ACQUIRED IMMUNODEFICIENCY SYNDROME

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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. Since Pneumocystis carinii pneumonia is almost unheard of in adults without a known underlying condition causing immunosuppression, this cluster of cases caused the CDC to suggest tentatively 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, Pneumocystis carinii pneumonia was diagnosed in ten additional 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. This outbreak of cases caused the CDC to recommend that physicians "be alert for Kaposi's sarcoma with immunosuppression in homosexual men".

The report of these cases signalled the beginning of an epidemic of a disease characterized by profound immunosuppression, opportunistic infections, and/or Kaposi's sarcoma which has come to be known as acquired immunodeficiency 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).

By June of 1982, the CDC had collected 355 cases of AIDS (4). 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 occurred in California, Florida, New Jersey, New York City and Texas. The remainder of the cases occurred in 15 other states. While the disease remained predominantly one of white homosexual males, increased numbers of heterosexual patients, especially those who used intravenous drugs were observed.

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 Haitians who had recently immigrated to the United States (5). Subsequently the disease was reported in female partners of intravenous drug users (6), homophiliacs (7,8), infants of possibly-affected mothers (9) and individuals receiving blood transfusions (10). Although the scope of the epidemic has expanded, more than 95% of all patients

in the United States belong to one of seven identifiable risk groups (Table I). Of all the patients reported to date, only 4.1% have not been shown to be a member of one of these groups (11).

TABLE I

AIDS: GROUPS AT RISK

1. Homosexual or bisexual males
2. Intravenous drug users
3. Haitians
4. Hemophiliacs
5. Recipients of multiple blood transfusions
6. Infants born of parents belonging to high risk groups
7. Heterosexual contacts of members of high risk groups

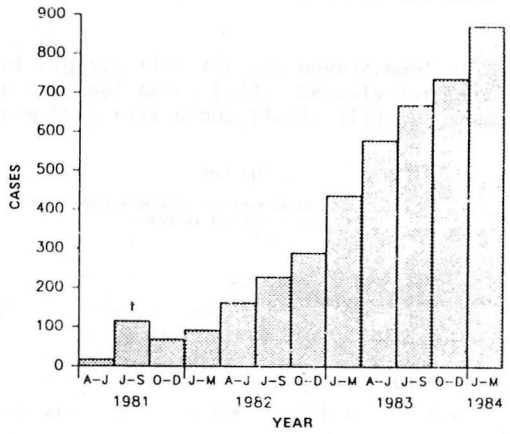
Definition of the Syndrome

Currently there does not exist a reliable, widely-available test for the diagnosis of AIDS. Therefore, a working definition has been developed to identify the syndrome for epidemiologic purposes. Currently, the CDC (12) considers AIDS to exist in a patient when that patient develops "a disease at least moderately predictive of a defect in cell-mediated immunity ...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. The complete definition is included in the Appendix (12,13). The diagnosis must be based on sufficiently reliable methods which should include either biopsy or culture.

It should be emphasized that the current definition of AIDS is an indirect one. Although the primary pathologic process is a profound depression of the cellular immune system, the diagnosis can only be made when a consequence of the underlying immunodeficiency develops. The disease cannot be diagnosed solely on the basis of the immunologic abnormalities before an opportunistic infection or neoplasm develops, as these abnormalities are not specific enough to be of significant predictive value in making the diagnosis.

The current definition is a fairly rigorous one which appears to include only the most severe forms of AIDS. As additional clinical information has been collected, however, the spectrum of potentially AIDS-related conditions has widened to include individuals with an absence of all clinical symptoms despite subtle laboratory evidence of immunodeficiency (14-19), patients with a variety of non-specific symptoms including weight loss, fever, generalized persistent lymphadenopathy, lymphopenia and immunodeficiency (20-23) and finally persons with a syndrome of cellular immunodeficiency and autoimmune thrombocytopenic purpura (24,25): The temporal occurrence of these various abnormalities in the subpopulations of individuals at risk for the development of AIDS has suggested that they might be incomplete manifestations of a similar pathologic process and thus have been referred to as the AIDS-related complex (26).

As of June 18, 1984, 4,918 patients with AIDS had been reported to the CDC (11). More than 70% of all cases have been reported since January of 1983 (Figure 1).



*Because of incomplete data, cases reported during the second quarter of 1984 are not shown.
†Includes backlog of cases identified at beginning of CDC surveillance.

***Figure 1:** Newly reported cases of AIDS per quarter year, 1981 → 1984*

TABLE II

ACQUIRED IMMUNODEFICIENCY SYNDROME
June, 1984
(MMWR 33:337, 1984)

Total cases:	4,918	
Deaths:	2,221	(45%)
Clinical spectrum:		
P. carinii pneumonia -		53%
Kaposi's sarcoma -		24%
PCP + KS -		6%
Other opportunistic disease -		17%
Age:		
20 - 49 years:	90%	
Sex:		
Male:	4585	(93%)
Female:	333	(7%)
Race:		
White:	58%	
Black:	25%	
Hispanic:	14%	
Other:	3%	

Of the 4,918 reported cases, 2,221 (45%) are known to have died (Table II). More than 3/4 of those patients diagnosed before July, 1982 are dead. AIDS remains largely a disease of young males (Table II). Pneumocystis carinii pneumonia continues to be the most frequent clinical manifestation.

The group at highest risk for the development of AIDS continues to be homosexual or bisexual males (11). Seventy-two percent of all patients come from this risk group (Table III). The percentage of

TABLE III

DISTRIBUTION OF AIDS PATIENTS IN THE UNITED STATES
(MMWR 33:337-339, 1984)

Patient Group	Time Period				
	≤2/83 (n = 1,216)	2/83 - 9/83 (n = 1,215)	9/83 - 2/84 (n = 1,215)	2/84 - 6/84 (n = 1,215)	Total (n = 4,861)
	(percentage of total)				
Homosexual/Bisexual	72.3	70.9	72.4	71.9	71.9
IV Drug User	16.4	17.2	18.0	18.4	17.5
Haitian	5.0	4.7	3.2	2.5*	3.8
Hemophiliac	0.9	0.6	0.4	1.2	0.8
Transfusion Recipient	0.4	1.4	1.2	1.3	1.1
Heterosexual Sex Partner	1.1	0.9	0.6	0.5	0.8
Other/Unknown	3.9	4.3	4.2	4.2	4.1

* $p<0.001$

total patients who are homosexual or bisexual males has not changed significantly during the course of the epidemic. This is shown in Table III, in which the total number of AIDS patients was divided into 4 equal parts and tabulated by date of report to the CDC (11). The continued accelerating nature of the AIDS epidemic is apparent. Thus, the first quarter of the cases was reported over a period of years (1978→2/83), whereas the next three quarters were reported in 7, 5 and 4 months, respectively. As the epidemic increased in magnitude, however, the percentage of AIDS patients who were homosexual or bisexual remained constant. In addition, the distribution of cases among the other risk groups has not changed significantly, with the exception of a modest decrease in the percentage of new case reports in Haitians.

The vast majority (78%) of AIDS cases have been reported from New York, California, Florida and New Jersey (Table IV). Since September, 1983, there has been a significant decrease in the percentage of patients from New York, with no change in the percentage of cases from California, Florida and New Jersey, and a concomitant increase in the number from other states. AIDS has now been reported from 45 states, the District of Columbia and Puerto Rico (11). Approximately 70 cases have occurred in Dallas, with most diagnosed in the last 18 months.

TABLE IV

DISTRIBUTION OF AIDS PATIENTS IN THE UNITED STATES
(MMWR 33:337-339, 1984)

Residence at time of Onset	Time Period				
	→2/83 (n = 1,216)	2/83 → 9/83 (n = 1,215)	9/83 → 2/84 (n = 1,215)	2/84 → 6/84 (n = 1,215)	Total (n = 4,861)
	(percentage of total)				
California	20.1	22.7	25.4	21.7	22.5
Florida	6.7	7.9	6.8	6.3	6.9
New Jersey	6.7	5.9	6.7	6.5	6.4
New York	49.5	41.2	37.0*	39.5*	41.8
Other	17.0	20.3	24.1*	26.0*	22.4

* $p<0.001$

Although most of the AIDS cases have occurred in the United States, cases have also been reported from Europe (27), Haiti (28,29) and Central Africa (30). The evidence indicates that AIDS appeared in these populations contemporaneously with its appearance in the United States (27-30). There is no convincing evidence that AIDS existed in Africa or Haiti for a substantial period of time before its appearance in the United States, although sporadic cases may have been seen in Central Africa during the mid-1970's (30). As shown in Tables V→VII, the clinical characteristics of these patients are quite similar to those found in AIDS patients in the United States with a few exceptions. Most importantly, the AIDS patients reported from central Africa were heterosexual men and women with no identifiable risk factors such as homosexuality, blood transfusion or intravenous drug use (30). It should be pointed out, however, that this was a highly selected group

TABLE V

AIDS IN HAITI (6/79 → 10/82)

Number:	61	
First case:	1978	
Median age:	32	
Sex: Male -	52	
Female -	9	
Manifestations:		
Opportunistic infections:	45	
Kaposi's sarcoma:	15	
Both:	1	
Deaths:	54	(89%)
Immunological findings:	Lymphopenia	52 (80%)
	Skin-test anergy	61 (100%)
Risk factors:		
Bisexuality:	24%	
Blood transfusion:	20%	

Pape, JW et al, N. Engl. J. Med. 309:945-950, 1983

TABLE VI

AIDS IN EUROPE THROUGH OCTOBER, 1983
MMWR 32:610-611, 1983

Country	›1979	1980	1981	1982	1983	TOTAL
			(number of cases)			
France	7	5	5	30	47	94
FR Germany	2	-	-	7	33	42
Belgium	-	2	4	8	24	38
UK	-	-	2	5	17	24
Switzerland	-	2	3	5	7	17
Denmark	-	1	2	4	6	13
Netherlands	-	-	-	3	9	12
Austria	-	-	-	-	7	7
Spain	-	-	1	1	4	6
Sweden	-	-	-	1	3	4
Finland	-	-	-	-	2	2
Ireland	-	-	-	-	2	2
Italy	-	-	-	2	-	2
Norway	-	-	-	-	2	2
Czechoslovakia	-	-	-	1	1	2
TOTAL:	9	10	17	67	164	267

of upper socioeconomic status Africans evaluated in Belgium. The patients reported from Haiti came from a variety of socioeconomic classes. There was also a low incidence of identifiable risk factors in this group (28,29). By contrast, the European AIDS patients were similar to those reported in the United States in that most were either homosexual men, patients with hemophilia or those who had had blood transfusion.

TABLE VII

AIDS IN AFRICA (5/79 → 4/83)
(Clumeck N, et al: N Eng J Med 310:492-498, 1984)

Number:	AIDS:	18
	AIDS-related complex:	5
Country of origin:	Zaire -	18
	Chad -	1
	Rwanda -	2
	Burundi-	1
Sex:	Male -	12
	Female -	6
Risk factors:		
	Homosexuality:	0
	Blood product transfusion:	0
	Intravenous drug use:	0
Deaths:		10 (56%)
Presentation:	Opportunistic infection -	15
	Kaposi's sarcoma + opportunistic infection -	3
	P. carinii pneumonia:	5
Immunologic abnormalities:		
	Cutaneous anergy:	20/20
	↓ T4 cells:	20/20
	↓ in vitro blastogenic response:	15/15

Risk Groups

1. Homosexual and bisexual males: The vast majority of AIDS cases continues to be reported in young homosexual and bisexual males. Early studies suggested that a number of risk factors may have played a role in the development of AIDS in this group. These included the use of recreational drugs (31), exposure to sexually-transmitted diseases (31), and the high inidence of cytomegalovirus infection (32-35) and hepatitis B (31).

To identify risk factors for the occurrence of AIDS in homosexual men, the CDC conducted a case-control study in New York City, San Francisco, Los Angeles and Atlanta (36,37). Fifty patients with AIDS and 120 matched homosexual male controls from sexually transmitted disease clinics and private medical practices were studied. As seen in Table VIII, the variable most strongly associated with AIDS was a larger number of male sex partners per year (36). In addition, AIDS patients were more likely to have met sex partners in bath houses, to have been exposed to feces during sex, and to have had syphilis and non-B hepatitis. The other variables were not significantly different

TABLE VIII

FREQUENCY OF SELECTED VARIABLES AMONG 50 HOMOSEXUAL PATIENTS WITH KAPOSI'S SARCOMA AND PNEUMOCYSTIS CARINII PNEUMONIA AND 120 HOMOSEXUAL CONTROLS
(Jaffe, et al: Ann Int Med 99:144, 1983)

Variable	Patients (n = 50)	Controls	
		Clinic (n = 78)	Private (n = 42)
Previous illnesses, %			
Gonorrhea	86	73	74
Syphilis	68*	36	36
Mononucleosis	14	17	7
Hepatitis B	14	14	21
Non-B hepatitis	48*	30	33
Parasitic diarrhea	32	15	48
Use of illicit substances			
Nitrite inhalants, %	96	96	95
Sexual activity			
Median male sex partners per year, n	61*	27	25
Median proportion of sex partners from bathhouses in past year, %	50*	23	4
Median age at initiating regular sex with men, yrs	19	20	22
Mean feces exposure score	2.3*	1.9	1.9

* $p<0.05$

in patients and controls. The results indicated that the variables most strongly associated with AIDS were those related to the number of male sex partners.

When compared to controls, as shown in Table IX patients were also found to have a high titer of antibody to Epstein-Barr virus and a higher prevalence of antibody to hepatitis A and Treponemia pallidum (37). Cytomegalovirus complement fixation titers (but not indirect homagglutination titers) were also higher in AIDS patients than controls but only when venereal disease clinic controls or all controls combined were compared. Moreover, culture of AIDS patients' urine and throat swab specimens were positive for cytomegalovirus more frequently than all controls combined (25% vs 7%). Thus, certain features shared by a subpopulation of the male homosexual population are associated with an increased risk of developing AIDS. These included a larger number of male sex partners per year and higher titers of antibody to Epstein-Barr virus and cytomegalovirus, a higher prevalence of antibody to hepatitis A virus and Treponema pallidum and a higher frequency of isolation of cytomegalovirus. These latter abnormalities were felt to reflect the life style of the patients at risk with the number of sex partners per year being the most important discriminator between patients and controls.

TABLE IX
MICROBIAL ANTIBODY PREVALENCE RATES AND MEAN TITERS
IN AIDS PATIENTS AND CONTROL SERUM SAMPLES
(Rogers et al: Ann Int Med 99:151, 1983)

Agent	Cases	Controls		
		Friend	Venereal Disease Clinic	Private Practice
Cytomegalovirus				
Complement fixation ≥ 8				
Prevalence	50/50	19/19	59/61	36/37
Mean titer	66	53	52*	45
Indirect hemagglutination ≥ 8				
Prevalence	50/50	19/19	59/61	36/37
Mean titer	3327	3795	1105	1046
Epstein-Barr virus				
Viral capsid antigen-IgG ≥ 10				
Prevalence	49/49	19/19	60/60	37/37
Viral capsid antigen-IgG ≥ 800				
Prevalence	11/49	1/19	3/60	2/37*
Mean titer	410	223*	186*	193*
Hepatitis A prevalence				
IgG	42/49	12/19	34/61*	20/37*
Syphilis				
Microhemagglutination ≥ 1+	35/50	6/19*	25/61*	11/37*

* $p<0.05$

No differences between patients and controls in antibody prevalence or titer to Herpes simplex virus, Varicella zoster virus, respiratory syncytial virus, adenovirus, Chlamydia, Hepatitis B, Toxoplasma gondii, Entamoeba histolytica, Aspergillus, Candida albicans.

Additional epidemiologic evidence has supported the contention that AIDS can be transmitted by sexual contact. Detailed sexual histories were obtained of thirteen homosexual males who developed Kaposi's sarcoma and/or Pneumocystis carinii pneumonia in Los Angeles and Orange County, California between June 1, 1981 and April 12, 1982, the "Los Angeles cluster" (38). 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 at least 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. These epidemiologic findings support the conclusion that AIDS is caused by an infectious agent or agents that can be sexually transmitted among homosexually-active males. The observations, however, do not rule out the alternative hypothesis that these patients have not infected each other directly, but rather have been exposed to a common environmental agent, as a result of their sharing of a particular style of life.

In the Los Angeles cluster, 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. These data would suggest the conclusion that if AIDS is caused by a sexually-transmitted infectious agent, there is quite a long incubation period from the time the AIDS agent is encountered to the onset of illness.

The overall incidence and prevalence of AIDS in homosexual and bisexual men is not known. In San Francisco, 6,500 homosexually-active men have been followed since 1978 for other purposes. The overall prevalence of AIDS in this group is 1% and, for the subset of 30-40 year old men is nearly 2% (26). The yearly incidence of AIDS in this group is about 0.5%. The incidence of AIDS-related complex may be as much as 5-10%. It is not known whether these prevalence and incidence rates are reflective of those anticipated among homosexual males in other geographic locations.

2. Intravenous drug users: AIDS has been reported in more than 850 users of intravenous drugs, many of whom are heterosexual males (11). Of note, as shown in Table X, is the finding that nearly 90% of these patients have been reported from the New York/New Jersey area (13). The explanation of this finding is unclear.

TABLE X

REPORTED CASES OF AIDS IN INTRAVENOUS DRUG ABUSERS WITHOUT A HISTORY OF MALE HOMOSEXUALITY
(Selik et al: Am J Med 76:493, 1984)

State of Residence	Year of Diagnosis						
	1978	1979	1980	1981	1982	1983	Total
	Number (percentage of total)						
New York	0	0	5 (83.3)	18 (69.2)	98 (71.5)	35 (72.9)	156 (71.9)
New Jersey	0	0	0 (0.0)	4 (15.4)	25 (18.2)	6 (12.5)	35 (16.1)
California	0	0	1 (16.7)	1 (3.8)	4 (2.9)	2 (4.2)	8 (4.7)
Florida	0	0	0 (0.0)	0 (0.0)	3 (2.2)	0 (0.0)	3 (1.4)
Other states	0	0	0 (0.0)	3 (11.5)	7 (5.1)	24 (10.4)	15 (6.9)
Total	0	0	6 (100.0)	26 (100.0)	137 (100.0)	48 (100.0)	217 (100.0)
Number of states	0	0	2	6	9	6	11

3. Haitians: AIDS has been reported in more than 185 Haitians living in the United States (5,13,39,40). Although cases have been reported from nine states, the majority have been residents of Miami, New York City, or Newark. Less than 10% have been women while more than 85% have been heterosexual men (13). Less than 2% of Haitian AIDS patients have admitted to intravenous drug use. Of note is the recent finding that no immunologic abnormalities have been found in asymptomatic Haitians living in New York City (41).

4. Females: There have been 333 cases of AIDS in females. Most of these persons have had known risk factors such as intravenous drug use, blood transfusion, Haitian origin or sexual contact with a person of a known risk group.

5. Hemophilia: AIDS has been reported in 21 patients with hemophilia in the United States and at least 7 in other countries (7,8,42-46). As noted in Table XI, it can be associated with a very

TABLE XI

AIDS IN HEMOPHILIACS, JANUARY, 1982 → NOVEMBER, 1983
(MMWR 32:613, 1983)

Total number:	21
(other countries:	7)
Other risk factors:	Homosexual - 1; IV drugs - 1
Age:	9 → 74
Race:	White - 20; Black - 2
Year diagnosed:	1981 - 1
	1982 - 8
	1983 - 12
Interval between onset of symptoms and diagnosis:	1 → 12 months (median, 3 months)
Clinical manifestations:	
1. P. carinii pneumonia:	20 (95%)
Multiple infections:	8
Kaposi's sarcoma:	0
2. Prodrome:	
a) length:	weeks to months
b) symptoms:	malaise, weight loss, fever, lymphadenopathy
Deaths:	14 (64%)
Survival from date of diagnosis:	Days → 11 months (median ~ 2 months)

rapid course in these patients leading to death from opportunistic infection in 2/3 of cases within days to 1 year of diagnosis. Lyophilized Factor VIII concentrate which is prepared from pools of serum from 2000 → 20,000 donors appears to be implicated in the transmission of the disease to hemophiliacs (7,8), although many of the patients (9/21) have also received other blood products within the five years

preceding their diagnosis (45). Whereas the number of reported cases of AIDS in hemophiliacs is low, it represents an attack rate of 1 per 800 in the 17,000 patients with hemophilia in the United States (46).

6. Pediatric AIDS: AIDS has been reported to occur in 57 patients under the age of 5 (9,11). It may be difficult to distinguish AIDS from congenital immune deficiency states, starvation or the manifestations of various neonatal infections such as cytomegalovirus. The CDC has promulgated a provisional case definition (47) which takes these distractors into account (see Appendix). Of the 57 patients, 79% were residents of New York, Florida, California or New Jersey at the time of disease onset. Ninety percent of the children came from families in which one or both parents were members of known risk groups (Table XII). Risk factor information on the other children is incomplete.

TABLE XII

PEDIATRIC AIDS (→ 6/84)
(MMWR 33:337, 1984)

Number:	57	
Age:	< 5	
Residence:	New York, Florida, California, New Jersey:	45 (79%)
Sex:	Male	31 (54%)
	Female	26 (46%)
Onset:	P. carinii pneumonia	44 (77%)
	Kaposi's sarcoma:	1 (2%)
	PCP + KS:	2 (4%)
	Other infections:	10 (18%)
Deaths:	39 (68%)	
Race:	White	17 (29%)
	Black	28 (49%)
	Hispanic	12 (21%)
Family:	IV drug use:	23 (40%)
	Haitian ancestry:	13 (23%)
	Transfusion:	12 (21%)
	AIDS:	3 (6%)

7. Recipients of blood transfusions: AIDS has been reported in 52 adults with no other risk factors for AIDS but who were transfused with blood or blood components within 5 years of illness onset (11). Of these, 27 (52%) are known to have died. Analysis of 18 cases of "transfusion-associated AIDS" indicated that they had received blood 12-43 months before the onset of illness and 15-57 months before the diagnosis of AIDS (48). Many of these patients had received multiple transfusions. Thus, patients with transfusion-associated AIDS received blood from a mean of 15.9 donors (range 2→48), nearly 5 times the

national average (49). Detailed investigation of seven cases identified at least one potential high risk donor in each case (Table XIII). Six

TABLE XIII

TRANSFUSION HISTORIES OF 18 ADULTS WITH P. CARINII PNEUMONIA AND TRANSFUSION-ASSOCIATED AIDS
(Curran et al: N Engl J Med 310:69, 1984)

Case No	Age/Sex; Ethnic Group	Reasons for Transfusion	No. of Units	Months From Transfusion To Onset Of Illness	High-Risk Donors: All Donors	High-Risk Donors: Belonging to Group at High Risk for AIDS	High-Risk Donors: Having T_H/T_S Ratio <1.00
1	52/M; white	Laparotomy	4	15	-	-	-
2	64/M; Hispanic	Coronary bypass	20	15	14	1	1
3	56/F; white	Mastectomy Hysterectomy	3	14-43	3	0	1
4	19/M; white	Trauma	2	34	2	1	1
5	49/F; white	Thrombocytopenia	6	27	6	1	1
6	45/F; white	Cardiac surgery	28	10-38	24	1	1
7	53/M; white	Coronary bypass	16	26	-	-	-
8	52/F; white	Mastectomy	4	24	-	-	-
9	33/F; Asian	Cardiac surgery	34	17	34	1	1
10	62/M; white	Vascular surgery	31	12	-	-	-
11	61/M; white	Coronary bypass	23	26	-	-	-
12	55/F; white	Coronary bypass	4	33	-	-	-
13	66/M; white	Coronary bypass	6	17	6	1	1
14	60/M; white	Bleeding ulcers	12	24-26	-	-	-
15	67/F; white	Intestinal polyps Cardiac surgery	20	18-34	-	-	-
16	44/M; white	Trauma	48	11-12	-	-	-
17	40/M; white	Coronary bypass	22	37	-	-	-
18	60/F; white	Hysterectomy	4	39	-	-	-

donors were members of high risk groups including an asymptomatic intravenous drug user (case 2), homosexual males with multiple sex partners, lymphadenopathy and abnormal T4/T8 ratios (cases, 4, 5, 6) and homosexual males with multiple sex partners and abnormal T4/T8 ratios (cases 9, 13). In addition, one of the donors to case 3 had a persistently decreased T4/T8 ratio, lymphadenopathy and a history of syphilis and hepatitis B but denied risk factors for AIDS. These findings strengthen the conclusions that AIDS is caused by an infectious agent that can be transmitted by blood. Moreover, these results suggest that the incubation period from the time of exposure to the putative infectious agent to the development of symptoms may be anywhere from 1 to 4 years and up to 5 years for the development of the complete syndrome. It should be emphasized that the risk of contracting AIDS by blood transfusion is extremely small since more than 3 million persons in the United States received transfusions during the period of time when these cases were diagnosed (49).

8. No known risk factors: Nearly 200 persons with AIDS fall into no known risk group (Table III). Forty percent of such cases have been reported from New York (13). In some of these patients, there is inadequate information but others appear not to have any risk factors. It remains possible that such patients belong to an as yet unidentified risk group or alternatively do not have AIDS even though they fit the CDC case definition.

The Clinical Spectrum of Acquired Immunodeficiency Syndrome

1. Kaposi's sarcoma and/or opportunistic infections: Currently the CDC definition of AIDS requires the demonstration of 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 infectious or neoplastic process. Such diseases include Kaposi's sarcoma, Pneumocystis carinii pneumonia, and other 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 is a profound defect in cell-mediated immunity. While treatment of the opportunistic infection may prolong life (50-52), there is no indication that the underlying immune defect is reversible. As shown in Tables II and XIV, the overall case mortality rate has remained constant at about 45% (11,12). In addition, the two year survival rate also appears to have remained constant at approximately 25% (Table XIV, XV).

TABLE XIV

ACQUIRED IMMUNODEFICIENCY SYNDROME:
CASE MORTALITY RATES BY YEAR OF DIAGNOSIS,
SEPTEMBER, 1982
(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

TABLE XV

AIDS: CASE MORTALITY RATE OF CASES
DIAGNOSED BEFORE JULY, 1982

Total cases (→July, 1982)	Deaths by 9/82	Deaths by 6/84
	number (percentage)	
506	233 (46%)	385 (76%)

Patients may present with opportunistic infections (53%), Kaposi's sarcoma (24%), or both (6%). In addition, 17% will present with other opportunistic infections (11). Both groups of patients often present with a prolonged prodrome of fever, weight loss and lymphadenopathy. A considerable delay frequently occurs between the initial onset of symptoms and diagnosis in both the Kaposi's sarcoma and P. carinii pneumonia groups (53). For the Kaposi's sarcoma group, the time from the onset of symptoms to diagnosis ranges from one to thirty months (median, 5.5 months); for P. carinii pneumonia, the range is one to eighteen months (median, 3.5 months).

In one study, the most striking early clinical feature in patients who subsequently presented with opportunistic infections was progressive weight loss (54). This is usually out of proportion to reduction in food intake or steatorrhea and may exceed 10 kg during the weeks or months prior to diagnosis. The etiology of this wasting syndrome is not known.

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 (53). In addition, as shown in Table XVI, the case mortality rate for those with

TABLE XVI

ACQUIRED IMMUNODEFICIENCY SYNDROME: REPORTED CASES AND CASE MORTALITY RATES BY DISEASE CATEGORY (JUNE 1981 - MAY 1983) (Gottlieb et al, Ann. Int. Med. 99:208-220, 1983)

Disease Category	Cases	Deaths	Case Mortality Rate
	n (%)	n	(%)
Kaposi's sarcoma without Pneumocystis	383 (26.4)	82	21.4
Pneumocystis without Kaposi's sarcoma	740 (51.0)	324	43.8
Both Kaposi's sarcoma and Pneumocystis	114 (7.9)	62	54.4
Other opportunistic infection	213 (14.7)	90	42.3
Total	1450	558	38.5

Kaposi's sarcoma alone appears to be much less than for those in the P. carinii pneumonia group (54). 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).

A host of life-threatening opportunistic infections is seen in AIDS patients as listed in Table XVII. Treatment of some of these

TABLE XVII

INFECTIOUS COMPLICATIONS OF ACQUIRED IMMUNODEFICIENCY SYNDROME

- Viral
  - Cytomegalovirus
    - Disseminated (59-63)
    - Pneumonia (61)
    - Retinitis (64-67)
    - Encephalitis (68)
  - Herpes simplex
    - Progressive (62)
  - Herpes zoster
    - Limited cutaneous (54)
  - Progressive multifocal leukoencephalopathy (69)
- Fungal
  - Candida albicans
    - Oral thrush (61)
    - Esophagitis (61)
    - Disseminated (63)
  - Cryptococcus neoformans
    - Meningitis (53)
    - Disseminated (54)
  - Histoplasma capsulatum
    - Disseminated (54)
  - Petriellidium boydii
    - Pneumonia (54)
  - Aspergillus
    - Pulmonary (70)
  - Coccidioidomycosis (71)
- Protozoal
  - Pneumocystis carinii
    - Pneumonia (50,61,72,73)
    - Retinal infection (74,75)
  - Toxoplasma gondii
    - Encephalitis (76-80)
  - Cryptosporidium
    - Bronchitis (85)
    - Enteritis (81-86)
  - Isospora belli
    - Enteritis (54)
- Mycobacterial
  - Mycobacterium avium-intracellulare
    - Disseminated (87-89))
  - Mycobacterium tuberculosis
    - Disseminated (90)
- Others
  - Nocardia (91)
  - Legionella (54)

infectious processes is successful and can prolong life (50-52) but no effective therapy exists for many other of these opportunistic infections. Moreover, there appears to be an increased incidence of toxic side effects to some anti-microbial agents in AIDS patients, such as the increased incidence of adverse reactions to trimethoprim-sulfamethoxazole (55,56) or pentamidine (57). In the absence of an effective way to restore immune competence (58), AIDS patients develop repeated bouts of opportunistic infection, with death from infection and/or inanition within 2 years. At death, evidence of disseminated cytomegalovirus infection is found in most patients (59), often associated with adrenal necrosis (59,60).

Kaposi's sarcoma was the initial malignant neoplasm found in association with acquired immunodeficiency syndrome (2). Initial evidence, as shown in Table XVIII, suggested that the incidence of Kaposi's sarcoma was much higher in homosexual or bisexual men than in other risk groups (92). More recent evidence indicates that 93% (1,396 cases) of all cases of AIDS-related Kaposi's sarcoma have occurred in homosexual or bisexual men (11). Although Kaposi's sarcoma has been reported to occur in AIDS patients in Haiti (28), it is uncommon in Haitians in the United States (5,13,39,40), African AIDS patients (30), hemophiliacs (45), and infants (11).

TABLE XVIII

INCIDENCE OF KAPOSI'S SARCOMA IN AIDS RISK GROUPS (- DEC. 15, 1983)
(De Jarlais et al: N Engl J Med 310:1119, 1984)

Group	Total AIDS Cases	KS in Initial Diagnosis
		(percentage)
Homosexual/bisexual males without IV drug use	728	46.0
Homosexual/bisexual males with IV drug use	97	27.8
Females with IV drug use	72	12.5
Heterosexual males with IV drug use	213	3.8

The nature of the Kaposi's sarcoma found in individuals with AIDS is somewhat unusual. The non-epidemic form of Kaposi's sarcoma is a rare disease predominantly seen in elderly Jewish and Italian men. It usually presents as blue or brown nodules or plaques confined to the skin especially of the lower extremities and follows an indolent course. By contrast, the epidemic form of Kaposi's sarcoma is a much more rapidly progressive and aggressive disease. While the non-epidemic form has only a 10% incidence of extracutaneous organ involvement, the epidemic form has about a 72% incidence of organ involvement (58). Lymph nodes (81%) and the gastrointestinal tract (81%) are most often involved. The lung is involved in 11% of cases. About 5% of cases have extracutaneous disease in the absence of skin involvement.

Regardless of clinical presentation, the histopathology of Kaposi's sarcoma consists of vascular proliferation and spindle-shaped neoplastic cells in a network of reticulin fibers. These cells appear to be of endothelial origin since they synthesize factor VIII antigen and proliferate in vitro in response to endothelial cell growth factor (58). The generalized distribution of skin lesions, presence of lesions on the head and neck, absence of predominantly lower extremity involvement, generalized lymphadenopathy, visceral involvement and rapid clinical course closely resembles the lymphadenopathic form of Kaposi's sarcoma found in young adults in equatorial Africa (93-96). A similar form of Kaposi's sarcoma has been reported to develop in renal transplant patients and other individuals receiving immunosuppressive therapy (97-104). In these cases, the lesions of Kaposi's sarcoma often regress when immunosuppressive therapy is discontinued.

Two features of the homosexual male population may contribute to the development of Kaposi's sarcoma in this population at risk for AIDS. These include a possible genetic predisposition and the high incidence of infection with cytomegalovirus as noted above.

Evidence from New York City (94) 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 XIX). It should be pointed out, however, that one study (22) also found a higher incidence of HLA-DR 5 in homosexual

TABLE XIX

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

men with generalized lymphadenopathy compared to controls (40.3% (+) vs 20% (+), $p<0.005$). No association with any histocompatibility gene product has been observed for any of the other manifestations of AIDS or the AIDS-related complex.

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 (105). Moreover, Herpes virus-like particles have been observed in cell lines derived from Kaposi's sarcoma tumors (106). Finally, studies utilizing DNA-DNA association kinetics have suggested the presence of CMV DNA and early antigens in Kaposi's sarcoma cells (107). These results have suggested the possibility that CMV might be oncogenic (108) and in the setting of immunosuppression, such virally transformed endothelial cells might not be effectively eliminated (54). This has suggested a "two-hit" theory of AIDS related Kaposi's sarcoma in which an unknown transmissible agent is thought to induce profound immunosuppression that permits the development of CMV-induced Kaposi's sarcoma in genetically-susceptible chronic carriers of cytomegalovirus.

A number of other malignant neoplasms have also been reported to develop in patients with AIDS. These include malignant lymphomas of several histologic types including non-Hodgkins lymphoma (109), Burkitt's lymphoma (110-112), immunoblastic lymphoma (111,113), lymphoblastic lymphoma (114), Hodgkin's disease (58) and plasmacytoid lymphocytic lymphoma (111), and plasmacytoma (115). These lymphomas are of various origins but lymphomas of B lymphocyte lineage appear to predominate. In addition, the incidence of two other malignancies is increased in one of the groups at high risk of developing AIDS namely, male homosexuals. These are squamous cell carcinoma of the tongue and cloacogenic carcinoma of the rectum. The occurrence of these two malignancies in young homosexual men was recognized in the early 1970s before the appearance of AIDS in the same group. Therefore, it is felt that tongue and rectal cancers are not related to AIDS but coincidentally occur in a common risk group, male homosexuals (58).

Because of the underlying immunodeficiency, therapy of Kaposi's sarcoma in AIDS has not been as successful as therapy of non-epidemic Kaposi's sarcoma, where mean survivals of 13 years are observed. Although AIDS-related Kaposi's sarcoma has responded to chemotherapy (116,117), the danger of exacerbating the underlying immunodeficiency has prompted trials of recombinant alpha (leukocyte) interferon therapy. Nearly 80 patients have received some type of interferon (Table XX). Less than 10% of patients have had complete responses and another 25% have had short duration partial responses. The causes of death in most patients are overwhelming opportunistic infections and irreversible cachexia and wasting. Tumor-related deaths comprise only about 25% of the total (58).

TABLE XX

TREATMENT OF EPIDEMIC KAPOSI'S SARCOMA WITH INTERFERON

Regimen	Treated Patients	Complete Response	Partial Response	Reference
		n (%)		
Recombinant leukocyte A interferon				
36-54 x 10^6U every day x 28 d	31	6 (19)	9 (29)	118
Recombinant alpha 2 interferon				
1 x 10^6U/m^2 every day x 5 d, every other week	9	0	1 (11)	119
50 x 10^6U/m^2 every day x 5 d, every other week	9	0	4 (44)	
Recombinant alpha 2 interferon				
1 x 10^6U/m^2 every day x 5 d, every other week	10	1 (10)	1 (10)	120
50 x 10^6U/m^2 every day x 5 d, every other week	10	0	4 (40)	
(low dose → high dose	4	1	1)	
Human lymphoblastoid interferon				
7.5 x 10^6U/m^2 every day x 28 d	10	0	2 (20)	58
TOTAL:	79	7 (9)	20 (25)	

2. Idiopathic Thrombocytopenic Purpura: Thirteen homosexual males have been reported who developed idiopathic thrombocytopenic purpura (24). Although these patients had no evidence of opportunistic infection, they did have immunological deficits characteristic of acquired immunodeficiency syndrome. Each of these patients responded to corticosteroid therapy and three patients had splenectomy with excellent responses. Five patients with hemophilia who had received repeated transfusions with lyophilized factor VIII concentrate also have been reported to develop idiopathic thrombocytopenic purpura (25). Immunologic evaluation of these patients also suggested abnormalities characteristic of AIDS, 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. Generalized lymphadenopathy has been reported in patients who are members of risk groups for AIDS (20). Since the diffuse lymphadenopathy syndrome was first noted at the time AIDS appeared and most of the affected patients were members of risk groups for AIDS, a relationship between these two clinical entities was suspected. This possible relationship has been intensely studied. The CDC has followed 57 homosexual men with diffuse lymphadenopathy (20). 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 immunologic abnormalities characteristic of patients with AIDS. Between October, 1981 and May, 1982, one of the 57 patients with lymphadenopathy developed Kaposi's sarcoma. None developed significant opportunistic infections. Causes for the persistent lymphadenopathy in these patients could not be identified.

Two additional prospective studies have followed the courses of homosexual men with generalized lymphadenopathy. Ninety such patients were followed in New York City for 8 → 19 (median: 14) months (22). During that time, 15 patients (17%) progressed, with 11 developing opportunistic infections and 7 malignant lymphomas. Regression of lymphadenopathy occurred in 4 patients but 3 of these subsequently developed opportunistic infections. Another prospective study evaluated 70 homosexual men in San Francisco with persistent diffuse lymphadenopathy (23). Most of these patients had constitutional symptoms and recurrent non-life-threatening infections. None of these patients progressed and developed AIDS. Thus, the relationship of the syndrome of persistent lymphadenopathy to AIDS remains unclear, especially in view of the relatively low incidence of progression of this syndrome into the complete syndrome of acquired immunodeficiency. However, a number of features suggest that it might be part of the spectrum of AIDS. Epidemiological characteristics including age, racial composition and city of residence of the homosexual patients with lymphadenopathy are similar to homosexual patients with AIDS 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 lympha-

denopathy before diagnosis, suggesting the possibility of a relationship between the syndrome of persistent lymphadenopathy and AIDS (20). Diffuse persistent lymphadenopathy has also been reported in members of other risk groups including hemophiliacs treated with factor VIII concentrate (21) and female sexual contacts of members of risk groups (6).

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 (14-18). At this time, however, there is no convincing evidence that these individuals are at increased risk to develop full-blown AIDS.

The capacity to identify the individuals with the AIDS-related complex who are at risk to progress to the complete syndrome would be of great prognistic value. One study found that the development of unexplained oral candidiasis in high-risk patients might be useful in predicting the subsequent development of AIDS in more than 50% of cases (121). A group of 22 intravenous drug users or homosexual men who developed oral candidiasis were compared to twenty similar individuals without candidiasis (Table XXI). Most of the members of each group had lymphadenopathy, non-specific symptoms and abnormal T4/T8 ratios. Of the patients with oral candidiasis, 59% (13/22) acquired a major opportunistic infection or Kaposi's sarcoma after a median of 3 months (1→23

TABLE XXI

CLINICAL AND IMMUNOLOGIC CHARACTERISTICS OF PATIENTS WITH AIDS-RELATED COMPLEX
(Klein et al, N Eng J Med 311:354, 1984)

Characteristic	PATIENT GROUP: AIDS-Related Complex, with Candidiasis	PATIENT GROUP: AIDS-Related Complex, without Candidiasis	PATIENT GROUP: AIDS
	Number of patients (%)		
Total No. of Patients	22	20	20
1. Characteristics			
Male/female	18/4	18/2	16/4
Age in years (mean ± S.D.)	30.0±5.2	31.4±6.3	36.5±7.7
Homosexual or bisexual male	9 (41)	7 (35)	2 (10)
Intravenous drug abuse	16 (73)	16 (80)	14 (70)
2. Clinical features			
Oral candidiasis	22 (100)	0 (0)	18 (90)
Generalized lymphadenopathy	20 (91)	20 (100)	9 (45)
Weight loss ≥ 4.5 kg	9 (41)	5 (25)	15 (75)
Fever	15 (68)	7 (35)	18 (90)
Diarrhea	6 (27)	1 (5)	4 (20)
3. Immunologic features			
Cutaneous anergy	19 (100)	8 (47)	19 (100)
Lowest lymphocyte count <1500/mm³	13 (62)	11 (61)	20 (100)
T4/T8 (range; normal: 1.4-3.6)	0.05-0.80	0.00-0.98	0.00-0.71
4. Outcome			
Follow-up, months (mean,range)	3 (1-23)	12 (5-21)	-
AIDS	13 (59)	0 (0)	-

months) as compared with none of the twenty patients without candidiasis who were followed for a median of 12 months (5→21 months). AIDS developed in 12 of 15 patients with candidiasis and T4/T8 ratios less than or equal to 0.5 (normal:1.4→3.6) as compared with none of four with ratios greater than 0.6. These results suggest that oral candidiasis in persons who are members of high risk groups might be predictive of the development of AIDS.

Methods of Transmission

As the AIDS epidemic has evolved, it has become apparent that horizontal transmission of this disease can occur but that such transmission requires intimate sexual contact or blood product exposure (Table XXII). It has also become apparent, however, that the source of the transmissible agent need not have had clinically apparent AIDS (9,38,48), since for example, cases of transfusion-associated AIDS have occurred when no risk factors could be identified in the donors (123).

TABLE XXII

AIDS: METHODS OF TRANSMISSION

1. Intimate sexual contact
2. Sharing contaminated needles
3. Transfusion of blood or blood products
4. No evidence for transmission by:
    a. casual contact with AIDS patients or with persons in at-risk groups
    b. food
    c. water
    d. air
    e. environmental surfaces
    f. hepatitis B virus vaccine (122)

As of July, 1983, only 4 cases of AIDS had been reported in health-care personnel not known to belong to groups at increased risk for AIDS (124). The source of AIDS in these four patients is unclear since none had documented contact with an AIDS patient. It seems that the risk of the transmission of AIDS to health care personnel is minimal as no convincing case of transmission of AIDS within hospitals has been reported. Current recommendations for prevention of the transmission of AIDS (125-128) are included in the Appendix.

Immunologic Abnormalities in AIDS

AIDS is characterized by a profound deficit in the cellular immune system. This has been found to be a uniform characteristic of 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 AIDS 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. The predominant abnormality appears to be a deficiency of T lymphocytes, although abnormalities of natural killer cells, B cells and antigen presenting cells have also been demonstrated.

As can be seen in Table XXIII, patients with AIDS manifest a significant degree of lymphopenia which can be accounted for almost entirely by a marked decrease in the absolute number of the OKT4, Leu 3 subpopulation of T lymphocytes (36). It is thought that many of the in vivo manifestations of immunodeficiency including skin test anergy, opportunistic infections and increased susceptibility to the development of malignant neoplasms can be explained by these abnormalities. In addition, blastogenic responses to a variety of antigenic and mitogenic stimuli may be explained by the marked decrease in the number of OKT4, Leu 3 T cells.

TABLE XXIII

LABORATORY FINDINGS IN AIDS PATIENTS
AND MATCHED CONTROLS
(Jaffe et al: Ann Int Med 99:144, 1983)

	Normal Values	Cases+	Combined Controls
Absolute counts			
Total Lymphocytes, /mm³	1863 ± 388	1417 ± 339*	2210 ± 159
B Lymphocytes, /mm³	297 ± 113	376 ± 111	274 ± 32
T Lymphocytes, /mm³	1298 ± 322	889 ± 226*	1543 ± 129
T4 cells, /mm³	850 ± 238	333 ± 96*	928 ± 86
T8 cells, /mm³	396 ± 126	488 ± 128	619 ± 63
Mitogen response			
Pokeweed mitogen	87 ± 39	55 ± 12*	98 ± 6
Concanavalin A	106 ± 54	52 ± 18*	175 ± 16
Phytohemagglutinin	120 ± 27	56 ± 19*	127 ± 11
Immunoglobulins			
IgG, mg/dL	1047 ± 300	1865 ± 117*	1296 ± 35
IgA, mg/dL	177 ± 75	376 ± 35*	213 ± 8
IgM, mg/dl	126 ± 51	166 ± 13	182 ± 7

\+ Data for lymphocyte counts and mitogen responsiveness are derived from 18 cases and 29 controls while Ig levels are the means from 50 cases and 116 controls.

* Significantly different from controls, $p<0.05$, Student's t-test

AIDS patients exhibit increased levels of IgG and IgA, and circulating immune complexes (14,61,62,72,129). The number of circulating B cells is usually normal (Table XXIII) as is the secondary antibody response to environmental antigens. However, primary antibody responses to challenge with new exogenous antigens may be abnormal (130).

In addition to these abnormalities, a variety of other defects in immune responsiveness have been demonstrated in patients with AIDS, as shown in Table XXIV. It remains unclear whether these represent primary abnormalities or changes that are secondary to chronic infection, inanition or drug therapy.

TABLE XXIV

IMMUNOLOGIC ABNORMALITIES IN PATIENTS WITH AIDS

1. Altered T cell function
   - a. Decreased blast transformation
   - b. Decreased alloreactivity
   - c. Decreased cytotoxic T cell function (131)
   - d. Decreased production of γ-interferon (132,133)
   - e. Decreased helper function for antibody formation (130)
   - f. Production of soluble suppressor factor that inhibits T cell dependent responses (134,135)
2. Altered natural killer function
   - responsive to interleukin 2 but not interferon (131)
3. Altered B lymphocyte function (130)
   - a. Increased number of circulating spontaneous antibody secreting cells
   - b. Decreased stimulation in vitro
4. Antigen presenting cells
   - a. Decreased Ia expression on epidermal Langerhans cells (136)
5. Miscellaneous serologic abnormalities
   - a. Presence of acid-labile α-interferon (137-139)
   - b. Elevated levels of α-1 thymosin (140,141)
   - c. Depressed levels of serum thymic factor (thymulin) (142)
   - d. Serum factors that suppress in vitro responses of normal lymphocytes (143)

Patients suspected of having AIDS are commonly evaluated by measuring the number of circulating T cells bearing determinants identified by the monoclonal antibodies OKT4 (Leu 3) and OKT8 (Leu 2). These monoclonal antibodies have been shown to recognize non-overlapping sub-populations of human T lymphocytes (144). These antibodies 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 although these antibodies identify phenotypically distinct subpopulations of T cells, cells within each subpopulation may have a variety of different additional functions. Thus, for example, the T4+ population contains cytotoxic lymphocytes which specifically identify Class II histocompatibility antigens (145) as well as a suppressor population of T cells (146), while the T8 population contains some helper cells (147) as well as a subset of the natural killer cell population (148). Nonetheless, these monoclonal antibodies have been widely used to evaluate T lymphocyte subpopulations in a variety of clinical conditions.

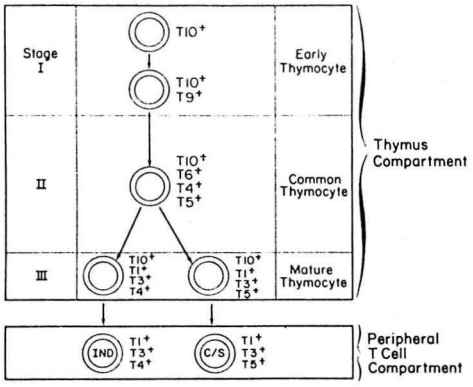


Figure 2: Stages of T-Cell Differentiation in Man. Three discrete stages of thymic differentiation can be defined on the basis of reactivity with monoclonal antibodies. The most mature thymocyte population (Stage III) gives rise to the peripheral T-cell helper/inducer and cytotoxic/ suppressor subsets. The cell-surface antigens expressed during T-cell ontogeny are shown. The T5+ population is equivalent to the OKT8+ Leu 2 population. Reprinted from Reinherz and Schlossman, N. Engl. J. Med. 303:370, 1980.

It has become clear that the most typical abnormality in the AIDS patients is a decrease in the number of T4(+) cells (149). More recent evidence suggests that only a subpopulation of T4 cells is decreased in AIDS (150). Thus, using additional monoclonal antibodies it was found that only the T4(+)TQ1(+) (or T4(+)Leu 8(+)) T cells were depressed (Table XXV). By contrast, the T4(+) TQ1(-) (or T4(+) Leu 8(-)) subset which contains most of the helper cells for B cell responses is normal in AIDS. 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. As indicated in Table XXVI, other

TABLE XXV

T4 SUBSETS IN LYMPHADENOPATHY SYNDROME (LAS)
(Nicholson et al, J Clin Invest 73:191, 1984)

T Cell Subset	Percentage of Lymphocytes		Percentage of T Cells		Percentage of T4+ Cells		Absolute Number	
	LAS	Control	LAS	Control	LAS	Control	LAS	Control
T4(+)	24*	48	34*	64	100	100	412*	869
T4+:TQ1(+)	14*	33	19*	42	52*	72	289*	530
T4+:TQ1(-)	12	13	17	16	48	28	262	183
T4+:Leu-8(+)	19*	39	27*	49	72*	82	403*	604
T4+:Leu-8(-)	7	8	10	11	28	18	148	131

* Significantly decreased

patients with AIDS or AIDS related complex also exhibit T cell subset abnormalities, although these tend to be less severe and not to be associated with lymphopenia.

TABLE XXVI

SPECTRUM OF IMMUNOLOGIC ABNORMALITIES
IN AIDS AND RELATED SYNDROMES

Patient Group	Lymphopenia	T4/T8	T4+	T8+
		(Percent of Normal)		
Asymptomatic	No	60%	90%	170%
Lymphadenopathy	No	50%	60%	150%
Thrombocytopenia	No	50%	60%	150%
Kaposi's sarcoma	No	20%	40%	180%
Opportunistic infection	Yes	0-10%	0-10%	50%

Fifty to eighty percent of asymptomatic homosexual men (14-16) and more than 50% of asymptomatic hemophiliacs who are users of factor VIII concentrate (17-19) have been shown to manifest immunological abnormalities. 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.

Abnormalities in the T4+ to T8+ ratio appear to be most marked in homosexual men having more than 50 sexual partners per year (16). All of the hemophiliac patients with T lymphocyte abnormalities had received factor VIII concentrate. Abnormalities have not been seen or were of a lesser magnitude 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 minimal T lymphocyte abnormalities.

It should be noted that the abnormalities reported in asymptomatic homosexual men have been reported from areas in which AIDS 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. Moreover, a number of exogenous stimuli that might be encountered by risk groups have been shown to alter the number of circulating T cell sub-populations. Thus, for example, decreased numbers of OKT4, Leu 3 T cells may be observed during infection with CMV and Epstein Barr virus (151,152), while elevated numbers of OKT8, Leu 2 T cells may be seen during the convalescent phases of these viral illnesses. Moreover, the number of circulating OKT4, Leu 3 T cells may drop signi-

ficantly 3 to 14 days after booster immunization with tetanus toxoid (153), while multiple blood transfusions may cause severely depressed natural killer cell function without changes in T cell subsets (154). Thus, it is difficult to evaluate the clinical relevance of changes in circulating lymphocyte phenotype or function in asymptomatic individuals belonging to AIDS risk groups.

In summary, a spectrum of abnormalities in immunological function can be seen in individuals with various manifestations of AIDS or the AIDS-related complex (61,62,72, 94,155,24,25,20,21,14-18). Most of the abnormalities in circulating T lymphocytes result in a depressed T4+ to T8+ ratio and the extent of abnormalities in this ratio appear to correlate with the degree of immunosuppression and clinical involvement (156). However, examination merely of the "helper/suppressor" ratio masks the fact that abnormalities in this ratio in the various patient groups appear to result from independent changes in each of the populations. Thus, asymptomatic individuals tend to have hypergammaglobulinemia and increased numbers of circulating OKT8, Leu 2 positive T cells, with a resultant diminution in the 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 OKT4, Leu 3 positive T cell population. All of these patients have a tendency to develop hypergammaglobulinemia. 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.

Etiology of AIDS

As the epidemic of AIDS developed, a number of hypothetical etiologies were suggested. These included putative immunosuppressive effects of recreational drugs such as inhaled nitrites (31,157,158) or immunosuppressive effects of the transmission of allogeneic seminal lymphocytes (159-161) or other immunosuppressive factors in semen (162,163). As it became apparent that the epidemic of AIDS involved heterosexuals and could apparently be transmitted by blood product administration, a variety of potential infectious etologies were entertained, including cytomegalovirus (34,35), Epstein Barr virus (31,37), hepatitis B virus (164), a new virus associated with the hepatitis B virus (165), or a variant of African swine fever virus (166). More fanciful suggested etiologies included the possibility that the immunosuppression of AIDS resulted from the "systemic release of a potent cyclosporin-like immunosuppressive molecule from a chronic fungal infection" (167), although this possibility was quickly refuted (168).

More recently, a number of laboratories have developed evidence suggesting that a retrovirus of the human T cell lymphotropic virus (HTLV) family might be involved in the etiology of AIDS. The most

common member of the HTLV family, HTLV-I, is obtained mainly from patients with mature T cell malignancies (169). It has become apparent that this virus is the etiology of the T cell malignancy of adults that is endemic in certain areas of southern Japan, the Caribbean, and Africa. A second member of the family, HTLV-II, was first isolated from a patient with a T cell variant of hairy-cell leukemia. Although HTLV-II is less than 10% homologous to HTLV-I, a number of characteristics suggest that it is a member of the same family.

As retroviruses, members of the HTLV family contain a single stranded RNA genome consisting of three major genes, which from the 5^1 end of the genome include a gene for the viral internal core proteins called GAG, a gene for RNA dependent DNA polymerase (reverse transcriptase) called POL, and a gene for the surface envelope protein called ENV. Viruses of this family do not contain an oncogene (ONC). At each end of the genome there are sequences called long terminal repeats (LTRs) that contain signals for starting, stopping and enhancing gene expression. The target of a retrovirus infection depends on the interaction of the viral envelope with determinants on the cell surface. Retroviruses of the HTLV family appear to infect OKT4, Leu 3 positive T cells with great specificity. Upon entering the cell, the retrovirus RNA is transcribed into a DNA provirus by reverse transcriptase. The DNA provirus integrates into the host cell DNA, although the infected cell does not always express virus.

Certain characteristics of retroviruses of the HTLV family make them attractive candidates as etiological agents for AIDS. These include their T cell tropism with specificity for OKT4, Leu 3 cells (169). In vitro, these viruses have been shown to alter T cell function and under certain circumstances, to kill T cells selectively. Moreover, viruses of this family have been shown to be transmitted by intimate contact and blood products. In addition, other retroviruses have been shown to cause immune deficiency including feline leukemia virus (170), and Mason-Pfizer monkey virus (171) and another virus causing a syndrome similar to AIDS in monkeys (172,173).

Initial studies examined sera from patients with AIDS, AIDS-related complex, and a variety of controls for the presence of antibodies to an HTLV-associated membrane antigen (174). As seen in Table XXVII, 25% of sera from patients with AIDS or lymphadenopathy contained antibody against HTLV-associated membrane antigen (HTLV MA), whereas only about 1% of matched homosexual controls had this antibody. A variety of other controls showed no serological reactivity with HTLV MA. HTLV MA is a 61,000 dalton glycoprotein expressed by a variety of T cells and T cell lines, including HUT 102 and MT 2 after infection with HTLV-I. It appears to be a precursor of the 46,000 dalton envelope protein of HTLV-I. However, there is considerable cross-reactivity between this determinant and determinants expressed by other members of the HTLV family (174). Despite this, the data suggested that individuals with AIDS and AIDS-related complex had antibodies against antigens specific for members of the HTLV family. It could not, however, be determined whether these antibodies were directed specifically to HTLV-I or were cross-reactive antibodies induced by another member of the HTLV family.

TABLE XXVII

PRESENCE OF ANTIBODIES TO HTLV-ASSOCIATED MEMBRANE ANTIGEN IN PATIENTS WITH AIDS

Serum Source	Number Tested	Antibodies to HTLV-MA detected by immunofluorescence with HUT 102	MT 2
		Number positive (percentage)	
AIDS	75	19 (25)	18 (24)
Lymphadenopathy	23	6 (26)	6 (26)
Matched homosexual controls	81	1 (1)	1 (1)
Unmatched homosexual controls	118	0 (0)	0 (0)
Blood donors	137	1 (0.7)	2 (1.5)
Kidney dialysis patients	21	0 (0)	0 (0)
Chronic active hepatitis	29	0 (0)	0 (0)

Essex et al: Science 220:859, 1983

In addition, these studies could not determine whether HTLV was a candidate cause of AIDS or another example of an opportunistic infection in these immunocompromised hosts.

Subsequent studies have shown that antibodies to HTLV MA can be found in asymptomatic hemophiliacs from a number of locations (176). Thus, as shown in Table XXVIII, approximately 12% of asymptomatic hemophiliacs exhibit antibodies to HTLV MA. Of interest, the incidence of positivity was found to vary in different locations, with 10% of asymptomatic hemophiliacs from the New York City area exhibiting positive reactions, whereas only 5% of asymptomatic hemophiliacs from Birmingham, Alabama were positive. In addition, two of three hemophiliacs with AIDS or lymphadenopathy exhibited antibody to HTLV MA.

TABLE XXVIII

ANTIBODIES TO HTLV IN ASYMPTOMATIC HEMOPHILIACS AND HEMOPHILIACS WITH AIDS

Serum Source	Number	Antibodies to HTLV-MA Number (percentage) positive
Asymptomatic hemophiliacs		
Atlanta	45	5 (11)
Birmingham	41	2 (5)
Los Angeles	39	5 (13)
New York City	47	9 (19)
Total:	172	21 (12)
Healthy lab workers	47	0
Adult blood donors	137	1 (0.7)
Chronic active hepatitis	29	0
Hemodialysis patients	21	0
Hemophiliacs with AIDS or lymphadenopathy	3	2 (67)

Essex M, et al: Science 221:1061, 1983.

The presence of antibodies to HTLV MA could be detected in the serum of individuals with hemophilia before the first reported case of AIDS in a hemophiliac (177). Thus, when frozen sera collected between 1976 and 1981 from New York hemophiliacs were examined for the presence of antibodies to HTLV-MA, 17% (8/48) were found to be positive (Table XXIX). The first positive serum was from July of 1978 with the remaining

TABLE XXIX

ANTIBODIES TO HTLV-MA IN HEMOPHILIACS

Location of Asymptomatic Hemophiliacs	Number of Patients	Antibodies to HTLV-MA	Year of positive sera
New York	48	8 (17%)	July, 1978 → 1979
Georgia	45	5 (11%)	Current

Evatt BL: Lancet 2:698, 1983.

7 found between that time and 1979. Of interest, the first case of AIDS in a hemophiliac developed in New York in January, 1982 (7). Prodromal symptoms in another patient in Denver began in October, 1980, more than two years after the sera of New York hemophiliacs first exhibited antibodies to HTLV-MA. If the presence of this antibody indicates exposure to the infectious agent, then the results confirm the extremely long incubation period for this agent.

Asymptomatic hemophiliacs in Georgia were also examined for the presence of antibody to HTLV-MA and 11% (5/45) were found to be positive (177). When these patients were compared to patients who failed to exhibit antibody to HTLV-MA (Table XXX), it was found that the patients

TABLE XXX

COMPARISON OF T CELL POPULATIONS IN ANTI-HTLV-MA POSITIVE AND NEGATIVE GEORGIA HEMOPHILIACS

	HTLV-MA negative (N = 42)		HTLV-MA positive (N = 5)		
	Median	Range	Median	Range	P
T4/T8 ratio	0.935	0.3 - 1.87	0.76	0.21 - 1.0	0.20
T cells/mm^3	1380	625 - 4555	1156	576 - 1412	0.28
T4/mm^3	652	252 - 1891	396	253 - 668	<0.05
T8/mm^3	739	323 - 3089	686	330 - 1255	0.79

Evatt BL: Lancet 2:698, 1983

with antibody to HTLV-MA had significantly lower numbers of circulating OKT4, Leu 3 positive T cells. No other immunological findings were significantly different between these two groups. These data again supported the view that evidence of exposure to a member of the HTLV family could be found in individuals who received blood product exposure and was significantly correlated with the presence of immunologic abnormalities characteristic of AIDS.

Examination of patients with transfusion-related AIDS also supported the view that infection with HTLV might be etiological in this syndrome (123). Twelve cases of transfusion-related AIDS were examined in detail. Eight of these patients were examined for antibodies to HTLV-MA and three (38%) were found to be positive (Table XXXI). Eleven of

TABLE XXXI

ILLNESS, TRANSFUSION HISTORY, AND PRESENCE OF ANTIBODIES TO HTLV-MA IN PATIENTS WITH TRANSFUSION-RELATED AIDS

No.	Diagnosis	Antibodies to HTLV-MA	AIDS onset	Time from transfusion to illness onset (months)	Donors Total	Donors Studied	High-risk donors: AIDS risk group	Generalized lymphadenopathy	T_H:T_S	Antibodies to HTLV-MA	Other Donors: HTLV-MA (+)	Other Donors: total No.
1	PCP	+	June 1981	15-44	3	3	None	Yes	0.6	+	0	2
2	PCP	-	April 1982	11-39	28	18	Homosexual man	Yes	0.8	+	0	7
3	PCP	NA	April 1982	16	20	13	Intravenous drug user	No	1.5	+	0	11
4	PCP	+	May 1982	28	6	6	Homosexual man	No	0.5	+	0	5
5	KS	NA	September 1982	17	3	1	Homosexual man	No	0.4	+	0	0
6	PCP	NA	October 1982	35	2	2	Homosexual man	Yes	0.7	-	0	1
7	PCP	-	November 1982	40	4	4	Homosexual man who used intravenous drugs	Yes	1.7	+	0	3
8	PCP	-	December 1982	34	4	2	None	No	0.6	-	0	1
9	PCP	-	January 1983	18	6	3	Homosexual man	No	0.7	-	0	2
10	PCP	+	January 1983	27	16	11	None	No	0.3	-	1	10
11	PCP	NA	January 1983	13	31	28	No high risk donor identified				1	28
12	PCP	-	February 1983	18	34	26	Homosexual man	No	0.6	-	1	25

Jaffe HW, et al: Science 223:1309, 1984

these individuals received blood from an individual who was a member of an AIDS risk group, had generalized lymphadenopathy, or an abnormal T T4:T8 ratio. As seen in Table XXXII, the overall prevalence of antibodies to HTLV-MA was significantly higher in the donors to AIDS patients than in random blood donors. As seen in Table XXXI, nine of twelve patients with transfusion-related AIDS had received blood from an individual who was HTLV-MA positive, while eleven of 12 received blood from a patient who was a member of a risk group. Each of the patients with transfusion-related AIDS had a donor who was either a member of a risk group or had antibody to HTLV-MA. When the high risk donors were examined, 50% were found to have antibody to HTLV-MA (Table XXXII). These data support the conclusion that a virus serologically related to HTLV may be the etiologic agent of AIDS. Moreover, the data suggested that the antibodies directed against HTLV-MA might not protect against transmission of this infectious agent.

TABLE XXXII

PREVALENCE OF ANTIBODIES TO HTLV-MA IN BLOOD DONORS TO PATIENTS WITH TRANSFUSION-ASSOCIATED AIDS, RANDOM BLOOD DONORS, AND HEALTHY HOMOSEXUAL MEN (Jaffe HW, et al: Science 223:1309, 1984)

Category	Number Tested	Antibody Positive Number	Antibody Positive Percent
Blood donors to AIDS patients			
High-risk donors	12	6	50.0
Other donors	105	3	2.9
Total	117	9	7.7*
Random blood donors			
Philadelphia	100	0	
Madison	99	0	
Tucson	99	1	1.0
Total	298	1	0.3*
Healthy homosexual men			
Matched with AIDS patients	81	1	1.2
Unmatched	45	0	0
Total	126	1	0.8

* $p < 0.0001$

Although antibodies to HTLV-MA could be detected in individuals with AIDS, a number of pieces of evidence suggested that HTLV-I was not the etiologic agent in AIDS. First, antibody against HTLV-MA was found in only a minority of AIDS patients as indicated above. Secondly, proviral DNA of HTLV-I could be detected in lymphocytes of only two of 33 AIDS patients (178). Moreover, HTLV-I could be cultured from T cells of only a very small number of AIDS patients (179). Finally, the utilization of more specific tests for antibody to HTLV-I core proteins indicated that AIDS patients or patients with AIDS-related complex have a low incidence of antibody to HTLV-I (180). Thus, 7% of AIDS patients or patients with AIDS-related complex exhibited antibody to HTLV-I core proteins (Table XXXIII) in the United States. Using even more specific tests for HTLV-I, AIDS patients in London were not found to have antibody

TABLE XXXIII

HTLV-I-SPECIFIC ANTIBODIES IN AIDS PATIENTS AND OTHERS AT RISK FOR AIDS

Subjects	HTLV-I-specific antibody (percent positive)
All AIDS patients	14/198 (7%)
AIDS patients with only *Pneumocystis carinii* pneumonia	6/31 (19%)
AIDS patients with only Kaposi's sarcoma	8/126 (6%)
Patients with lymphadenopathy or AIDS-related complex	3/45 (7%)
Healthy homosexual men	0/145 (0%)
Healthy Haitian adults	6/52 (12%)
Healthy US individuals	4/538 (<1%)

Robert-Guroff M, et al: Lancet 2:128, 1984

to HTLV-I (181), although 5% of patients with lymphadenopathy had antibody to HTLV-I (Table XXXIV). Of interest, intravenous drug users in England were found to have antibody to HTLV-II more frequently than HTLV-I, but again, the incidence was low (3.5%). These data do not support the conclusion that HTLV-I is the etiology of AIDS. Rather, they suggest either that this virus can act as an opportunistic infection in individuals with AIDS or AIDS-related complex, or that the antibody tests are identifying cross-reacting antibodies in the serum of some AIDS patients.

TABLE XXXIV

HTLV ANTIBODIES IN AIDS RISK GROUPS, LONDON

	Proportion with antibody to HTLV	Specificity of Antibody HTLV I	HTLV II
AIDS	0/22	0	0
Lymphadenopathy	4/80	4	1
AIDS related complex	1/60	1	0
AIDS contacts	0/27	0	0
Control homosexuals	2/621	2	0
Drug abusers	4/113	1	3
Hemophiliacs	0/85	0	0
Promiscuous male heterosexuals	0/26	0	0
Unselected blood donors	0/500	0	0
Blood donors born outside NW Europe	0/440	0	0

Tedder RS, et al: Lancet 2:125, 1984

The demonstration that a retrovirus distinct from HTLV-I might be the cause of AIDS resulted from the work of Montagnier and colleagues at the Pasteur Institute in Paris, who were able to isolate a T lymphotropic retrovirus from a patient with lymphadenopathy (182). As shown in Table XXXV, this virus was isolated from the lymph nodes of a 33 year old male homosexual with lymphadenopathy. The virus had many of the characteristics of a T cell lymphotropic retrovirus but could be distinguished from HTLV-I. These results caused the authors to suggest that the T lymphotropic retrovirus they had isolated, as well as HTLV isolates, belonged to a larger family of retroviruses that could be horizontally transmitted in humans and may be involved in several pathological syndromes, including AIDS. The French named the virus lymphadenopathy-associated virus (LAV). A very similar virus has subsequently been isolated by this group from two siblings with hemophilia, only one of whom had AIDS and several patients with AIDS (183).

Gallo and colleagues were subsequently also able to detect, isolate and grow a T cell lymphotropic retrovirus from cells of patients with AIDS and AIDS-related complex (184). This virus had antigenic and morphologic differences from HTLV-I and HTLV-II and in addition, caused

TABLE XXXV

ISOLATION OF A T CELL LYMPHOTROPIC RETROVIRUS
FROM A PATIENT WITH LYMPHADENOPATHY
(Barré-Sinoussi F, et al: Science 220:868, 1983)

Patient:

33 y/o male homosexual

Lymphadenopathy and asthenia

Lymph node

Biopsy → follicular hyperplasia

Cell suspension - 62% OKT3(+)
44% OKT4(+)
16% OKT8(+)

Cell culture → reverse transcriptase production
day 15 → 30

Virus

1. Could infect normal T cells and cord blood T cells by co-culture with patient cells or cell-free culture supernatant of patient cells

2. Could not infect B lymphoblastoid cells, immature T cell lines or normal fibroblasts

3. Characteristics of retrovirus

   a. buoyant density

   b. produced reverse transcriptase

   c. electron microscopy - particles budding from plasma membrane

4. Relation to HTLV-I

   a. did not produce p19 and p24 core proteins of HTLV-I

   b. virus produces a p25 protein immunologically distinct from HTLV-I p24

   c. patient serum does contain antibody against HTLV antigens

the death of infected cells rather than their malignant transformation. Nonetheless, the evidence suggested to Gallo's group that the isolated virus belonged to the HTLV family of retroviruses, as indicated in Table XXXVI and they therefore named it HTLV-III.

TABLE XXXVI

EVIDENCE THAT HTLV-III BELONGS TO THE
HTLV FAMILY OF RETROVIRUSES

1. T cell tropism (T4 cells)
2. Mg^{++} dependent reverse transcriptase of high molecular weight (100 KD)
3. Antigenic cross reactivity with HTLV-I and II
4. Cytopathic effect on T lymphocytes
5. Morphologic appearance in the electron microscope

When cells from a number of individuals with Kaposi's sarcoma or opportunistic infections were examined, HTLV-III could be cultured from 30 and 48% of them, respectively (185). In addition, as shown in Table XXXVII, HTLV-III could be grown from lymphocytes of more than 85% of individuals with chronic lymphadenopathy and/or lymphopenia. The virus could be grown from cells of only one clinically normal, non-promiscuous

TABLE XXXVII

DETECTION AND ISOLATION OF HTLV-III FROM PATIENTS WITH AIDS AND AIDS-RELATED COMPLEX
(Gallo RS, et al: Science 224:500, 1984)

Diagnosis	Number Tested	Number positive for HTLV-III	Percent Positive
Chronic lymphadenopathy, and/or lymphopenia	21	18	85.7
Clinically normal mothers of juvenile AIDS patients	4	3	75.0
Juvenile AIDS	8	3	37.5
Adult AIDS with Kaposi's sarcoma	43	13	30.2
Adult AIDS with opportunistic infections	21	10	47.6
Clinically normal non-promiscuous homosexual males	22	1	4.5
Clinically normal heterosexual donors	115	0	0

Peripheral blood mononuclear cells were cultured with PHA and interleukin 2 and then assayed for the presence of HTLV-III

Samples exhibiting more than one of the following were considered positive:

1. Detection of Mg^{++} dependent reverse transcriptase in supernatant fluids
2. Virus observed by electron microscopy
3. Intracellular expression of virus related antigens detected with antibodies from seropositive donors or with a rabbit antiserum to HTLV-III
4. Transmission of particles to fresh human cord blood, bone marrow or peripheral blood T lymphocytes

homosexual male of 22 tested. Six months after being tested, this individual developed AIDS. The virus could be grown from the cells of none of the normal heterosexual donors. Of interest, virus could be detected in cells of about one-third of the individuals with juvenile AIDS, and three of four mothers of patients with juvenile AIDS. These results supported the contention that HTLV-III was the etiologic agent of AIDS. However, the inability to culture it from a higher percentage of patients with AIDS was of concern, although many of these individuals had marked lymphopenia.

Additional support for the role of HTLV-III in the etiology of AIDS came from serological analysis of these patients (186). As shown in Table XXXVIII, more than 85% of patients with AIDS had antibodies specific for HTLV-III and nearly 80% of patients with AIDS-related complex also had such antibodies. In addition, nearly one quarter of 34 homosexual men tested had antibodies to HTLV-III. These data supported the view that HTLV-III might play an etiologic role in AIDS. Similar results were reported when antibodies to LAV were determined (187). Thus, about 1/3 of AIDS patients were found to have IgG antibody to LAV whereas 3/4 of lymphadenopathy sera were positive (Table XXXIX). When a more sensitive test was employed, 75% of AIDS patients and more than 90% of lymphadenopathy patients were LAV seropositive (187). Additional support for the conclusion that a T lymphotropic virus causes AIDS derives from the observation that LAV has been isolated from a blood donor-recipient pair, each of whom developed AIDS (188). These results support the conclusion that these viruses are etiologically associated with the AIDS syndrome. Finally, a virus that is very similar

TABLE XXXVIII

ANTIBODIES TO HTLV-III IN SERUM SAMPLES FROM
PATIENTS WITH AIDS, AIDS-RELATED COMPLEX AND FROM CONTROL SUBJECTS
(Sarngadharan MG, et al: Science 224:506, 1984)

Subject	Number Tested	Number positive for antibodies to HTLV-III	Percent Positive
Patients with AIDS	49	43	87.8
Patients with AIDS-related complex	14	11	78.6
Intravenous drug users	5	3	60
Homosexual men	17	6	35.3
Sexual contact of AIDS patient	1	1	
Persistent fatigue	1	1	
Other	15	4	26.6
Other controls	186	1	0.5
Normal subjects	164	1	0.6
Patients with hepatitis B virus infection	3	0	
Patient with rheumatoid arthritis	1	0	
Patients with systemic lupus erythematosus	6	0	
Patients with acute mononucleosis	4	0	
Patients with lymphatic leukemias	8	0	

or identical to LAV called AIDS-associated retrovirus (ARV) has been cultured from cells of 22 of 45 randomly selected patients with AIDS, 5 of 10 patients with lymphadenopathy, 3 of 14 male sexual partners of AIDS patients and 2 of 9 clinically normal homosexual men from San Francisco (189). The ARV virus cross-reacted with an antiserum to LAV. Moreover, 100% of AIDS patients, 92% of patients with lymphadenopathy and 64% of normal homosexuals had antibodies to ARV (Table XXXX). These observations indicate the widespread presence of these lymphocytopathic retroviruses and also their close association with AIDS.

A number of pieces of evidence support the view that HTLV-III is related to HTLV-I and II (190). Thus, extensive cross-reactivity of antisera raised against each of these viruses has been demonstrated as have similarities of nucleotide sequence. Serological analysis indicates that HTLV-III is more closely related to HTLV-II than HTLV-I (189). There are, however, a number of differences between these viruses including the protein patterns of purified viral preparations and morphological differences, with HTLV-I and II showing characteristics of Type C retroviruses, while HTLV-III appears to be a Type D retrovirus (186). Moreover, HTLV-I and II appear to have the capacity to transform T lymphocytes while HTLV-III inhibits their growth.

Additional evidence indicates that HTLV-III and LAV are similar or identical viruses (191). First, they have the same appearance by electron microscopy, both appearing to be Type D retroviruses. Secondly, both are lymphotropic and cytopathic for OKT4, Leu 3 T cells. Third, isolates from American AIDS patients are indistinguishable from LAV. Fourth, serological tests of specimens from patients with AIDS or

TABLE XXXIX

ANTIBODIES TO LAV IN PATIENTS WITH AIDS AND AIDS-RELATED COMPLEX
(Brun-Vezinet et al: Lancet 2:1253, 1984)

Patient Group	LAV IgG
AIDS:	18/48 (37.5%)
Opportunistic infection	12/30
Kaposi's sarcoma	3/12
Infection + KS	2/5
Brain lymphoma	1/1
Haemophilia	1/1
Homosexual men	10/35
Haitians	3/4
Africans	4/8
LYMPHADENOPATHY:	38/51 (74.5%)
Homosexual men	29/40
Drug abusers	6/8
Haitians	3/3
HOMOSEXUAL CONTROLS	8/44 (18%)
BLOOD DONORS	1/100 (1%)
LABORATORY WORKERS	0/30

When all sera were tested for HTLV p24 by core protein radioimmunoassay, only one (from a homosexual man with lymphadenopathy) was positive.

AIDS-related complex show similar results when either LAV or HTLV-III is used as antigen. Finally, LAV and HTLV-III are similar based on competitive radioimmunoassay of their core proteins. Thus, it appears that these two agents are similar or identical.

TABLE XXXX

ANTIBODIES TO AIDS-ASSOCIATED RETROVIRUS (ARV) IN
AIDS PATIENTS AND NORMAL HOMOSEXUAL MEN
(Levy et al: Science 225:840, 1984)

Subjects	Serum Antibody		
	HTLV-I	LAV	ARV
	Number (percentage)		
Patients with diagnosis of			
AIDS with Kaposi's sarcoma	7/55 (13)	20/38 (53)	59/67 (88)
AIDS with opportunistic infection	1/5 (20)	2/2 (100)	19/19 (100)
Lymphadenopathy syndrome	1/13 (8)	1/4 (25)	22/27 (81)
Other individuals			
Male sexual partners of AIDS patients	1/19 (5)	7/18 (39)	13/14 (93)
Clinically healthy homosexual men	1/13 (8)	1/4 (25)	27/47 (57)
Clinically healthy heterosexual individuals	0/12 (0)	0/9 (0)	0/56 (0)

More recent evidence has supported the view that LAV/HTLV-III is involved in the etiology of AIDS (191). Thus, as pointed out in Table XXXXI, the incidence of antibodies to LAV has increased over the past six years such that 65% of normal homosexual males attending a sexually-

TABLE XXXXI

SEROLOGIC EVIDENCE OF EXPOSURE TO LAV/HTLV-III IN POPULATIONS AT RISK FOR AIDS

1.	HTLV-III		
	a) Normal homosexual males	-	6/17 (35%)
2.	LAV		
	a) Normal homosexual males attending STD clinic		
	1. Paris		8/44 (18%)
	2. San Francisco		
	1978		1/100 (1%)
	1980		12/48 (25%)
	1984		150/215 (65%)
	b) Drug users in NYC		
	Intravenous -		75/86 (87%)
	Methadone -		3/35 (9%)
	c) Asymptomatic hemophiliacs who had received factor VIII concentrate:		18/25 (72%)

transmitted disease clinic in San Francisco exhibit antibodies to this agent, as do 87% of intravenous drug users in New York City (192). Moreover, 72% of asymptomatic hemophiliacs that received factor VIII concentrate exhibit antibodies to this agent. These results all support the contention that HTLV-III/LAV is related to the etiology of AIDS and that exposure to the virus is widespread in the community.

The relationship of the exposure to this agent and the development of AIDS has not been completely delineated. One feature of the virus may be important, however. That is, its tropism for activated as opposed to resting T cells (193). It is possible that chronic antigenic stimulation from sexually-transmitted diseases or from recurrent challenge with foreign blood products leads to the activation of sufficient T cells to support the successful initiation of an infection with HTLV-III. The role of serum antibody in preventing HTLV-III infection has also not been determined, although the high incidence of antibody in patients with AIDS suggests that this antibody may not be protective.

The recent development of T cell clones (184) and lines (189) that permit the productive growth of HTLV-III and the adaptation of the virus to grow in Epstein-Barr virus-transformed B lymphoblastoid cells (194), has made it possible to produce large quantities of HTLV-III. Thus, a test to screen for the presence of antibody to this virus

should soon be available and permit a more complete understanding of the scope of clinical manifestations resulting from infection with HTLV-III/LAV.

Treatment

Currently treatment is directed toward control of opportunistic infection and therapy for underlying malignant neoplasms. There is no evidence that the underlying immune deficiency is reversible. A number of therapeutic modalities have been attempted in the hope of reversing the immunodeficiency of AIDS patients. These have included therapy with a variety of immune modulators such as isoprinosine (195), biological products such as interferon (58,118-120), and interleukin 2 (58), as well as bone marrow transplantation (196). None has provided convincing evidence of reconstitution of the immune system in patients with AIDS. At the current time, the most likely mechanism to effect the course of AIDS remains prevention. Hopefully, the imminent availability of a test to provide serological information concerning HTLV-III/LAV exposure should provide a more effective way to screen blood donors and to identify individuals who have been exposed to this virus.

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APPENDIX

I. CENTERS FOR DISEASE CONTROL SURVEILLANCE DEFINITION OF AIDS (MMWR 31:507-514, 1982; Amer J. Med. 76:493-500, 1984)

Diseases must be at least moderately indicative of underlying cellular immunodeficiency and must occur in the absence of known causes of reduced resistance to them. These are listed below in five etiologic categories: protozoal and helminthic, fungal, bacterial, viral, and neoplastic. Within each category, the diseases are listed in alphabetic order. "Disseminated infection" refers to involvement of liver, bone marrow, or multiple organs, not simply involvement of lungs or multiple lymph nodes. The required diagnostic methods with positive results are shown in parentheses.

Protozoal and helminthic infections

- Cryptosporidiosis, intestinal, causing diarrhea for more than one month (on histologic study or stool microscopic study)

- Pneumocystis carinii pneumonia (on histologic study or microscopic study of a "touch" preparation or bronchial washings)

- Strongyloidosis, causing pneumonia, central nervous system infection, or disseminated infection (on histologic study)

- Toxoplasmosis, causing pneumonia or central nervous system infection (on histologic study or microscopic study of a "touch" preparation)

Fungal infections

- Candidiasis, causing esophagitis (on histologic study or microscopic study of a "wet" preparation from the esophagus, or endoscopic findings of white plaques on an erythematous mucosal base)

- Cryptococcosis, causing central nervous system or disseminated infection (on culture, antigen detection, histologic study, or India ink preparation of cerebrospinal fluid)

Bacterial infections

- "Atypical" mycobacteriosis (species other than tuberculosis or tepra), causing disseminated infection (on culture)

Viral infections

- Cytomegalovirus, causing pulmonary, gastrointestinal tract, or central nervous system infection (on histologic study)

- Herpes simplex virus, causing chronic mucocutaneous infection with ulcers persisting more than one month, or pulmonary, gastrointestinal

tract, or disseminated infection (on culture, histologic study, or cytologic study)

- Progressive multifocal leukoencephalopathy (presumed to be caused by a papovavirus) (on histologic study)

Cancer

- Kaposi's sarcoma in persons less than 60 years of age (on histologic study)

- Lymphoma limited to the brain (on histologic study)

Case Reporting

For the epidemiologic surveillance of AIDS, any patient who has a disease at least moderately indicative of underlying cellular immunodeficiency (as just listed) but who has no known cause of reduced resistance to that disease should be reported by clinicians to their state or local public health department. Those agencies should, in turn, report the case to the AIDS Program, Centers for Disease Control, Atlanta, Georgia 30333.

II. PEDIATRIC AIDS: PROVISIONAL CASE DEFINITION (MMWR 32:688, 1984)

For the limited purposes of epidemiologic surveillance, CDC defines a case of pediatric acquired immunodeficiency syndrome (AIDS) as a child who has had:

A. a reliably diagnosed disease at least moderately indicative of underlying cellular immunodeficiency and

B. no known cause of underlying cellular immunodeficiency or any other reduced resistance reported to be associated with that disease.

The diseases accepted as sufficiently indicative of underlying cellular immunodeficiency are the same as those used in defining AIDS in adults, with the exclusion of congenital infections, e.g., toxoplasmosis or herpes simplex virus infection in the first month after birth or cytomegalovirus infection in the first 6 months after birth.

Specific conditions that must be excluded in a child are:

A. Primary immunodeficiency diseases severe combined immunodeficiency, DiGeorge syndrome, Wiskott-Aldrich syndrome, ataxia-telangiectasis, graft versus host disease, neutropenia, neutrophil function abnormality, agammaglobulinemia, or hypogammaglobulinemia with raised IgM.

B. Secondary immunodeficiency associated with immunosuppressive therapy, lymphoreticular malignancy, or starvation.

III. RECOMMENDED PRECAUTIONS TO CONTROL TRANSMISSION OF AIDS (MMWR 32:101-103, 1983)

A. Sexual contact should be avoided with persons known or suspected to have AIDS. Members of high risk groups should be aware that multiple sexual partners increase the probability of developing AIDS.

B. As a temporary measure, members of groups at increased risk for AIDS should refrain from donaating plasma and/or blood. This recommendation includes all individuals belonging to such groups, even though many individuals are at little risk of AIDS. Centers collecting plasma and/or blood should inform potential donors of this recommendation.

C. Physicians should adhere strictly to medical indications for transfusions, and autologous blood transfusions are encouraged.

IV. 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 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 designated 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 needly-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 de-contaminated 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 acitvities 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.

V. INFECTION CONTROL GUIDELINES FOR PATIENTS WITH AIDS PROMULGATED BY THE UNIVERSITY OF CALIFORNIA, SAN FRANCISCO, TASK FORCE ON THE ACQUIRED IMMUNODEFICIENCY SYNDROME

(N. Eng. J. Med. 309:740-744, 1983)

A. Persons for whom precautions should be taken

1. AIDS patients

2. Members of risk groups with

   a. chronic generalized lymphadenopathy
   b. unexplained weight loss
   c. prolonged unexplained fever

3. Persons with "possible AIDS" hospitalized for evaluation

B. Precautions

1. Specimens should have biohazard warning without mention of specific disease and should be transported in waterproof containers

2. Gloves should be worn by persons in contact with blood, blood specimens, tissues, blood fluids, excretions or articles or surfaces potentially contaminated by them

3. Thorough hand-washing before and after contact

4. Gowns are recommended for those likely to have direct contact with patients' secretions, excretions or blood.

5. Environmental surfaces contaminated with blood or other body fluids should be cleaned immediately with disinfectant (1:10 dilution of 5.25% sodium hypochlorite solution)

6. Masks are not routinely necessary

   - masks should be worn by coughing patients who leave hospital room and by individuals who have direct and sustained contact with coughing patient.

7. Protective eyewear should be worn in situations in which splatter with blood or excretions is expected.

8. Needles and syringes should be disposed of in rigid-wall puncture-resistant containers. Needles should not be resheathed.

9. All contaminated linen and other objects should be considered "infectious waste" and double-bagged.

10. Private rooms are not necessary if the patient is not coughing.

11. Any instrument that comes into contact with blood, secretions, or tissue must be sterilized before reuse.

C. Refusal to Care for Patients with AIDS

1. There is no scientific reason for healthy personnel to be excused from delivering care to patients with AIDS. Immunosuppressed persons or pregnant women should not engage in direct care of AIDS patients.

2. CPR should make use of resuscitation bags or disposable devices for mouth-to-mouth resuscitation. The decision to withhold direct mouth-to-mouth resuscitation from a patient with AIDS when a CPR device is not available is solely that of the individual employee.

D. Direct patient-care responsibilities for employees with AIDS

The hospital may elect to advise asymptomatic employees with AIDS to accept positions not involving patient care in order to protect the employee from nosocomial pathogens and to protect high-risk patients from opportunistic pathogens carried by the employee.

E. Outpatients

The same guidelines should apply to outpatient and emergency settings.

- Separate examining rooms are not necessary
- AIDS patients may use common waiting rooms and bathroom facilities
- Efforts should be made to minimize contact between AIDS patients and other immunocompromised patients.

VI. AIDS: PRECAUTIONS FOR HEALTH CARE WORKERS AND ALLIED PROFESSIONALS (MMWR 32:450-451, 1983)

A. Dental-Care Personnel

1. Personnel should wear gloves, masks, and protective eyewear when performing dental or oral surgical procedures.

2. Instruments used in the mouths of patients should be sterilized after use.

B. Persons Performing Necropsies or Providing Morticians' Services

1. As part of immediate postmortem care, deceased persons should be identified as belonging to one of the above three groups, and that identification should remain with the body.

2. The procedures followed before, during, and after the postmortem examination are similar to those for hepatitis B. All personnel involved in performing an autopsy should wear double gloves, masks, protective eyewear, gowns, waterproof aprons, and waterproof shoe coverings. Instruments and surfaces contaminated during the postmortem examination should be handled as potentially infective items.

3. Morticians should evaluate specific procedures used in providing mortuary care and take appropriate precautions to prevent the parenteral or mucous-membrane exposure of personnel to body fluids.