 to T8 ratios (16). Immunoglobulins tend to be elevated in these individuals, especially IgG. Two individuals with hemophilia and diffuse lymphadenopathy were found to be anergic, while 8 of 30 homosexual men with diffuse lymphadenopathy followed by the CDC were found to be anergic (16).

Fifty to eighty percent of asymptomatic homosexual men (11-13) and more than 50% of asymptomatic hemophiliacs who are users of factor VIII concentrate (14,15) have been shown to manifest immunological abnormalities. As shown

in Tables XXIV, XXVI→XXVIII, these patients are usually not lymphopenic and show no or only marginal decreases in the absolute number of circulating T4+ lymphocytes. However, the number of circulating T8 positive lymphocytes is elevated, yielding an abnormally low T4+ to T8+ ratio. In addition, at least half of these individuals exhibit increased serum immunoglobulin concentrations of at least one isotype.

TABLE XXIV

Immunologic abnormalities in Homosexual Men
with Diffuse Lymphadenopathy
(Stahl et al, Amer. J. Med. 73:171, 1982)

Immunologic Test	Homosexuals with Lymphadenopathy (n = 8)	Homosexual Controls (n = 19)	Heterosexual Controls
Leukocytes per mm^3	6506 ± 1613	5932 ± 2215	6800 ± 3200
Lymphocytes per mm^3	2410 ± 219	2095 ± 840	2600 ± 1050
T cells (%) absolute number	66.7 ± 10.7 (1607)	72.4 ± 9.9 (1517)	62.4 ± 7.4 (1622)
T4 + absolute number	35.0 ± 9.4* (844)	45.3 ± 12.5 (949)	51.8 ± 9.2 (1347)
T8 + absolute number	52.8 ± 9.1* (1272)	42.2 ± 12.2* (884)	32.2 ± 7.9 (837)
T4+/T8+	0.7 ± 0.25	1.2 ± 0.55	1.79 ± 0.84

$p < 0.01$

TABLE XXV

Immunologic Abnormalities in Hemophiliacs
with Diffuse Lymphadenopathy
(Ragni et al, Lancet 1:213, 1983)

Immunologic Test		Patients 1	Patients 2	Controls
Leukocytes per mm^3		4600	4400	4100 - 10,700
Lymphocytes per mm^3		874	1144	1500 - 4000
T lymphocytes per mm^3		646	801	1050 - 2800
T4 +		280	400	750 - 2000
T8 +		297	343	300 - 800
T4+/T8+		0.9	1.2	1.0 - 3.0
Immunoglobulins (mg/dl)	IgG	1810	4560	975 ± 201
	IgA	172	191	202 ± 83
	IgM	127	241	93 ± 30
Delayed-type skin reactivity		Absent	Absent	

TABLE XXVI

Immunologic Abnormalities in Homosexual Men
(Kornfeld et al, N. Engl. J. Med. 307:729, 1982)

T Cell Subset	Symptomatic Homosexuals (n = 31)	Asymptomatic Homosexuals (n = 50)	Control (n = 20)
T4 + - (%)	22.4 ± 1.6	27.4 ± 1.4	36.6 ± 1.0
(cells/mm³)	483.5 ± 43.0	643.9 ± 41.5*	813.3 ± 60.6
T8 + - (%)	31.1 ± 1.6	28.8 ± 1.1	20.5 ± 0.8
(cells/mm³)	651.2 ± 42.5**	675.1 ± 33.3**	454.0 ± 37.3
T4+/T8+	0.8 ± 0.1*	1.1 ± 0.1*	1.8 ± 0.1

Symptomatic: weight loss, 2; fever, 7; lymphadenopathy, 11; diarrhea, 5; oral candidiasis, 2; amebiasis, 18; multiple, 11

* $p < 0.05$

** $p < 0.01$ compared to controls

TABLE XXVII

Immunologic Abnormalities in Asymptomatic Hemophiliacs
(Lederman et al, N. Engl. J. Med. 308:79, 1983)

Test	Controls (n = 19)	Hemophiliacs VIII Concentrate (n = 11)	Hemophiliacs Cryoprecipitate (n = 8)
Leukocytes per mm³	4793 ± 261	5172 ± 418	6350 ± 485
Lymphocytes per mm³	1519 ± 87	1974 ± 122	1651 ± 241
B lymphocytes per mm³	142 ± 15	185 ± 33	153 ± 77
T lymphocytes per mm³	1044 ± 62	1505 ± 107*	982 ± 160
T4 + per mm³	685 ± 43	745 ± 73	639 ± 115
T8 + per mm³	412 ± 41	810 ± 74*	433 ± 80
T4+/T8+	1.84 ± 0.16	1.02 ± 0.17**	1.64 ± 0.31

* $p < 0.001$

** $p < 0.01$

TABLE XXVIII

Immunologic Abnormalities in
Asymptomatic Patients with Hemophilia
(Menitove et al, N. Engl. J. Med. 308:83, 1983)

Test	Controls	Hemophiliacs Concentrate (n = 14)	Hemophiliacs Cryoprecipitate (n = 8)
Lymphocytes per mm³	2,400 ± 230	2330 ± 190	2030 ± 190
T4 + (%)	50.4 ± 0.9	44.0 ± 2.6	49.3 ± 0.8
T8 + (%)	24.6 ± 0.6	32.2 ± 1.9*	22.3 ± 0.8
T4+/T8+	2.06 ± 0.06	1.44 ± 0.14*	2.23 ± 0.07
Serum IgG (mg/dl)	972.1 ± 68.5	1607.3 ± 257.8**	1223.6 ± 88.7**

* $p < 0.01$

** $p < 0.02$

All of the hemophiliac patients with T lymphocyte abnormalities had received factor VIII concentrate. Abnormalities were not seen in individuals who received cryoprecipitate. There was, however, no correlation between the amount of factor VIII concentrate used and abnormalities in the ratio of T4+ to T8+ cells. Similarly the abnormalities could not be related to a particular source or lot of factor VIII concentrate. Of interest, hemophiliacs receiving cryoprecipitate exhibit hypergammaglobulinemia of a significant, albeit lesser degree than individuals receiving factor VIII concentrate, but no evidence of T lymphocyte abnormalities.

As shown in Figure 4, abnormalities in the T4+ to T8+ ratio appear to be most marked in homosexual men having more than 50 sexual partners per year (13). It is unclear whether these ratios also vary with the use of amyl nitrite or other recreational drugs (12,13).

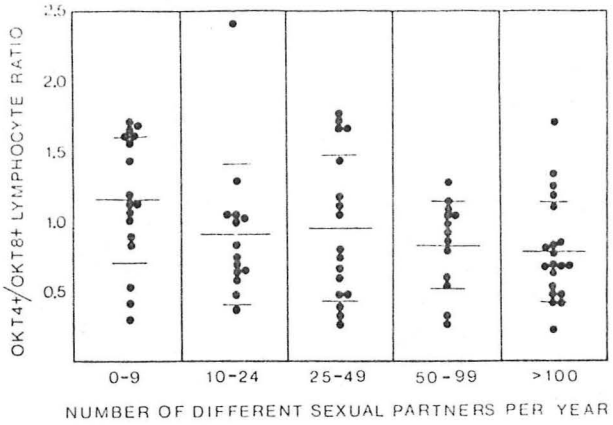

Figure 4: T4/T8 ratios and sexual promiscuity in homosexual men. The OKT4/OKT8 ratio was higher in subjects reporting nine or fewer different secual partners per year than in those reporting 50 to 99 partners ($p<0.05$) or 100 or more partners ($p<0.01$) per year. Reprinted from Kornfeld et al, N. Engl. J. Med. 307:729, 1982.

It should be noted that the abnormalities reported in asymptomatic homosexual men have been reported from areas in which acquired immune deficiency syndrome itself is endemic. Little information is currently available concerning lymphocyte subset analysis in homosexual men living in areas in which this disease is less prevalent. Therefore, it cannot be concluded that the homosexual lifestyle per se predisposes to development of lymphocyte subset abnormalities.

In summary, a spectrum of abnormalities in immunological function can be seen in individuals with various manifestations of acquired immune deficiency. Most of the abnormalities in circulating T lymphocytes result in a depressed T4+ to T8+ ratio and as shown in Figure 5, the extent of abnormalities in this ratio appear to correlate with the degree of immunosuppression and clinical involvement (58). However, examination merely of the T4+ to T8+ ratio masks the fact that abnormalities in this ratio in the various patient groups appear to result from independent changes in each of the population. Thus, asymptomatic individuals tend to have hypergammaglobulinemia and increased numbers of circulating T8 positive T cells, with a resultant diminution in the T4 to T8 ratio. Individuals with the diffuse lymphadenopathy

syndrome additionally develop modestly diminished numbers of T4 positive cells but maintain their T8 positive cells at normal or somewhat elevated levels, with the resultant tendency for a further decline in the T4 to T8 ratio. These abnormalities are somewhat more marked in individuals with autoimmune thrombocytopenic purpura and Kaposi's sarcoma. Finally, only the individuals with opportunistic infections appear to develop marked lymphopenia, which again predominantly involves the T4 positive T cell population but may also involve the T8 positive population and even B lymphocytes. All of these patients have a tendency to develop hypergammaglobulinemia. The finding that hemophiliacs receiving cryoprecipitate also develop hypergammaglobulinemia suggests that this abnormality may be independent of the T cell subset abnormalities. Autoantibodies such as rheumatoid factor, antinuclear antibodies and anti-DNA antibodies are not seen in patients with AIDS and complement levels tend to be normal.

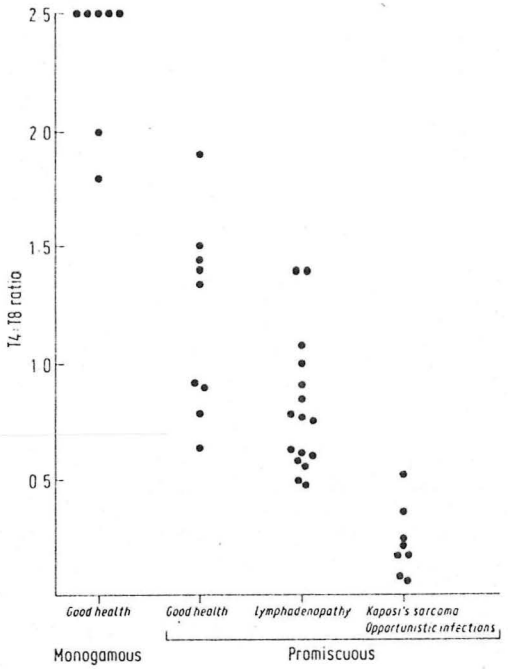

Figure 5: T4:T8 ratios in homosexual males. Promiscuous males had more than 50 sexual partners per year. Monogamous males had essentially one partner for the previous 5 years. Reprinted from Wallace et al. Lancet 1:908, 1982.

The cause of the various T cell subset abnormalities within the spectrum of acquired immunodeficiency has not been clearly elucidated. Abnormalities in T4 to T8 ratios resulting from increased numbers of T8 positive cells with or without decreased numbers of T4 positive cells have been reported during infections with cytomegalovirus and Epstein-Barr virus (59,60). Whether infections with these or other viruses play a role in the abnormalities observed in asymptomatic homosexual men remains to be determined. Although it is tempting to speculate that the progressive abnormalities in T lymphocyte function observed in the various categories of acquired immune deficiency represent various manifestations of a single abnormality perhaps caused by the same etiologic agent, or in fact stages of an inexorably progressive process leading to profound and fatal deficiencies of the cellular immune

system, these contentions have not been verified. It remains possible that these various immunologic abnormalities are caused by different unrelated events and that one does not predispose to the other.

Epidemiology

Acquired immune deficiency syndrome appears to have developed simultaneously in a number of different locations. In the United States, the majority of cases initially appeared in New York City, San Francisco, and Los Angeles. At about the same time, evidence of the disease appeared in the Haitian community in Miami and Newark, New Jersey and also appeared in Port au Prince, Haiti. There is no indication that the disease existed in any major way before 1979 in Haiti or in the United States (CDC Task Force on Acquired Immune Deficiency Syndrome, unpublished observation). Although not commonly recognized, the CDC has received reports of 41 cases of AIDS occurring in 10 foreign cases through September 15, 1982 (10). Whereas many of these have had contact with American homosexuals or with Haitians (61,62), a number of others appear to have had no contact with either of these groups (63). By September of 1982, AIDS had appeared in 33 states in the United States and the District of Columbia. However, as seen in Table XXIX, the majority of cases still appear to occur in the New York City metropolitan area, San Francisco, Los Angeles and Miami. Even when calculated in terms of cases per million population, New York, San Francisco and Miami are the leading centers of this illness and the incidence in the six major centers of the disease in the United States is anywhere between eight and 50 times that occurring in the remainder of the population.

TABLE XXIX

Acquired Immune Deficiency Syndrome:
Distribution of Cases, June 1, 1981 → Sept. 15, 1982
(MMWR 31:507, 1982)

Standard metropolitan statistical area of residence	Total number of cases	Percentage of total	Cases per million population
New York City	288	48.6	31.6
San Francisco	78	13.2	24.0
Miami	31	5.2	19.1
Newark	15	2.5	7.6
Houston	15	2.5	5.2
Los Angeles	37	6.2	4.9
Elsewhere	129	21.8	0.6
TOTAL:	593	100	2.6

Evidence of Transmissibility of the Disease

1) The Los Angeles Cluster. Detailed sexual histories were obtained concerning thirteen homosexual males who developed Kaposi's sarcoma and/or Pneumocystic carinii pneumonia in Los Angeles and Orange County, California between June 1, 1981 and April 12, 1982 (64). Nine of these patients were found to have had direct sexual contact with other patients in this cluster. Four of the nine had been exposed to more than one patient with either Kaposi's sarcoma or Pneumocystis carinii pneumonia. Four other patients, who had no known contact with additional patients, were found to have had the potential of contact with mutual intermediaries. One patient with Kaposi's sarcoma had an apparently healthy sex partner who also had sexual contact with two persons in the cluster with Pneumocystis carinii pneumonia. One patient with Kaposi's sarcoma had had sexual contact with two friends of an additional patient in the cluster with Kaposi's sarcoma. Finally, two patients with Pneumocystis carinii pneumonia had more than 80% of their anonymous sexual contacts with persons in bath houses attended frequently by other persons in Los Angeles with Kaposi's sarcoma and Pneumocystis carinii pneumonia.

The nine patients who had had direct sexual contact with each other appeared to be part of an interconnected series of 15 cases in 8 other cities. One person in this series had had contact with four of the California patients and at least two other patients in New York City. One interpretation of these results is that an infectious agent or agents is being sexually transmitted among homosexually-active males. This agent may cause the acquired immune deficiency syndrome. The observations, however, do not rule out the alternative hypothesis that these patients, as a result of their sharing of a particular style of life, have been exposed to a common environmental agent that predisposes to the illness.

2) Hemophiliacs. At least 8 cases of AIDS have been reported in hemophiliac patients, all of whom have received very large amounts of factor VIII concentrate (6,7). It is clear that these individuals have had enormous exposure to blood products since each lot of concentrate is prepared from plasma obtained from 2,000-5,000 donors. The average severe hemophiliac requires about 40,000 units of factor VIII yearly. To date, no common lot of factor VIII concentrate has been identified among the hemophiliac patients who have developed AIDS.

3) Transmission to female sex partners of intravenous drug users. The CDC has reported that 13 women developed AIDS who were sexual partners with either intravenous drug users or men with AIDS (5). It should be pointed out, however, that in at least four of the 13 cases reported the male partner had no overt illness suggesting AIDS. These cases suggest that AIDS may be sexually transmitted among heterosexuals. Moreover, they suggest that carriers of AIDS may be able to transmit the disease but not themselves have symptoms.

4) Transmission from mother to offspring. As mentioned above, a number of cases have been reported in which apparent transmission of AIDS from a potentially affected mother to offspring in utero is likely to have occurred (8).

5) Transmission by blood transfusion. As mentioned above, an infant who received the exchange transfusion subsequently developed a syndrome characteristic of AIDS. The donor of platelets in this circumstance subsequently developed AIDS (9).

Incubation Time

A number of pieces of evidence suggest that if AIDS is transmitted from person to person by blood products or sexual contact, the incubation period is quite prolonged. For example, in the Los Angeles cluster (64), three patients developed Kaposi's sarcoma after sexual contact with persons who already had Kaposi's sarcoma. One of these developed his initial symptoms nine months after sexual contact, one after thirteen months, and one 22 months after sexual contact. In the situation in which an infant apparently developed AIDS secondary to blood transfusion (9), the donor was normal at the time of the transfusion. However, 8 months later he began to experience fatigue and decreased appetite and subsequently developed lymphadenopathy and Pneumocystis carinii pneumonia. In one of the circumstances in which an infant developed AIDS (8), the mother of the infant was well at the time of the infant's birth but developed symptoms of acquired immune deficiency 11 months later. All of these results suggest that if AIDS is caused by a transmissible agent, the incubation is at least 8 and perhaps as long as 22 months. If a transmissible agent is involved, it would appear to require intimate direct contact of mucosal surfaces as occurs during sexual contact between either homosexuals or heterosexuals, or parenteral spread by means of either intravenous drug use or extremely large exposure to blood products. Spread via airborne routes or casual interpersonal contact does not seem to be involved. Moreover, the data suggest that persons might be carriers of AIDS and be able to transmit the disease but not themselves have identifiable symptoms. These patterns strongly resemble the mode of spread of hepatitis B virus infection which is very common among all AIDS patients.

Treatment

Currently treatment is directed toward control of opportunistic infection and therapy for malignant neoplasms. There is no convincing evidence that the underlying immune deficiency is reversible. However, a number of modalities are currently being tested such as bone marrow transplantation, interferon therapy, interleukin 2 therapy, and a variety of immunomodulatory drugs in an attempt to enhance the depressed cellular immunity characteristic of these patients. It is still too early to evaluate results of these various therapeutic modalities.

Summary

Acquired immune deficiency syndrome is a new epidemic disease of major proportion that has affected nearly 1,000 persons since its onset in 1979. Essentially it represents an epidemiologically restricted acquired profound deficiency of the cellular immune system with consequent opportunistic infections and neoplastic malignancies. The overwhelming bulk of information suggests that the disease is caused by an as yet unidentified transmittable agent. It appears to be transmitted through intimate sexual contact or by

parenteral exposure to blood or blood products or through in utero contact from mother to fetus. Moreover, the agent must be capable of maintaining its infectivity during the preparation of lyophilized factor VIII concentrate. The bulk of the current evidence suggests that routine exposure to blood or blood products has a very low incidence of disease transmission but nonetheless the suspicion that this entity has been transmitted in a few circumstances by routine transfusions has caused considerable concern both from the scientific community and the lay press. It remains to be seen, however, whether or not the degree of concern is justified. As yet, routine transfusions even from patients with AIDS, do not appear to have resulted in transmission of the condition (Task Force on Acquired Immune Deficiency Syndrome, unpublished observation), but the variable and quite long incubation period does not allow one to be confident of this conclusion.

There are a number of major unanswered questions in this disease, foremost of which is the nature of the transmittable agent. Moreover, it is not entirely clear who is susceptible to this agent. It is possible that only individuals with underlying subtle derangements of their immune system caused by recurrent bacterial, viral and protozoal infections such as occur in sexually promiscuous homosexual males or who have experienced repeated antigenic stimulation such as might occur in the hemophiliacs, are more susceptible to this entity. The risk of routine blood transfusion is also not entirely clear. Therefore, the nature of precautions that ought to be taken in screening blood donors is not immediately apparent. Moreover, the possibility of transmission to medical or scientific personnel has not been completely evaluated to date. No health professional has contracted the illness. Nonetheless, precautions appear to be the order of the day and the CDC has promulgated a list of precautions for health personnel which is included in the appendix. Until the cause of this potentially lethal syndrome is identified, however, the need or appropriateness for these precautions remains speculative.

A recent observation may be quite important in understanding the etiology of AIDS in man (65). A syndrome closely resembling AIDS has been identified in a colony of rhesus monkeys in Davis, California. The syndrome is characterized by generalized lymphadenopathy, chronic wasting, severe opportunistic infections including cytomegalovirus, the development of fibrosarcomas and a high mortality. Since 1969, there have been four outbreaks of acquired immune deficiency syndrome in rhesus and macaque monkeys at the California Primate Research Center. In an attempt to study the possible transmissibility of this disease, 55 rhesus monkeys were housed in the same cage in which the previous outbreak had occurred. Nine apparently healthy juvenile females remaining from the previous outbreak of this illness were also housed in thise cage. The monkeys were followed for 15 months. Controls consisted of 558 animals housed in additional separate cages at the same facility. As seen in Table XXX, 37.5% of the monkeys died during this time period with evidence of severe immune deficiency and opportunistic infections. This outbreak may serve as a valuable model for AIDS in man by providing insight into the nature of transmissible agents that can cause this syndrome.

TABLE XXX

On Outbreak of AIDS
(Hendrickson et al, Lancet 1:388, 1983)

	Subjects	
	Experimental	Control
Number	n = 64	n = 558
Duration of observation	15 months	15 months
Deaths (%)	24 (37.5%)	30 (5.5%)
Abnormalities in those dying		
Weight loss	19 (79%)	
Infections (multiple)	17 (71%)	
Diarrhea	17 (71%)	
Anemia	16 (67%)	
Lymphadenopathy	15 (63%)	
Lymphopenia	12 (50%)	
Splenomegaly	10 (42%)	
Fever	7 (29%)	
Cutaneous anergy	5/7 (14%)	
Fibrosarcoma	3 (13%)	

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APPENDIX

Precautions for Clinical and Laboratory Staffs
(MMWR 31:577-579, 1982)

A. The following precautions are advised in providing care to AIDS patients:

1. Extraordinary care must be taken to avoid accidental wounds from sharp instruments contaminated with potentially infectious material and to avoid contact of open skin lesions with material from AIDS patients.

2. Gloves should be worn when handling blood specimens, blood-soiled items, body fluids, excretions, and secretions, as well as surfaces, materials, and objects exposed to them.

3. Gowns should be worn when clothing may be soiled with body fluids, blood, secretions, or excretions.

4. Hands should be washed after removing gowns and gloves and before leaving the rooms of known or suspected AIDS patients. Hands should also be washed thoroughly and immediately if they become contaminated with blood.

5. Blood and other specimens should be labeled prominently with a special warning, such as "Blood Precautions" or "AIDS Precautions." If the outside of the specimen container is visibly contaminated with blood, it should be cleaned with a disinfectant (such as a 1:10 dilution of 5.25% sodium hypochlorite [household bleach] with water). All blood specimens should be placed in a second container, such as an impervious bag, for transport. The container or bag should be examined carefully for leaks or cracks.

6. Blood spills should be cleaned up promptly with a disinfectant solution, such as sodium hypochlorite (see above).

7. Articles soiled with blood should be placed in an impervious bag prominently labeled "AIDS Precautions" or "Blood Precautions" before being sent for reprocessing or disposal. Alternatively, such contaminated items may be placed in plastic bags of a particular color disignated solely for disposal of infectious wastes by the hospital. Disposable items should be incinerated or disposed of in accord with the hospital's policies for disposal of infectious wastes. Reusable items should be reprocessed in accord with hospital policies for hepatitis B virus-contaminated items. Lensed instruments should be sterilized after use on AIDS patients.

8. Needles should not be bent after use, but should be promptly placed in a puncture-resistant container used solely for such disposal. Needles should not be reinserted into their original sheaths before being discarded into the container, since this is a common cause of needle injury.

9. Disposable syringes and needles are preferred. Only needle-locking syringes or one-piece needle-syringe units should be used to aspirate fluids from patients, so that collected fluid can be safely discharged through the

needle, if desired. If reusable syringes are employed, they should be decontaminated before reprocessing.

10. A private room is indicated for patients who are too ill to use good hygiene, such as those with profuse diarrhea, fecal incontinence, or altered behavior secondary to central nervous system infections.

Precautions appropriate for particular infections that concurrently occur in AIDS patients should be added to the above, if needed.

B. The following precautions are advised for persons performing laboratory tests or studies on clinical specimens or other potentially infectious materials (such as inoculated tissue cultures, embryonated eggs, animal tissues, etc.) from known or suspected AIDS cases:

1. Mechanical pipetting devices should be used for the manipulation of all liquids in the laboratory. Mouth pipetting should not be allowed.

2. Needles and syringes should be handled as stipulated in Section A (above).

3. Laboratory coats, gowns, or uniforms should be worn while working with potentially infectious materials and should be discarded appropriately before leaving the laboratory.

4. Gloves should be worn to avoid skin contact with blood, specimens containing blood, blood-soiled items, body fluids, excretions and secretions, as well as surfaces, materials, and objects exposed to them.

5. All procedures and manipulations of potentially infectious material should be performed carefully to minimize the creation of droplets and aerosols.

6. Biological safety cabinets (Class I or II) and other primary containment devices (e.g., centrifuge safety cups) are advised whenever procedures are conducted that have a high potential for creating aerosols or infectious droplets. These include centrifuging, blending, sonicating, vigorous mixing, and harvesting infected tissues from animals or embryonated eggs. Fluorescent activated cell sorters generate droplets that could potentially result in infectious aerosols. Translucent plastic shielding between the droplet-collecting area and the equipment operator should be used to reduce the presently uncertain magnitude of this risk. Primary containment devices are also used in handling materials that might contain concentrated infectious agents or organisms in greater quantities than expected in clinical specimens.

7. Laboratory work surfaces should be decontaminated with a disinfectant, such as sodium hypochlorite solution (see A5 above), following any spill of potentially infectious material and at the completion of work activities.

8. All potentially contaminated materials used in laboratory tests should be decontaminated, preferably by autoclaving, before disposal or reprocessing.

9. All personnel should wash their hands following completion of laboratory activities, removal of protective clothing, and before leaving the laboratory.

C. The following additional precautions are advised for studies involving experimental animals inoculated with tissues or other potentially infectious materials from individuals with known or suspected AIDS.

1. Laboratory coats, gowns, or uniforms should be worn by personnel entering rooms housing inoculated animals. Certain nonhuman primates, such as chimpanzees, are prone to throw excreta and to spit at attendants; personnel attending inoculated animals should wear molded surgical masks and goggles or other equipment sufficient to prevent potentially infective droplets from reaching the mucosal surfaces of their mouths, nares, and eyes. In addition, when handled, other animals may disturb excreta in their bedding. Therefore, the above precautions should be taken when handling them.

2. Personnel should wear gloves for all activities involving direct contact with experimental animals and their bedding and cages. Such manipulations should be performed carefully to minimize the creation of aerosols and droplets.

3. Necropsy of experimental animals should be conducted by personnel wearing gowns and gloves. If procedures generating aerosols are performed, masks and goggles should be worn.

4. Extraordinary care must be taken to avoid accidental sticks or cuts with sharp instruments contaminated with body fluids or tissues of experimental animals inoculated with material from AIDS patients.

5. Animal cages should be decontaminated, preferably by autoclaving, before they are cleaned and washed.

6. Only needle-locking syringes or one-piece needle-syringe units should be used to inject potentially infectious fluids into experimental animals.

The above precautions are intended to apply to both clinical and research laboratories. Biological safety cabinets and other safety equipment may not be generally available in clinical laboratories. Assistance should be sought from a microbiology laboratory as needed, to assure containment facilities are adequate to permit laboratory tests to be conducted safely.