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This publication includes all the articles related to AIDS that have appeared in the *Morbidity and Mortality Weekly Report*, published by the Centers for Disease Control. These articles, arranged in chronological order, track the reporting of information on AIDS from 1981, when CDC first published information on Kaposi's sarcoma and *Pneumocystis carinii* pneumonia occurring in young homosexual men. In 1981, CDC formed a task force to establish risk factors, carry out laboratory studies, and disseminate timely information on the disease now known as the acquired immunodeficiency syndrome (AIDS).

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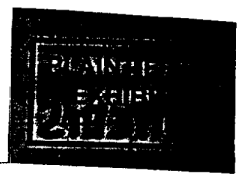

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1981 June 5;30:250-2

Pneumocystis Pneumonia – Los Angeles

In the period October 1980-May 1981, 5 young men, all active homosexuals, were treated for biopsy-confirmed *Pneumocystis carinii* pneumonia at 3 different hospitals in Los Angeles, California. Two of the patients died. All 5 patients had laboratory-confirmed previous or current cytomegalovirus (CMV) infection and candidal mucosal infection. Case reports of these patients follow.

Patient 1: A previously healthy 33-year-old man developed *P. carinii* pneumonia and oral mucosal candidiasis in March 1981 after a 2-month history of fever associated with elevated liver enzymes, leukopenia, and CMV viruria. The serum complement-fixation CMV titer in October 1980 was 256; in May 1981 it was 32.* The patient's condition deteriorated despite courses of treatment with trimethoprim-sulfamethoxazole (TMP/SMX), pentamidine, and acyclovir. He died May 3, and postmortem examination showed residual *P. carinii* and CMV pneumonia, but no evidence of neoplasia.

Patient 2: A previously healthy 30-year-old man developed *P. carinii* pneumonia in April 1981 after a 5-month history of fever each day and of elevated liver-function tests, CMV viruria, and documented seroconversion to CMV, i.e., an acute-phase titer of 16 and a convalescent-phase titer of 28* in anticomplement immunofluorescence tests. Other features of his illness included leukopenia and mucosal candidiasis. His pneumonia responded to a course of intravenous TMP/SMX, but, as of the latest reports, he continues to have a fever each day.

Patient 3: A 30-year-old man was well until January 1981 when he developed esophageal and oral candidiasis that responded to Amphotericin B treatment. He was hospitalized in February 1981 for *P. carinii* pneumonia that responded to oral TMP/SMX. His esophageal candidiasis recurred after the pneumonia was diagnosed, and he was again given Amphotericin B. The CMV complement-fixation titer in March 1981 was 8. Material from an esophageal biopsy was positive for CMV.

Patient 4: A 29-year-old man developed *P. carinii* pneumonia in February 1981. He had had Hodgkins disease 3 years earlier, but had been successfully treated with radiation therapy alone. He did not improve after being given intravenous TMP/SMX and corticosteroids and died in March. Postmortem examination showed no evidence of Hodgkins disease, but *P. carinii* and CMV were found in lung tissue.

Patient 5: A previously healthy 36-year-old man with a clinically diagnosed CMV infection in September 1980 was seen in April 1981 because of a 4-month history of fever, dyspnea, and cough. On admission he was found to have *P. carinii* pneumonia, oral candidiasis, and CMV retinitis. A complement-fixation CMV titer in April 1981 was 128. The patient has been treated with 2 short courses of TMP/SMX that have been limited because of a sulfa-induced neutropenia. He is being treated for candidiasis with topical nystatin.

The diagnosis of *Pneumocystis* pneumonia was confirmed for all 5 patients antemortem by closed or open lung biopsy. The patients did not know each other and had no known common contacts or knowledge of sexual partners who had had similar illnesses. The 5 did not have comparable histories of sexually transmitted disease. Four had serologic evidence of past hepatitis B infection but had no evidence of current hepatitis B surface antigen. Two of the 5 reported having frequent homosexual contacts with various partners. All 5 reported using inhalant drugs, and 1 reported parenteral drug abuse. These patients had profoundly depressed numbers of thymus-dependent lymphocyte cells and profoundly depressed *in vitro* proliferative responses to mitogens and antigens. Lymphocyte studies were not performed on the other 2 patients.

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Editorial Note: *Pneumocystis* pneumonia in the United States is almost exclusively limited to severely immunosuppressed patients (1). The occurrence of pneumocystosis in these 5 previously healthy individuals without a clinically apparent underlying immunodeficiency is unusual. The fact that these patients were all homosexuals suggests an association between some aspect of a homosexual lifestyle or disease acquired through sexual contact and *Pneumocystis* pneumonia in this population. All 5 patients described in this report had laboratory-confirmed CMV disease or virus shedding within 5 months

*Paired specimens not run in parallel.

of the diagnosis of *Pneumocystis* pneumonia. CMV infection has been shown to induce transient abnormalities of *in vitro* cellular-immune function in otherwise healthy human hosts (2,3). Although all 3 patients tested had abnormal cellular-immune function, no definitive conclusion regarding the role of CMV infection in these 5 cases can be reached because of the lack of published data on cellular-immune function in healthy homosexual males with and without CMV antibody. In 1 report, 7 (3.8%) of 184 patients with pneumocystosis also had CMV infection; 40 (21%) of the same group had at least 1 other major concurrent infection (1). A high prevalence of CMV infections among homosexual males was recently reported: 179 (94%) of 190 males reported to be exclusively homosexual had serum antibody to CMV, and 14 (7.4%) had CMV viruria; rates for 101 controls of similar age who were reported to be exclusively heterosexual were 54% for seropositivity and zero for viruria (4). In another study of 64 males, 4 (6.3%) had positive tests for CMV in semen, but none had CMV recovered from urine. Two of the 4 reported recent homosexual contacts. These findings suggest not only that virus shedding may be more readily detected in seminal fluid than in urine, but also that seminal fluid may be an important vehicle of CMV transmission (5).

All the above observations suggest the possibility of a cellular-immune dysfunction related to a common exposure that predisposes individuals to opportunistic infections such as pneumocystosis and candidiasis. Although the role of CMV infection in the pathogenesis of pneumocystosis remains unknown, the possibility of *P. carinii* infection must be carefully considered in a differential diagnosis for previously healthy homosexual males with dyspnea and pneumonia.

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1981 July 4;30:305–8

Kaposi's Sarcoma and *Pneumocystis* Pneumonia Among Homosexual Men – New York City and California

During the past 30 months, Kaposi's sarcoma (KS), an uncommonly reported malignancy in the United States, has been diagnosed in 26 homosexual men (20 in New York City [NYC], 6 in California). The 26 patients range in age from 26-51 years (mean 39 years). Eight of these patients died (7 in NYC, 1 in California)—all 8 within 24 months after KS was diagnosed. The diagnoses in all 26 cases were based on histopathological examination of skin lesions, lymph nodes, or tumor in other organs. Twenty-five of the 26 patients were white, 1 was black. Presenting complaints from 20 of these patients are shown in Table 1.

Skin or mucous membrane lesions, often dark blue to violaceous plaques or nodules, were present in most of the patients on their initial physician visit. However, these lesions were not always present and often were considered benign by the patient and his physician.

A review of the New York University Coordinated Cancer Registry for KS in men under age 50 revealed no cases from 1970-1979 at Bellevue Hospital and 3 cases in this age group at the New York University Hospital from 1961-1979.

Seven KS patients had serious infections diagnosed after their initial physician visit. Six patients had pneumonia (4 biopsy confirmed as due to *Pneumocystis carinii* [PC]), and one had necrotizing toxoplasmosis of the central nervous system. One of the patients with *Pneumocystis* pneumonia also experienced severe, recurrent, herpes simplex infection; extensive candidiasis; and cryptococcal meningitis. The results of tests for cytomegalovirus (CMV) infection were available for 12 patients. All 12 had serological evidence of past or present CMV infection. In 3 patients for whom culture results were available, CMV was isolated from blood, urine and/or lung of all 3. Past infections with amebiasis and hepatitis were commonly reported.

TABLE 1. Presenting complaints in 20 patients with Kaposi's sarcoma

Presenting complaint	Number (percentage) of patients
Skin lesion(s) only	10 (50%)
Skin lesions plus lymphadenopathy	4 (20%)
Oral mucosal lesion only	1 (5%)
Inguinal adenopathy plus perirectal abscess	1 (5%)
Weight loss and fever	2 (10%)
Weight loss, fever, and pneumonia (one due to *Pneumocystis carinii*)	2 (10%)

Since the previous report of 5 cases of *Pneumocystis* pneumonia in homosexual men from Los Angeles (*1*), 10 additional cases (4 in Los Angeles and 6 in the San Francisco Bay area) of biopsy-confirmed PC pneumonia have been identified in homosexual men in the state. Two of the 10 patients also have KS. This brings the total number of *Pneumocystis* cases among homosexual men in California to 15 since September 1979. Patients range in age from 25 to 46 years.

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Editorial Note: KS is a malignant neoplasm manifested primarily by multiple vascular nodules in the skin and other organs. The disease is multifocal, with a course ranging from indolent, with only skin manifestations, to fulminant, with extensive visceral involvement (*2*).

Accurate incidence and mortality rates for KS are not available for the United States, but the annual incidence has been estimated between 0.02-0.06 per 100,000; it affects primarily elderly males (*3,4*). In a series of 92 patients treated between 1949 and 1975 at the Memorial Sloan-Kettering Cancer Institute in NYC, 76% were male, and the mean age was 63 years (range 23-90 years) at the time of diagnosis (*5*).

The disease in elderly men is usually manifested by skin lesions and a chronic clinical course (mean survival time is 8-13 years) (*2*). Two exceptions to this epidemiologic pattern have been noted previously. The first occurs in an endemic belt across equatorial Africa, where KS commonly affects children and young adults and accounts for up to 9% of all cancers (*3*). Secondly, the disease appears to have a higher incidence in renal transplant recipients (*6-9*) and in others receiving immunosuppressive therapy (*10-12*).

The occurrence of this number of KS cases during a 30-month period among young, homosexual men is considered highly unusual. No previous association between KS and sexual preference has been reported. The fulminant clinical course reported in many of these patients also differs from that classically described for elderly persons.

The histopathologic diagnosis of KS may be difficult for 2 reasons. Changes in some lesions may be interpreted as nonspecific, and other cutaneous and soft tissue sarcomas, such as angiosarcoma of the skin, may be confused with KS (*13,14*).

That 10 new cases of *Pneumocystis* pneumonia have been identified in homosexual men suggests that the 5 previously reported cases were not an isolated phenomenon (*1*). In addition, CDC has a report of 4 homosexual men in NYC who developed severe, progressive, perianal herpes simplex infections and had evidence of cellular immunodeficiencies. Three died, 1 with systemic CMV infection. The fourth patient is currently undergoing therapy. It is not clear if or how the clustering of KS, pneumocystis, and

other serious diseases in homosexual men is related. What is known is that the patients with *Pneumocystis* pneumonia described in the previous report showed evidence of impaired cellular immunity and previous or current CMV infection (*1*). Furthermore, serologic evidence of past CMV infection and active shedding of CMV have been shown to be much more common among homosexual men than heterosexual men attending a sexually transmitted disease clinic (*15*). A specific serologic association with CMV infection has been demonstrated among American and European patients with KS (*16, 17*) and herpes-type virus particles have been demonstrated in tissue culture cell lines from African cases of KS (*18*). It has been hypothesized that activation of oncogenic virus during periods of immunosuppression may result in the development of KS (*19*). Although immunosuppression often results in CMV infection, it is not yet clear whether CMV infection precedes or follows the above-mentioned disorders.

Although it is not certain that the increase in KS and PC pneumonia is restricted to homosexual men, the vast majority of recent cases have been reported from this group. Physicians should be alert for Kaposi's sarcoma, PC pneumonia, and other opportunistic infections associated with immunosuppression in homosexual men.

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1981 Aug 28;30:409–10

Follow-Up on Kaposi's Sarcoma and *Pneumocystis* Pneumonia

Twenty-six cases of Kaposi's sarcoma (KS) and 15 cases of *Pneumocystis carinii* pneumonia (PCP) among previously healthy homosexual men were recently reported (*1,2*). Since July 3, 1981, CDC has received reports of an additional 70 cases of these 2 conditions in persons without known underlying disease. The sex, race, sexual preference, and mortality data known for 108 persons with either or both conditions are summarized in Table 1.

The majority of the reported cases of KS and/or PCP have occurred in white men. Patients ranged in age from 15-52 years; over 95% were men 25-49 years of age. Ninety-four percent (95/101) of the men for whom sexual preference was known were homosexual or bisexual. Forty percent of the reported cases were fatal. Of the 82 cases for which the month of diagnosis is known, 75 (91%) have occurred since January 1980, with

55 (67%) diagnosed from January through July 1981. Although physicians from several states have reported cases of KS and PCP among previously healthy homosexual men, the majority of cases have been reported from New York and California.

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Editorial Note: KS is a rare, malignant neoplasm seen predominantly in elderly men in this country. In elderly men the disease is manifested by skin lesions and a chronic clinical course; it is rarely fatal (3). In contrast, the persons currently reported to have KS are young to middle-aged men, and 20% of the cases have been fatal. Although some of the patients have presented with the violaceous skin or mucous membrane lesions

TABLE 1. Cases of Kaposi's sarcoma (KS) and *Pneumocystis carinii* pneumonia (PCP) reported to CDC with dates of onset between January 1976 and July 1981

Diagnosis (number of patients)	Sex		Race of men				Sexual preference of men			Fatality (percentage)
	Male	Female	White	Black	Hispanic	Unknown	Homosexual or bisexual	Heterosexual	Unknown	
KS and PCP (N=7)	7	0	5	0	1	1	7	0	0	3/7 (43%)
KS only (N=47)	47	0	41	3	3	0	44	1	2	8/47 (17%)
PCP only (N=54)	53	1	33	9	7	4	44	5	4	32/54 (59%)
Total (N=108)	107	1	79	12	11	5	95	6	6	43/108 (40%)

typical of KS, many such lesions have been initially overlooked. Other patients have been diagnosed by lymph-node biopsy after a prodrome consisting of fever, weight loss, and lymphadenopathy. Seven (13%) of fifty-four KS patients also had PCP. In many cases the histopathologic diagnosis from skin, lymph node, or visceral-lesion tissue has been difficult even in specialized hands.

The occurrence of *Pneumocystis carinii* pneumonia in patients who are not immunosuppressed due to known underlying disease or therapy is also highly unusual (*4*). Although 7 (11%) of the 61 patients with PCP also had KS, in many instances pneumonia preceded the tumor. Although most of the patients with PCP reported recent respiratory symptoms, some gave a history of weeks to months of systemic symptoms including weight loss and general malaise, similar to the prodrome described by patients who developed lymphadenopathic KS. Several of the patients with PCP had other serious infections, including gastrointestinal candidiasis, cryptococcal meningitis, and disseminated infections with Mycobacteriaceae and herpes simplex. Many of the PCP and KS patients have had positive cultures or serologic evidence of infection with cytomegalovirus.

The apparent clustering of both *Pneumocystis carinii* pneumonia and KS among homosexual men suggests a common underlying factor. Both diseases have been associated with host immunosuppression (*4-6*), and studies in progress are showing immunosuppression in some of these cases. The extent or cause of immune suppression is not known. Physicians should be aware of the possible occurrence of these diseases and other opportunistic infections, particularly among men with symptoms suggestive of these disorders or their prodromes, since therapy is specific and verification of the diagnosis requires biopsy.

Several state and local health departments and CDC are conducting active surveillance for KS, PCP, and opportunistic infections in persons without known predisposing underlying disease. A national case-control study will be implemented shortly.

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Persistent, Generalized Lymphadenopathy among Homosexual Males

Since October 1981, cases of persistent, generalized lymphadenopathy—not attributable to previously identified causes—among homosexual males have been reported to CDC by physicians in several major metropolitan areas in the United States. These reports were prompted by an awareness generated by ongoing CDC and state investigations of other emerging health problems among homosexual males (*1*).

In February and March 1982, records were reviewed for 57 homosexual men with lymphadenopathy seen at medical centers in Atlanta, New York City, and San Francisco. The cases reviewed met the following criteria: 1) lymphadenopathy of at least 3 months' duration, involving 2 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 the following characteristics: all were male, 81% were white, 15% black, and 4% Hispanic; 83% were single, 6% married, and 11% divorced. 86% were homosexual, 14% bisexual. The median duration of lymphadenopathy was 11 months. Ninety-five percent of patients had at least 3 node chains involved (usually cervical, axillary, and inguinal). Forty-three patients had had lymph node biopsies showing reactive hyperplasia. Approximately 70% of the patients had some constitutional symptoms including fatigue, 70%; fever, 49%; night sweats, 44%; and weight loss of ≥5 pounds, 28%. Hepatomegaly and/or splenomegaly was noted among 26% of patients.

Recorded medical histories for the 57 patients suggested that the use of drugs such as nitrite inhalants, marijuana, hallucinogens, and cocaine was common. Many of these patients have a history of sexually transmitted infections (gonorrhea 58%, syphilis 47%, and amebiasis 42%). Of 30 patients skin-tested for delayed hypersensitivity response, 8 were found to be anergic on the basis of at least 2 antigens other than purified protein derivative (PPD).

Immunologic evaluation performed at CDC for 8 of the above patients demonstrated abnormal T-lymphocyte helper-to-suppressor ratios (<0.9) for 2 patients. Since this review, immunologic evaluations at CDC of 13 additional homosexual males with lymphadenopathy from Atlanta and San Francisco revealed 6 with ratios of <0.9. The normal range of T-lymphocyte helper-to-suppressor ratios established in the CDC laboratory for healthy heterosexual patients is 0.9-3.5 (mean of 2.3). The normal range is being established for apparently healthy homosexual males.

Since the initiation of this study, 1 patient with lymphadenopathy has developed Kaposi's sarcoma.

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Editorial Note: The report above documents the occurrence of cases of unexplained, persistent, generalized lymphadenopathy among homosexual males. There are many known causes of generalized lymphadenopathy including viral infections (e.g., hepatitis B, infectious mononucleosis, cytomegalovirus infection, rubella), tuberculosis, disseminated *Mycobacterium avium-intracellulare*, syphilis, other bacterial and fungal infections, toxoplasmosis, connective tissue disorders, hypersensitivity drug reactions, heroin use, and neoplastic diseases (including leukemia and lymphoma) (*2*). Causes for the persistent lymphadenopathy among patients discussed above were sought but could not be identified.

This unexplained syndrome is of concern because of current reports of Kaposi's sarcoma (KS) and opportunistic infections (OI) that primarily involve homosexual males (*1,3*). Epidemiologic characteristics (age, racial composition, city of residence) of the homosexual patients with lymphadenopathy discussed here are similar to those of the homosexual KS/OI patients. Thirty-two (44%) of 73 Kaposi's sarcoma patients and 14 (23%) of 61 *Pneumocystis*

carinii pneumonia patients reported to CDC in the period mid-June 1981-January 1982 had a history of lymphadenopathy before diagnosis (3). *Mycobacterium avium-intracellulare* (an opportunistic agent) has been isolated from the lymph nodes of a homosexual patient (4). Moreover, the findings of anergy and depressed T-lymphocyte helper-to-suppressor ratios in some of the patients with lymphadenopathy suggest cellular immune dysfunction. Patients with KS/OI have had severe abnormalities of cellular immunity (5,6). The relationship between immunologic findings for patients with lymphadenopathy and patients with KS/OI remains to be determined.

Although these cases have been identified and defined on the basis of the presence of lymphadenopathy, this finding may be merely a manifestation of an underlying immunologic or other disorder that needs to be characterized further. Virologic and immunologic studies of many of these patients are currently under way. An analysis of trends in incidence for lymphadenopathy over the past several years is being conducted to determine whether this syndrome is new and whether homosexual males are particularly affected. Results of these studies and follow-up of these patients are necessary before the clinical and epidemiologic significance of persistent, generalized lymphadenopathy among homosexual males can be determined. Homosexual male patients with unexplained, persistent, generalized lymphadenopathy should be followed for periodic review.

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1982 June 4;31:277-79

Diffuse, Undifferentiated Non-Hodgkins Lymphoma among Homosexual Males — United States

A recent outbreak of Kaposi's sarcoma, *Pneumocystis carinii* pneumonia, and other opportunistic infections (KSOI) involving homosexual males and associated with an acquired cellular immunodeficiency syndrome has been described (1,2). While the pathogenesis of these disorders among homosexual males in San Francisco was being studied, 4 cases of diffuse, undifferentiated non-Hodgkins lymphoma (DUNHL) were diagnosed between March 1981 and January 1982. Because of the rarity of this malignancy and the potential relationship of these cases to the KSOI syndrome, they are reported here.

Patient 1: A 28-year-old hospital clerk complained of back and shoulder pain starting in early March 1981. Within a few days he had swelling of the right eye and an unsteady gait, and he was hospitalized on March 21. "Shotty" peripheral lymphadenopathy was present. A biopsy of an orbital mass and an enlarged cervical lymph node disclosed DUNHL. A myelogram revealed a T4-T6 block by an extradural mass. Radiation and chemotherapy led to complete remission. In September 1981, another tumor in the spinal cord was treated with radiation. The ensuing remission was temporary, and the patient died with disseminated DUNHL on January 15, 1982.

Patient 2: A 33-year-old nurse developed a tumor in his left lower jaw in October 1981. Penicillin was given for a suspected abscess, but the mass enlarged. A biopsy on November 24 disclosed DUNHL. Tumor cells contained surface IgM, kappa type, indicating a B-cell tumor. The tumor involved a left axillary lymph node, the retroperitoneum, the bone marrow, and the meninges. Generalized "reactive" lymphadenopathy and mild splenomegaly were present. Systemic and intrathecal chemotherapy led to temporary tumor regression; the patient relapsed and died in March 1982.

Patient 3: A 35-year-old janitor developed an enlarged cervical lymph node in October 1981. A dental extraction was performed for a suspected abscess, but lymphadenopathy persisted. A biopsy on December 12 revealed DUNHL. Tumor cells contained surface IgM, kappa type. Tumor was detected in the mediastinum, retroperitoneum, both kidneys, bone marrow, and meninges. Moderate generalized lymphadenopathy and splenomegaly were present. Systemic and intrathecal chemotherapy led to rapid tumor regression; however, this patient has recently relapsed.

Patient 4: A 24-year-old clerk developed backache and fatigue in November 1981. On January 21, 1982, an exploratory laparotomy showed DUNHL with extensive retroperitoneal involvement. Tumor cells contained surface IgM, kappa type. Combination chemotherapy has led to complete remission.

All these patients were homosexual males living in San Francisco. They had no known contact with each other, had no known sexual partners in common, and had no known contact with patients with Kaposi's sarcoma (KS). Each gave a history of a life style that included use of such drugs as nitrite inhalants, amphetamines, and marijuana. Medical histories indicated that all 4 patients had had 1 or more of such infections as hepatitis B, anal warts, gonorrhea, and syphilis. All patients had generalized lymphadenopathy, and 3 had splenomegaly of uncertain duration. Detailed virology and immunology studies are in progress.

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Editorial Note: Since July 1981, CDC has received reports of 162 cases of Kaposi's sarcoma among young homosexual males; the above report documents the possible appearance of a second unusual malignancy among this group of young males—i.e., DUNHL, a B-cell lymphoma (*3*).

The difficulty in distinguishing DUNHL histologically from Burkitt's lymphoma (BL) (*3*), a tumor often associated with Epstein-Barr virus, and the lack of consensus on the classification of non-Hodgkin's lymphoma (NHL) (*4*) make the precise determination of incidence difficult. About 0.7%-2.4% of all cases of NHL are DUNHL (*4,5*)—for a crude incidence rate of 0.06-0.21/100,000 population/year. No cases of DUNHL and only 1 case of BL were reported in 1977-1980 among 20-39 year olds to the Surveillance Epidemiology and End Results Cancer Registry in the San Francisco-Oakland-Standard Metropolitan Statistical Area, emphasizing the unusual occurrence of 4 cases within 10 months in the San Francisco homosexual male population. CDC has also recently received a report from Chicago of another case of DUNHL affecting a young homosexual male.

Underlying immune deficiency appears to be the common denominator for the development of the opportunistic infections and tumors associated with the KSOI syndrome (*6-8*). A similar syndrome, with an increased risk for NHL but a different time course and spectrum of opportunistic diseases, appears among renal allograft recipients (*4,9*). Lymphoreticular tumors also occur much more frequently among patients with primary immunodeficiency disorders (*4*). The cause of the acquired cellular immunodeficiency among homosexual males is being studied.

This report of DUNHL suggests that more than one kind of tumor may occur in association with the KSOI syndrome; assessment of these patients' immunologic findings will help to document the relationship between such tumors and the KSOI syndrome. The full range of potential outcomes (i.e., opportunistic tumors and infections) is probably only now being elucidated. There have also been recent case reports of other malignancies affecting the homosexual population, including carcinoma of the anal rectum (*10*) and squamous cell carcinoma of the oral cavity (*11;12*). The excess of carcinoma of the anus and anal rectum appears to antedate the onset of KSOI syndrome (*13*). The relationship between these malignancies and the KSOI syndrome is uncertain.

Many homosexual males with persistent, unexplained, generalized lymphadenopathy and biopsies reportedly demonstrating only reactive hyperplasia have also been reported to CDC and are under active investigation (*14*). Homosexual males with clinical findings similar to DUNHL or lymphadenopathic KS (*15*) should be carefully evaluated and followed.

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Update on Kaposi's Sarcoma and Opportunistic Infections in Previously Healthy Persons — United States

Between June 1, 1981, and May 28, 1982, CDC received reports of 355 cases* of Kaposi's sarcoma (KS) and/or serious opportunistic infections (OI), especially *Pneumocystis carinii* pneumonia (PCP), occurring in previously healthy persons between 15 and 60 years of age. Of the 355, 281 (79%) were homosexual (or bisexual) men, 41 (12%) were heterosexual men, 20 (6%) were men of unknown sexual orientation, and 13 (4%) were heterosexual women. This proportion of heterosexuals (16%) is higher than previously described (*1*).

Five states—California, Florida, New Jersey, New York, and Texas—accounted for 86% of the reported cases. The rest were reported by 15 other states. New York was reported as the state of residence for 51% of homosexual male patients, 49% of the heterosexual males, and 46% of the females. The median age at onset of symptoms was 36.0 years for homosexual men, 31.5 years for heterosexual men, and 29.0 years for women. The distribution of homosexual and heterosexual KSOI cases by date of onset is shown in Figure 2. Overall, 69% of all reported cases have had onset after January 1, 1981.

PCP accounted for a significantly higher proportion of the diagnoses for both male (63%) and female (73%) heterosexual patients than for homosexual patients (42%) ($p<0.05$). The ratio of homosexual to heterosexual males with PCP only, by year of onset of symptoms, was 5:1 in 1980, 3:1 in 1981 and 4:1 thus far in 1982. Reported case-fatality ratios for PCP cases with onset in 1980 and 1981 were 85% and 47%, respectively, for homosexual men and 67% and 41% for heterosexual men. The distribution of PCP cases by diagnosis, sexual orientation, race, and overall case-fatality ratio is shown in Table 1.

Both male and female heterosexual PCP patients were more likely than homosexual patients to be black or Hispanic ($p=0.0001$). Of patients with PCP for whom drug-use information was known, 14% of homosexual men had used intravenous drugs at some time compared with 63% of heterosexual men ($p=0.001$) and 57% of heterosexual women ($p=0.001$) (Table 1).

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Editorial Note: Sexual orientation information was obtained from patients by their physicians, and the accuracy of reporting cannot be determined; therefore, comparisons between KSOI cases made on the basis of sexual orientation must be interpreted cautiously. Similarities between homosexual and heterosexual cases in diagnoses and geographic and temporal distribution suggest that all are part of the same epidemic. Masur et al (*2*) also reported that lymphocyte dysfunction and lymphopenia were similar in heterosexual and homosexual cases of PCP. However, differences in race, proportion of PCP cases, and intravenous drug use suggest that risk factors may be different for these groups. A laboratory and interview study of heterosexual patients with diagnosed KS, PCP, or other OI is in progress to determine whether their cellular immune function, results of virologic studies, medical history, sexual practices, drug use, and life-style are similar to those of homosexual patients.

*A case is defined as illness in a person who 1) has either biopsy-proven KS or biopsy- or culture-proven, life-threatening opportunistic infection, 2) is under age 60, and 3) has no history of either immunosuppressive underlying illness or immunosuppressive therapy.

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FIGURE 2. Cases of KSOI by specific diagnosis, year of onset, sex, and sexual orientation, United States, 1978-1982

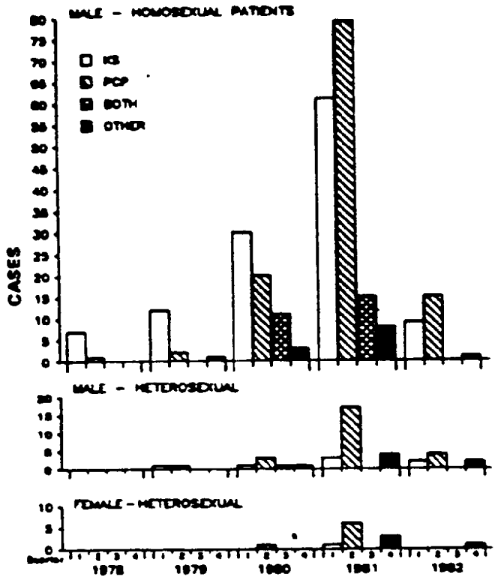

TABLE 1. Reported cases of *Pneumocystis carinii* pneumonia in previously healthy persons, June 1, 1981-May 28, 1982, United States

	Race					
	Total	White	Black	Hispanic	Case-fatality ratio	IV-Drug Use†
Homosexual men*	118	80	22	15	51%	11/80 (14%)
Heterosexual men*	26	8	11	6	35%	17/26 (65%)
Heterosexual women*	8	1	4	2	50%	4/7 (57%)

*Race data lacking for 1 case
†Data not available on all cases

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A Cluster of Kaposi's Sarcoma and *Pneumocystis carinii* Pneumonia among Homosexual Male Residents of Los Angeles and Orange Counties, California

In the period June 1, 1981-April 12, 1982, CDC received reports of 19 cases of biopsy-confirmed Kaposi's sarcoma (KS) and/or *Pneumocystis carinii* pneumonia (PCP) among previously healthy homosexual male residents of Los Angeles and Orange counties, California. Following an unconfirmed report of possible associations among cases in southern California, interviews were conducted with all 8 of the patients still living and with the close friends of 7 of the other 11 patients who had died.

indications for the cluster study

Data on sexual partners were obtained for 13 patients, 8 with KS and 5 with PCP. For any patient to be considered as a sexual contact of another person, the reported exposures of that patient had to be either substantiated or not denied by the other person involved in the relationship (or by a close friend of that person).

Within 5 years of the onset of symptoms, 9 patients (6 with KS and 3 with PCP) had had sexual contact with other patients with KS or PCP. Seven patients from Los Angeles County had had sexual contact with other patients from Los Angeles County, and 2 from Orange County had had sexual contact with 1 patient who was not a resident of California. Four of the 9 patients had been exposed to more than 1 patient who had KS or PCP. Three of the 6 patients with KS developed their symptoms after sexual contact with persons who already had symptoms of KS. One of these 3 patients developed symptoms of KS 9 months after sexual contact, another patient developed symptoms 13 months after contact, and a third patient developed symptoms 22 months after contact.

The other 4 patients in the group of 13 had no known sexual contact with reported cases. However, 1 patient with KS had an apparently healthy sexual partner in common with 2 persons with PCP; 1 patient with KS reported having had sexual contact with 2 friends of the non-Californian with KS; and 2 patients with PCP had most of their anonymous contacts (≥80%) with persons in bathhouses attended frequently by other persons in Los Angeles with KS or PCP.

The 9 patients from Los Angeles and Orange counties directly linked to other patients are part of an interconnected series of cases that may include 15 additional patients (11 with KS and 4 with PCP) from 8 other cities. The non-Californian with KS mentioned earlier is part of this series. In addition to having had sexual contact with 2 patients with KS from Orange County, this patient said he had sexual contact with 1 patient with KS and 1 patient with PCP from New York City and 2 of the 3 patients with PCP from Los Angeles County.

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Editorial Note: An estimated 185,000-415,000 homosexual males live in Los Angeles County.* Assuming that they had a median of 13.5 to 50 different sexual partners per year over the past 5 years,† the probability that 7 of 11 patients with KS or PCP would have sexual contact with any one of the other 16 reported patients in Los Angeles County would seem to be remote. The probability that 2 patients with KS living in different parts of Orange County would have sexual contact with the same non-Californian with KS would appear to be even lower. Thus, observations in Los Angeles and Orange counties imply the existence of an unexpected cluster of cases.

The cluster in Los Angeles and Orange counties was identified on the basis of sexual contact. One hypothesis consistent with the observations reported here is that infectious agents are being sexually transmitted among homosexually active males. Infectious agents not yet identified may cause the acquired cellular immuno-

*Estimates of the homosexual male population are derived from Kinsey *et al*(*1*) who reported that 8% of adult males are exclusively homosexual and that 18% have at least as much homosexual as heterosexual experience for at least 3 years between the ages of 16 and 55 years; and the U. S. Bureau of the Census, which reported that approximately 2,304,000 males between the ages of 18 and 64 years lived in Los Angeles County in 1980.

†Estimates of sexual activity are derived from data collected by Jay and Young (*2*), indicating that 130 homosexual male respondents in Los Angeles had a median of 13.5 different sexual partners in 1978, and from CDC data showing that 13 patients with KS and/or PCP in the Los Angeles area tended to report having more sexual partners in the year before onset of symptoms (median=50) than did homosexual males surveyed by Jay and Young.

deficiency that appears to underlie KS and/or PCP among homosexual males (3-6). If infectious agents cause these illnesses, sexual partners of patients may be at increased risk of developing KS and/or PCP.

Another hypothesis to be considered is that sexual contact with patients with KS or PCP does not lead directly to acquired cellular immunodeficiency, but simply indicates a certain style of life. The number of homosexually active males who share this lifestyle may be much smaller than the number of homosexual males in the general population.

Exposure to some substance (rather than an infectious agent) may eventually lead to immunodeficiency among a subset of the homosexual male population that shares a particular style of life. For example, Marmor et al. recently reported that exposure to amyl nitrite was associated with an increased risk of KS in New York City (7). Exposure to inhalant sexual stimulants, central-nervous-system stimulants, and a variety of other "street" drugs was common among males belonging to the cluster of cases of KS and PCP in Los Angeles and Orange counties.

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Opportunistic Infections and Kaposi's Sarcoma among Haitians in the United States

Reports of opportunistic infections and Kaposi's sarcoma among Haitians residing in the United States have recently been received at CDC. A total of 34 cases in 5 states have been reported to date.

Florida. From April 1, 1980, through June 20, 1982, 19 Haitian patients admitted to Jackson Memorial Hospital, Miami, had culture, biopsy, or autopsy evidence of opportunistic infections, and 1 other patient had biopsy- and autopsy-confirmed Kaposi's sarcoma. The infections identified included *Pneumocystis carinii* pneumonia (6 patients), cryptococcal meningitis or fungemia (4), toxoplasmosis of the central nervous system (CNS) (7), *Candida albicans* esophagitis (7) and thrush (5), esophageal or disseminated cytomegalovirus infection (3), progressive herpes simplex virus infection (1), disseminated tuberculosis (3), and chronic enteric *Isospora belli* infection (2). Fourteen patients had multiple opportunistic infections. Three patients had recurring infection. The clinical course has been severe; 10 patients have died. The type of infection was initially recognized at autopsy for 6 patients.

The 20 patients ranged in age from 22 to 43 years (mean 28.4 years); 17 were males. All the patients had been born in Haiti and had resided in the Miami-Dade County area for periods ranging from 1 month to 7 years (median 20.5 months).

When initially seen, 18 of the 20 patients had peripheral lymphopenia (< 1,000 lymphocytes/mm³). Skin tests performed on 17 patients with various combinations of tuberculin, mumps, streptokinase/streptodornase, *Candida*, and *Trichophyton* antigens were all negative. Immunologic studies at CDC on specimens from the 11 patients tested showed severe T-cell dysfunction. Monoclonal antibody analysis of peripheral-blood T-cell subsets revealed a marked decrease of the T-helper cell subset with inversion of the normal ratio of T-helper to T-suppressor cells.

Of the 7 patients with histologically confirmed toxoplasmosis of the CNS, 5 have died. Because there was no history of underlying conditions or drugs associated with immunosuppression, CNS toxoplasmosis was not considered in the premortem diagnosis of the first 4 cases. Pathology findings for all these patients were confirmed with an immuno-peroxidase method

for toxoplasmosis and, in one instance, with electron microscopy as well. Tachyzoites were the predominant form of the parasite observed; encysted forms were rare or absent in many tissue blocks.

In addition to the 20 cases reported from Miami, a Haitian female from Naples, Florida, was reported to have *P. carinii* pneumonia.

New York. From July 1, 1981, through May 31, 1982, 10 Haitian residents of Brooklyn were diagnosed as having the following opportunistic infections: *P. carinii* pneumonia (5 patients), CNS toxoplasmosis (2), disseminated cryptococcosis (1), esophageal candidiasis (1), and disseminated tuberculosis (2). None had any underlying disease or history of therapy known to cause immunosuppression. Five died of their infections.

All 10 patients were males and ranged in age from 22 to 37 years. Eight stated they were heterosexual; the sexual orientation of the other 2 was not known. One patient gave a history of intravenous (IV) drug abuse, 8 denied drug abuse, and for 1, no information was available on drug use. The 10 had resided in the United States for periods ranging from 3 months to 8 years (the majority, for 2 years or less). At least 1 patient had onset of illness before arriving in the United States. Immunologic studies performed at CDC on specimens from 2 patients showed results comparable to those for the 11 patients from Miami.

Other States. Opportunistic infections or Kaposi's sarcoma were also reported for 3 other Haitians located in California, Georgia, and New Jersey. All 3 were heterosexual males who denied IV drug abuse. One patient had *P. carinii* pneumonia, another had Kaposi's sarcoma, and the third had esophageal candidiasis.

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Editorial Note: The occurrence of severe opportunistic infections among 32 Haitians recently entering the United States is a new phenomenon. The in vitro immunologic findings and the high mortality rate (nearly 50%) for these patients are similar to the pattern recently described among homosexual males and IV drug abusers (*1-4*). None of the 23 Haitian males questioned reported homosexual activity, and only 1 of 26 gave a history of IV drug abuse—substantially lower than the prevalence reported for heterosexual patients of other racial/ethnic groups who had Kaposi's sarcoma or opportunistic infections. Of the 34 patients discussed above with opportunistic infections or Kaposi's sarcoma, 30 (88%) were males. All patients were between 20 and 45 years of age. Data from medical screening of 10,780 Haitians entering the United States between March and November 1980 indicated that 73% were adult males. Only 2% of those screened were <12 years old, and over 90% were <45 years old (*5*).

The occurrence of opportunistic infections among adult Haitians with no history of underlying immunosuppressive therapy or disease has not been reported previously. However, 11 cases of disseminated Kaposi's sarcoma have been diagnosed by dermatologists in Port au Prince, Haiti, over a period of 2 1/2 years (*6*). The reason for the high prevalence of disseminated tuberculosis among the group of patients discussed above is not known; but a high prevalence of tuberculosis has been documented among recent Haitian entrants (*7*), and the disease has been reported to disseminate more frequently among persons who are immunocompromised (*8,9*).

To date, it has not been established whether the cases of toxoplasmosis represent reactivation of old lesions acquired in Haiti or whether they are progressive primary infections acquired in the United States. However, serum specimens obtained from 2 patients in Miami and tested at CDC by indirect immuno-fluorescence (IIF) were negative for IgM antibody to *Toxoplasma*. This suggests that the infections of these 2 patients were not recently acquired. Serologic tests such as the IIF may be helpful in establishing or excluding a diagnosis of toxoplasmosis for patients with CNS symptoms. Tachyzoites in tissue specimens can be visualized more effectively using Giemsa stain or a recently developed immuno-peroxidase method (*10*) than with the standard hematoxylin and eosin staining.

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Pneumocystis carinii Pneumonia among Persons with Hemophilia A

CDC recently received reports of three cases of *Pneumocystis carinii* pneumonia among patients with hemophilia A and without other underlying disease. Two have died, one remains critically ill. All three were heterosexual males, none had a history of intravenous (IV) drug abuse. All had lymphopenia, and the two patients who were specifically tested have had *in vitro* laboratory evidence of cellular immune deficiency. The case reports follow.

Patient 1: A 62-year-old resident of Westchester County, New York, with a history of chronic hepatitis had received frequent injections of Factor VIII concentrate for severe hemophilia for many years. In February 1981 he began to experience weight loss and vague right upper quadrant abdominal discomfort associated with laboratory evidence of increasing hepatic dysfunction. In December 1981, while hospitalized in Miami, Florida, for elective knee surgery, he complained of cough and fever. He was lymphopenic, and chest X-ray revealed interstitial infiltrates compatible with viral pneumonia. He was discharged in late December after a brief course of corticosteroids associated with overall clinical improvement. He returned in severe respiratory distress a few days later. Open lung biopsy on January 5 revealed *P. carinii*, for which he received sulfamethoxazole/trimethoprim (SMZ/TMP) during the 2 weeks before death. *P. carinii* pneumonia and micronodular cirrhosis were documented at post-mortem examination.

Patient 2: A 59-year-old lifelong resident of Denver, Colorado, noted the onset of gradual weight loss, dysphagia associated with pharyngitis, aphthous-like ulcers, and anterior cervical adenopathy beginning in October 1980. As a patient with severe hemophilia, he had received frequent injections of Factor VIII concentrate for several years. Weight loss continued over a period of months. Oropharyngeal candidiasis was diagnosed in February 1982. He was hospitalized in May 1982 with symptoms including nausea, vomiting, and recurrent fever. Pneumonia was diagnosed, and *P. carinii* and cytomegalovirus (CMV) were repeatedly identified from lung tissue or bronchial secretions using histopathologic and culture techniques. Therapy with SMZ/TMP and pentamidine isethionate continued until death on July 5, 1982. Laboratory evidence for cellular immune dysfunction included absent mitogen responses and depletion of the T-helper lymphocyte cell population, relative increase in T-suppressor cells, and resultant inverted T-helper/T-suppressor ratio.

Patient 3: A previously healthy 27-year-old lifelong resident of northeastern Ohio developed fever, urinary frequency and urgency, and extreme lassitude in July 1981. He had frequently received parenteral Factor VIII concentrate for severe hemophilia. Bilateral pneumonia was diagnosed in October 1981, and open lung biopsy revealed *P. carinii*. He responded successfully to a 3-week course of SMZ/TMP. In February 1982, he received ketoconazole to suppress repeated episodes of oral candidiasis. He was hospitalized again in April with fever, splenomegaly, anemia, and lymphopenia. An extensive tumor work-up (including laparotomy) did not uncover an underlying malignancy. Cultures of bone marrow, liver, mesenteric lymph nodes, and blood grew *Mycobacterium avium*. *In vitro* immunological testing in March indicated a reduction in absolute number of circulating T-cells. Subsequent, more extensive testing documented the lack of lymphocyte responsiveness to mitogens, absolute and relative decrease in T-helper cells, relative increase in T-suppressor cells, and resultant inverted T-helper/T-suppressor ratio.

For each patient, records of the administration of Factor VIII concentrate were reviewed to determine manufacturer and lot numbers. No two of the patients are known to have received concentrate from the same lots.

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Editorial Note: *Pneumocystis carinii* pneumonia has not been previously reported among hemophilia patients who have had no other underlying diseases and have not had therapy commonly associated with immunosuppression. A review of the Parasitic Disease Drug Service's records of requests for pentamidine isethionate for 1980-1982 failed to identify hemophilia among the underlying disorders of patients for whom pentamidine was requested for *Pneumocystis carinii* therapy.

The clinical and immunologic features these three patients share are strikingly similar to those recently observed among certain individuals from the following groups: homosexual males, heterosexuals who abuse IV drugs, and Haitians who recently entered the United States (*1-3*). Although the cause of the severe immune dysfunction is unknown, the occurrence among the three hemophiliac cases suggests the possible transmission of an agent through blood products.

Hemophilia A is a sex-linked, inherited disorder characterized by a deficiency in Factor VIII activity. There are an estimated 20,000 patients with hemophilia A in the United States (*4*). Severity of disease is classified according to percentage of endogenous Factor VIII activity. Approximately 60% of the 20,000 are classified as severe, and 40% are classified as moderate (*4*). Factor VIII deficiency can be treated with intravenous administration of exogenous Factor VIII as either cryoprecipitate made from individual units of fresh frozen plasma or lyophilized Factor VIII concentrate manufactured from plasma pools collected from as many as a thousand or more donors.

CDC has notified directors of hemophilia centers about these cases and, with the National Hemophilia Foundation, has initiated collaborative surveillance. A Public Health Service advisory committee is being formed to consider the implication of these findings. Physicians diagnosing opportunistic infections in hemophilia patients who have not received antecedent immunosuppressive therapy are encouraged to report them to the CDC through local and state health departments.

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1982 Sept 3;31:465–67

Hepatitis B Virus Vaccine Safety: Report of an Inter-Agency Group

On June 25, 1982, the Immunization Practices Advisory Committee (ACIP) recommended using inactivated hepatitis B virus (HBV) vaccine for individuals who are at high risk for HBV infection because of their geographic origins, life styles, or exposures to HBV at home or work (*1*). The recommendations included statements on vaccine efficacy and safety. However, requests for additional information on safety continue to be received, primarily because of the plasma origins of the antigen used to prepare the vaccine. In response to these requests, the Inter-Agency Group to Monitor Vaccine Development, Production, and Usage, with representatives from the Centers for Disease Control (CDC), Food and Drug Administration (FDA), and National Institutes of Health (NIH), has further reviewed the available data. Its conclusions on vaccine production and safety evaluation follow.

HBV vaccine licensed in the United States is prepared from human plasma containing hepatitis surface antigen (HBsAg) (*2*). Hypothetical side effects from the vaccine include reactions to blood substances or to infectious agents present in donor plasma. In trials involving approximately 1900 persons, reactions among vaccine recipients were compared with reactions among placebo recipients, and only minor immediate complaints, primarily of soreness at the injection site, were observed (*3,4*). Infectious agents that might be present in donor plasma are most likely to be viruses. Virus transmission by blood or blood products requires the virus to circulate in plasma or in cellular elements such as leukocytes. The chance of virus transmission increases with the duration of the viremic state. HBV is the only well-characterized extra-cellular human virus with a prolonged carrier state. Other agents, presumably viruses, which remain unidentified despite their common association with post-transfusion hepatitis, are responsible for non-A/non-B hepatitis.

Beginning in 1978, a disease or group of diseases was recognized, manifested by Kaposi's sarcoma and opportunistic infections, associated with a specific defect in cell-mediated immunity. This group of clinical entities, along with its specific immune deficiency, is now called acquired immune deficiency syndrome (AIDS). The epide-

miology of AIDS suggests an unidentified and uncharacterized blood-borne agent as a possible cause of the underlying immunologic defect (*5-7*). Because AIDS occurs among populations that are sources of HBV-positive plasma, this syndrome should be considered in regard to the inherent safety of HBV vaccine.

Vaccine plasma donors are screened, and only healthy individuals (HBsAg positive) are selected. The plasmapheresis centers are licensed and inspected by the FDA. A physician gives each donor a complete physical examination, which includes a history and suitable laboratory tests. At the time of each donation, the donor's hemoglobin, hematocrit, and serum protein levels must be within normal limits. HBsAg-positive donors' levels of serum aminotransferase activity are permitted to exceed those limits set for otherwise healthy donors, but they must be stable.

The process for producing each lot of licensed HBV vaccine is designed to remove or inactivate infectious HBV and other viruses from the desired immunogen, the 22 nm HBsAg particle. The process relies on both biophysical elimination of infectious particles and treatments which inactivate viruses (pepsin at pH 2, 8M urea, and formalin). The elimination of infectious virus by biophysical purification depends on the density and flotational property of HBsAg in contrast with those of infectious virus particles. The double ultracentrifugation process (isopyknic and rate zonal) has been proven effective in removing 10^4 infectious doses of HBV/ml, as measured by chimpanzee inoculation (*8*). Pepsin treatment alone (1 μg/ml, pH 2.0, 37 C for 18 hours) inactivates 10^5 or more infectious doses of HBV/ml, as measured by chimpanzee inoculation, and has been shown to inactivate viruses in the rhabdovirus, poxvirus, togavirus, reovirus, herpesvirus and coronavirus groups (*9, 10*). Urea treatment alone (8M, 37 C for four hours) inactivates 10^5 or more infectious doses of HBV/ml and has been shown to inactivate viruses in the rhabdovirus, myxovirus, poxvirus, togavirus, reovirus, picornavirus, herpesvirus, and coronavirus groups (*9*). Slow viruses, characterized by the viruses of kuru and Creutzfeld-Jakob disease, are inactivated by 6M urea, a lesser concentration than that routinely applied to the HBV vaccine (*11*). Formalin alone inactivates HBV (*9*), as well as many other virus groups, including parvoviruses (*12*), retroviruses (*13, 14*) and the delta agent (*15*).

Each lot of HBV vaccine is tested for sterility, innocuousness in animals, and pyrogenicity and is free of detectable viruses, as shown by inoculation into both human and monkey cell-culture systems. Additionally, 22 doses of each vaccine lot are inoculated intravenously into four chimpanzees.

United States licensed vaccine (produced by Merck, Sharp, and Dohme) has been given to over 19,000 persons, 6,000 of whom received vaccine between October 1975 and December 1981 and 13,000 of whom received it in 1982. The vaccine has been demonstrated to protect recipients from HBV infection (*3,4*), and no evidence of hepatitis has been observed as a result of HBV vaccination. Also, studies by CDC, FDA, and others of aminotransferase levels in chimpanzees and humans confirm that HBV vaccine does not transmit the non-A/non-B agent(s).

In three vaccine-placebo trials (two among homosexual men between 1978 and 1980 [*3,4*] and one among hospital employees in 1981), 549, 714, and 664 persons, respectively, received vaccine, and equal numbers received placebo. Follow-up surveillance of participants in these studies was 24, 15, and 18 months, respectively, after the first dose of vaccine with no cases of AIDS being reported. In addition to the vaccine/placebo trials, 17,602 persons (including 8,941 health-care workers and 5,985 healthy adults, children, and infants from non-high-risk group settings) have received Merck HBV vaccine in various study settings. Periods of follow-up of these vaccine recipients have ranged from a few months to over 7 years. However, lots used in early studies may have been produced before the occurrence of AIDS. Some of the groups from which HBV vaccine is prepared or for which it is recommended are also at high risk for AIDS; therefore reports of AIDS among donors and vaccinees at some future time may be expected on the basis of chance alone.

To summarize, these findings support the ACIP statement on hepatitis vaccine: 1) immediate side effects are minimal after receipt of HBV vaccine; 2) no long-term reac-

tions have been reported; 3) the purification and inactivation process is known to inactivate representatives of all known groups of animal viruses; 4) each lot is safety tested in primates; 5) no known cases of hepatitis B or non-A/non-B hepatitis have been transmitted by the vaccine and no known occurrence of AIDS has been associated with the vaccine.

Reported by the Inter-Agency Group to Monitor Vaccine Development, Production, and Usage, represented by the Centers for Disease Control, Food and Drug Administration, and National Institutes of Health.

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Update on Acquired Immune Deficiency Syndrome (AIDS) — United States

Between June 1, 1981, and September 15, 1982, CDC received reports of 593 cases of acquired immune deficiency syndrome (AIDS).* Death occurred in 243 cases (41%).

Analysis of reported AIDS cases shows that 51% had *Pneumocystis carinii* pneumonia (PCP) without Kaposi's sarcoma (KS) (with or without other "opportunistic" infections [OOI] predictive of cellular immunodeficiency); 30% had KS without PCP (with or without OOI), 7% had both PCP and KS (with or without OOI); and 12% had OOI with neither PCP nor KS. The overall mortality rate for cases of PCP without KS (47%) was more than twice that for cases of KS without PCP (21%), while the rate for cases of both PCP and KS (68%) was more than three times as great. The mortality rate for OOI with neither KS nor PCP was 48%.

The incidence of AIDS by date of diagnosis (assuming an almost constant population at risk) has roughly doubled every half-year since the second half of 1979 (Table 1). An average of one to two cases are now diagnosed every day. Although the overall case-mortality rate for the current total of 593 is 41%, the rate exceeds 60% for cases diagnosed over a year ago.

Almost 80% of reported AIDS cases in the United States were concentrated in six metropolitan areas, predominantly on the east and west coasts of the country (Table 2). This distribution was not simply a reflection of population size in those areas; for example, the number of cases per million population reported from June 1, 1981, to September 15, 1982, in New York City and San Francisco was roughly 10 times greater than that of the entire country. The 593 cases

*Formerly referred to as Kaposi's sarcoma and opportunistic infections in previously healthy persons (7).

were reported among residents of 27 states and the District of Columbia, and CDC has received additional reports of 41 cases from 10 foreign countries.

Approximately 75% of AIDS cases occured among homosexual or bisexual males (Table 3), among whom the reported prevalence of intravenous drug abuse was 12%. Among the 20% of known heterosexual cases (males and females), the prevalence of intravenous drug abuse was about 60%. Haitians residing in the United States constituted 6.1% of all cases (2), and 50% of the cases in which both homosexual activity and intravenous drug abuse were denied. Among the 14 AIDS cases involving males under 60 years old who were not homosexuals, intravenous drug abusers, or Haitians, two (14%) had hemophilia A [†] (3).

Reported AIDS cases may be separated into groups based on these risk factors: homosexual or bisexual males—75%, intravenous drug abusers with no history of male homosexual activity—13%, Haitians with neither a history of homosexuality nor a history of intravenous drug abuse—6%, persons with hemophilia A who were not Haitians, homosexuals, or intravenous drug abusers—0.3%, and persons in none of the other groups—5%.

Reported by the Task Force on Acquired Immune Deficiency Syndrome, CDC

Editorial Note: CDC defines a case of AIDS as a disease, at least moderately predictive of a defect in cell-mediated immunity, occurring in a person with no known cause for diminished resistance to that disease. Such diseases include KS, PCP, and serious OOI.[§] Diagnoses are considered to fit the case definition only if based on sufficiently reliable methods (generally histology or culture). However, this case definition may not include the full spectrum of AIDS manifestations, which may range from absence of symptoms (despite laboratory evidence of immune deficiency) to non-specific symptoms (e.g., fever, weight loss, generalized, persistent lymphadenopathy) (4) to specific diseases that are insufficiently predictive of cellular immunodeficiency to be included in incidence monitoring (e.g., tuberculosis, oral candidiasis, herpes zoster) to malignant neoplasms that cause, as well as result from, immunodeficiency[¶] (5). Conversely, some patients who are considered AIDS cases on the basis of diseases only moderately predictive of cellular immunodeficiency may not actually be immunodeficient and may not be part of the current epidemic. Absence of a reliable, inexpensive, widely available test for AIDS, however, may make the working case definition the best currently available for incidence monitoring.

Two points in this update deserve emphasis. First, the eventual case-mortality rate of AIDS, a few years after diagnosis, may be far greater than the 41% overall case-mortality rate noted above. Second, the reported incidence of AIDS has continued to increase rapidly. Only a small percentage of cases have none of the identified risk factors (male homosexuality, intravenous drug abuse, Haitian origin, and perhaps hemophilia A). To avoid a reporting bias, physicians should report cases regardless of the absence of these factors.

TABLE 1. Reported cases and case-mortality rates of AIDS, by half-year of diagnosis,* 1979-1982, (as of September 15, 1982) — United States

Half-year of diagnosis		Cases	Deaths	Case-mortality rate (%)
1979	1st half	1	1	100
	2nd half	6	5	83
1980	1st half	17	13	76
	2nd half	26	22	85
1981	1st half	86	46	70
	2nd half	141	79	56
1982	1st half	249	67	27

*Excluding 4 cases with unknown dates of diagnosis.

[†] A third hemophiliac with pneumocystosis exceeded the 60-year age limit of the AIDS case definition.

[§] These infections include pneumonia, meningitis, or encephalitis due to one or more of the following: aspergillosis, candidiasis, cryptococcosis, cytomegalovirus, nocardiosis, strongyloidosis, toxoplasmosis, zygomycosis, or atypical mycobacteriosis (species other than tuberculosis or lepra), esophagitis due to candidiasis, cytomegalovirus, or herpes simplex virus, progressive multifocal leukoencephalopathy, chronic enterocolitis (more than 4 weeks) due to cryptosporidiosis, or unusually extensive mucocutaneous herpes simplex of more than 5 weeks duration.

[¶] CDC encourages reports of any cancer among persons with AIDS and of selected rare lymphomas (Burkitt's or diffuse, undifferentiated non-Hodgkins lymphoma) among persons with a risk factor for AIDS. This differs from the request for reports of AIDS cases regardless of the absence of risk factors.

Physicians aware of patients fitting the case definition for AIDS are requested to report such cases to CDC through their local or state health departments.

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4. CDC Persistent, generalized lymphadenopathy among homosexual males MMWR 1982;31:249-51.
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TABLE 2. AIDS cases per million population,* by standard metropolitan statistical area (SMSA) of residence, reported from June 1, 1981 to September 15, 1982 — United States

SMSA of residence	Cases	Percentage of total	Cases per million population
New York, N.Y.	288	48.6	31.6
San Francisco, Calif.	78	13.2	24.0
Miami, Fla.	31	5.2	19.1
Newark, N.J.	15	2.5	7.6
Houston, Texas	15	2.5	5.2
Los Angeles, Calif.	37	6.2	4.9
Elsewhere (irrespective of SMSA)	129	21.8	0.6
Total	593	100.0	2.6

*From the 1980 Census

TABLE 3. Cases of AIDS, by sexual orientation and intravenous drug abuse, reported from June 1, 1981, to September 15, 1982 — United States

Sex	Sexual orientation	Cases	Percentage distribution by sexual orientation	Intravenous drug abuse*			Percentage using IV drugs†
				Yes	No	Unknown	
Male	Homosexual or bisexual	445	75.0	42	300	103	12.3
	Heterosexual	84	14.2	49	33	2	59.8
	Unknown	30	5.1	11	11	8	50.0
Female	Heterosexual	34	5.7	20	12	2	62.5
Total		593	100.0	122	356	115	25.5

*Regardless of when the last such activity occurred

†Excluding cases with unknown history of IV drug abuse

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Acquired Immune Deficiency Syndrome (AIDS): Precautions for Clinical and Laboratory Staffs

The etiology of the underlying immune deficiencies seen in AIDS cases is unknown. One hypothesis consistent with current observations is that a transmissible agent may be involved. If so, transmission of the agent would appear most commonly to require intimate, direct contact involving mucosal surfaces, such as sexual contact among homosexual males, or through parenteral spread, such as occurs among intravenous drug abusers and possibly hemophilia patients using Factor VIII products. Airborne spread and interpersonal spread through casual contact do not seem likely. These patterns resemble the distribution of disease and modes of spread of hepatitis B virus, and hepatitis B virus infections occur very frequently among AIDS cases.

There is presently no evidence of AIDS transmission to hospital personnel from contact with affected patients or clinical specimens. Because of concern about a possible transmissible agent, however, interim suggestions are appropriate to guide patient-care and laboratory personnel, including those whose work involves experimental animals. At present, it appears

prudent for hospital personnel to use the same precautions when caring for patients with AIDS as those used for patients with hepatitis B virus infection, in which blood and body fluids likely to have been contaminated with blood are considered infective. Specifically, patient-care and laboratory personnel should take precautions to avoid direct contact of skin and mucous membranes with blood, blood products, excretions, secretions, and tissues of persons judged likely to have AIDS. The following precautions do not specifically address outpatient care, dental care, surgery, necropsy, or hemodialysis of AIDS patients. In general, procedures appropriate for patients known to be infected with hepatitis B virus are advised, and blood and organs of AIDS patients should not be donated.

The precautions that follow are advised for persons and specimens from persons with: opportunistic infections that are not associated with underlying immunosuppressive disease or therapy; Kaposi's sarcoma (patients under 60 years of age); chronic generalized lymphadenopathy, unexplained weight loss and/or prolonged unexplained fever in persons who belong to groups with apparently increased risks of AIDS (homosexual males, intravenous drug abusers, Haitian entrants, hemophiliacs); and possible AIDS (hospitalized for evaluation). Hospitals and laboratories should adapt the following suggested precautions to their individual circumstances; these recommendations are not meant to restrict hospitals from implementing additional precautions.

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

1. Extraordinary care must be taken to avoid accidental wounds from sharp instruments contaminated with potentially infectious material and to avoid contact of open skin lesions with material from AIDS patients.
2. Gloves should be worn when handling blood specimens, blood-soiled items, body fluids, excretions, and secretions, as well as surfaces, materials, and objects exposed to them.
3. Gowns should be worn when clothing may be soiled with body fluids, blood, secretions, or excretions.
4. Hands should be washed after removing gowns and gloves and before leaving the rooms of known or suspected AIDS patients. Hands should also be washed thoroughly and immediately if they become contaminated with blood.
5. Blood and other specimens should be labeled prominently with a special warning, such as "Blood Precautions" or "AIDS Precautions." If the outside of the specimen container is visibly contaminated with blood, it should be cleaned with a disinfectant (such as a 1:10 dilution of 5.25% sodium hypochlorite [household bleach] with water). All blood specimens should be placed in a second container, such as an impervious bag, for transport. The container or bag should be examined carefully for leaks or cracks.
6. Blood spills should be cleaned up promptly with a disinfectant solution, such as sodium hypochlorite (see above).
7. Articles soiled with blood should be placed in an impervious bag prominently labeled "AIDS Precautions" or "Blood Precautions" before being sent for reprocessing or disposal. Alternatively, such contaminated items may be placed in plastic bags of a particular color 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 needle-syringe units should be used to aspirate fluids from patients, so that collected fluid can be safely discharged through the needle, if desired. If reusable syringes are employed, they should be decontaminated before reprocessing.
10. A private room is indicated for patients who are too ill to use good hygiene, such as those with profuse diarrhea, fecal incontinence, or altered behavior secondary to central nervous system infections.

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

B. The following precautions are advised for persons performing laboratory tests or studies on clinical specimens or other potentially infectious materials (such as inoculated tissue

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cultures, embryonated eggs, animal tissues, etc.) from known or suspected AIDS cases

1. Mechanical pipetting devices should be used for the manipulation of all liquids in the laboratory. Mouth pipetting should not be allowed.
2. Needles and syringes should be handled as stipulated in Section A (above).
3. Laboratory coats, gowns, or uniforms should be worn while working with potentially infectious materials and should be discarded appropriately before leaving the laboratory.
4. Gloves should be worn to avoid skin contact with blood, specimens containing blood, blood-soiled items, body fluids, excretions, and secretions, as well as surfaces, materials, and objects exposed to them.
5. All procedures and manipulations of potentially infectious material should be performed carefully to minimize the creation of droplets and aerosols.
6. Biological safety cabinets (Class I or II) and other primary containment devices (e.g., centrifuge safety cups) are advised whenever procedures are conducted that have a high potential for creating aerosols or infectious droplets. These include centrifuging, blending, sonicating, vigorous mixing, and harvesting infected tissues from animals or embryonated eggs. Fluorescent activated cell sorters generate droplets that could potentially result in infectious aerosols. Translucent plastic shielding between the droplet-collecting area and the equipment operator should be used to reduce the presently uncertain magnitude of this risk. Primary containment devices are also used in handling materials that might contain concentrated infectious agents or organisms in greater quantities than expected in clinical specimens.
7. Laboratory work surfaces should be decontaminated with a disinfectant, such as sodium hypochlorite solution (see A5 above), following any spill of potentially infectious material and at the completion of work activities.
8. All potentially contaminated materials used in laboratory tests should be decontaminated, preferably by autoclaving, before disposal or reprocessing.
9. All personnel should wash their hands following completion of laboratory activities, removal of protective clothing, and before leaving the laboratory.

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

1. Laboratory coats, gowns, or uniforms should be worn by personnel entering rooms housing inoculated animals. Certain nonhuman primates, such as chimpanzees, are prone to throw excreta and to spit at attendants; personnel attending inoculated animals should wear molded surgical masks and goggles or other equipment sufficient to prevent potentially infective droplets from reaching the mucosal surfaces of their mouths, nares, and eyes. In addition, when handled, other animals may disturb excreta in their bedding. Therefore, the above precautions should be taken when handling them.
2. Personnel should wear gloves for all activities involving direct contact with experimental animals and their bedding and cages. Such manipulations should be performed carefully to minimize the creation of aerosols and droplets.
3. Necropsy of experimental animals should be conducted by personnel wearing gowns and gloves. If procedures generating aerosols are performed, masks and goggles should be worn.
4. Extraordinary care must be taken to avoid accidental sticks or cuts with sharp instruments contaminated with body fluids or tissues of experimental animals inoculated with material from AIDS patients.
5. Animal cages should be decontaminated, preferably by autoclaving, before they are cleaned and washed.
6. Only needle-locking syringes or one-piece needle-syringe units should be used to inject potentially infectious fluids into experimental animals.

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

Reported by Hospital Infections Program, Div of Viral Diseases, Div of Host Factors, Div of Hepatitis and Viral Enteritis, AIDS Activity, Center for Infectious Diseases, Office of Biosafety, CDC; Div of Safety, National Institutes of Health.

201208

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Cryptosporidiosis: Assessment of Chemotherapy of Males with Acquired Immune Deficiency Syndrome (AIDS)

Since December 1979, 21 males with severe, protracted diarrhea caused by the parasite, *Cryptosporidium*, have been reported to CDC by physicians in Boston, Los Angeles, Newark, New York, Philadelphia, and San Francisco. All 21 have acquired immune deficiency syndrome (AIDS); 20 are homosexual; and one is a heterosexual Haitian. Their ages range from 23 to 62 years with a mean of 35.7 years. Most had other opportunistic infections or Kaposi's sarcoma in addition to cryptosporidiosis. Eleven had *Pneumocystis carinii* pneumonia (PCP); nine had Candida esophagitis; two had a disseminated *Mycobacterium avium-intracellulare* infection; one had a disseminated cytomegalovirus infection; and two had Kaposi's sarcoma. T-lymphocyte helper-to-suppressor ratios were decreased (< 0.9) in all 18 patients on whom this test was performed. Fourteen patients have died.

The illness attributed to *Cryptosporidium* was characterized by chronic, profuse, watery diarrhea. The mean duration of diarrhea was 4 months, often continuing until the patient's death. Bowel movement frequency ranged from six to 25 per day. The estimated maximum volume of stool during illness ranged from 1 to 17 liters per day with a mean of 3.8 liters per day. Diagnosis of cryptosporidiosis was made by histologic examination of small bowel biopsies (13 patients) or large bowel biopsies (four patients), or by stool examination using a sucrose concentration technique (16 patients) (*1*). More than one type of diagnostic method was positive for several patients.

Table 1 shows the drugs given to the 21 patients while they had diarrhea attributed to *Cryptosporidium*. Only two patients (9.5%) have had sustained resolution of their diarrhea with negative follow-up stool examinations. The first was being treated with prednisone (60 mg daily) for chronic active hepatitis at the time his diarrhea began. When cryptosporidiosis was diagnosed, he was started on diloxanide furoate (500 mg three times daily for 10 days), and the prednisone was tapered over 2 weeks and then stopped. Two weeks later, his diarrhea was improving; in another 2 weeks, his diarrhea had completely resolved. He has had no diarrhea for 8 months. Follow-up stool examinations 2 weeks and 6 weeks after discontinuation of diloxanide furoate were negative for *Cryptosporidium*.

The second patient, who also had a clinical and parasitologic response, subsequently died of PCP. In early February 1982, 6 months before his death, he had onset of watery diarrhea, and a small bowel biopsy showed *Cryptosporidium*. Treatment with furazolidone (100 mg four times a day) was initiated on May 5, and within 6 days, the patient had gained 1.1 kilograms (2.4 pounds); parenteral nutrition was discontinued, although he continued to produce a liter of watery stool each day. Ten days after treatment was started, his stools became formed for the first time in 4 months, but *Cryptosporidium* oocysts were still present. Furazolidone was increased to 150 mg four times daily. Twenty days after therapy was started (10 days after the higher dose of furazolidone was begun), the patient had one bowel movement a day, but his stool was still positive for *Cryptosporidium* and remained positive despite continued use of furazolidone at 150 mg four times daily for a total of 2 months. At that time, two stool examinations failed to detect oocysts, and the furazolidone was stopped. One week later, the patient developed PCP; despite treatment with trimethoprim-sulfamethoxazole, he died 2 weeks later on July 22. An autopsy was not permitted.

After various treatment regimens, seven patients have had partial or transitory decreases in their diarrhea. Two received no anti-parasitic drugs. A third patient temporarily improved after treatment with furazolidone (100 mg orally four times a day for 7 days), although 2 weeks elapsed between the end of treatment with furazolidone and the onset of clinical improvement. The patient's diarrhea abated, but follow-up stool examinations remained positive for *Cryptosporidium*. Three months after furazolidone therapy, he again developed diarrhea, and his stools were positive for *Cryptosporidium*. Two patients had less diarrhea when given tetracycline. The first received tetracycline 500 mg orally four times a day for 4 months. His diarrhea decreased from 12 watery stools to three loose stools per day, but stool examination after 4 months of therapy still showed *Cryptosporidium*. The second patient, given the same treatment, also had a reduction in the number of stools. When the drug was discontinued, his diarrhea again increased.

Two patients' diarrhea stopped following treatment with opiates and metronidazole, given orally in one case and intravenously in the other. Neither patient had diarrhea after a few days of treatment, but both died within 1 week, and autopsies were not allowed. The first patient died from suspected peritonitis; the second died with disseminated Kaposi's sarcoma and pneumonia.

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The remaining 12 patients have had continuous, severe diarrhea. In addition to the drugs listed in Table 1, bovine-transfer factor has been given to one patient and intravenous gamma globulin to two patients; neither was effective. At present, 14 (66.7%) of the 21 individuals have died, and six are alive with persistent diarrhea. In no instance was cryptosporidiosis thought to be the direct cause of death, but the associated severe malnutrition was often considered a contributing factor.

Shortly before cryptosporidiosis was recognized in AIDS patients, investigators at the U.S Department of Agriculture National Animal Disease Center (NADC) began testing drugs for efficacy against *Cryptosporidium* in animals; results of these initial studies were published in February, 1982 (2). More recently, five additional drugs have been evaluated at the NADC. Calves or pigs up to 14 days old without infection were given the drugs orally twice daily. One day after the drugs were started, each animal received a single oral inoculation of *Cryptosporidium*. The following drugs (with doses in mg/kg/day) were tested: amprolium (10.7), difluoromethylornithine (1250) plus bleomycin (6 IM), diloxanide furoate (125.0), dimetridazole (19.0), ipronidazole (23.8), lasalocid (0.7), metronidazole (23.8), monensin (4.8), oxytetracycline (50.0), pentamidine (10.0), quinacrine (11.9), salinomycin (6.0), sulfaquinoxaline (200.0), sulfadimidine (119.0), and trimethoprim (4.8) plus sulfadiazine (23.8). Although small numbers of animals were tested in each treatment group, no drugs prevented fecal shedding of oocysts or reduced the number of *Cryptosporidium* seen on intestinal biopsies.

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TABLE 1. Drugs used to treat males with cryptosporidiosis and AIDS

Drug*	Dose and route of administration†	Number of patients	Unchanged n	Unchanged (%)	Improved‡ n	Improved (%)	Cured¶ n	Cured (%)
No treatment	–	2	0	(0.0)	2	(100.0)	0	(0.0)
Trimethoprim/ sulfamethoxazole	25 mg/kg QID of sulfamethoxazole	7	7	(100.0)	0	(0.0)	0	(0.0)
Trimethoprim/ sulfamethoxazole	800 mg PO BID of sulfamethoxazole	4	4	(100.0)	0	(0.0)	0	(0.0)
Furazolidone	100 mg PO QID	6	4	(66.7)	1	(16.7)	1	(16.7)
Furazolidone	300 mg PO QID	1	1	(100.0)	0	(0.0)	0	(0.0)
Metronidazole	750 mg PO TID	5	4	(80.0)	1	(20.0)	0	(0.0)
Metronidazole	750 mg IV TID	1	0	(0.0)	1	(100.0)	0	(0.0)
Pyrimethamine/ sulfa	25 mg PO per day of pyrimethamine	4	4	(100.0)	0	(0.0)	0	(0.0)
Diloxanide furoate	500 mg PO TID	3	2	(66.7)	0	(0.0)	1**	(33.3)
Quinacrine	100 mg PO TID	3	3	(100.0)	0	(0.0)	0	(0.0)
Diiodohydroxyquin	650 mg PO TID	2	2	(100.0)	0	(0.0)	0	(0.0)
Tetracycline	500 mg PO QID	3	1	(33.3)	2	(66.6)	0	(0.0)
Doxycycline	100 mg PO per day	2	2	(100.0)	0	(0.0)	0	(0.0)
Pentamidine	4 mg/kg IM per day	2	2	(100.0)	0	(0.0)	0	(0.0)
Chloroquine/ primaquine	500 mg PO per day of chloroquine	1	1	(100.0)	0	(0.0)	0	(0.0)

*Some patients received more than one drug.

†BID = twice daily; TID = three times daily; QID = four times daily; PO = orally; IV = intravenously

‡Decrease in number of stools by at least 50%.

¶Absence of diarrhea for more than 2 weeks and stool examination negative for *Cryptosporidium*.

**Improvement temporally related to stopping prednisone.

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Editorial Note: *Cryptosporidium* is a protozoan parasite; it is a well recognized cause of diarrhea in animals, especially calves, but has only rarely been associated with diarrhea in humans (*3*). Individuals with normal immune function who have developed cryptosporidiosis have self-limited diarrhea lasting 1-2 weeks, but immunosuppressed individuals have developed chronic diarrhea. An effective drug to treat cryptosporidiosis has not been identified, and the above reports are equally discouraging. Of seven patients who are still living, only one has no diarrhea at present. His recovery coincided with treatment with diloxanide furoate and discontinuation of prednisone. It seems unlikely that diloxanide furoate was responsible for his recovery, since three other patients who received the drug did not respond, and the drug was ineffective in experimentally infected pigs given nearly six times the recommended human dose. It is similarly difficult to be certain that improvement reported in other patients was due to the drugs they received because only a few patients receiving a drug responded, responses were brief, and the same or similar drugs were ineffective in preventing infection in experimental animals. The difficulty in interpreting isolated responses is underscored by the two patients who improved before any specific therapy began.

Since none of the drugs reported above appears clearly efficacious, additional tests of other anti-parasitic drugs in animals are needed. Until an effective drug for cryptosporidiosis is identified or the underlying immune deficiency in patients with AIDS becomes correctable, management of diarrhea due to cryptosporidiosis will continue to focus on supportive care.

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Update on Acquired Immune Deficiency Syndrome (AIDS) among Patients with Hemophilia A

In July 1982, three heterosexual hemophilia A patients, who had developed *Pneumocystis carinii* pneumonia and other opportunistic infections, were reported (*1*). Each had in vitro evidence of lymphopenia and two patients who were specifically tested had evidence of T-lymphocyte abnormalities. All three have since died. In the intervening 4 months, four additional heterosexual hemophilia A patients have developed one or more opportunistic infections accompanied by in-vitro evidence of cellular immune deficiency; these four AIDS cases and one highly suspect case are presented below. Data from inquiries about the patients' sexual activities, drug usage, travel, and residence provide no suggestion that disease could have been acquired through contact with each other, with homosexuals, with illicit drug abusers, or with Haitian immigrants—groups at increased risk for AIDS compared with the general U.S. population. All these patients have received Factor VIII concentrates, and all but one have also received other blood components.

Case 1: A 55-year-old severe hemophiliac from Alabama developed anorexia and progressive weight loss beginning in September 1981. He had developed adult-onset diabetes mellitus in 1973, which had required insulin therapy since 1978. He had had acute hepatitis (type unknown) in 1975. In March 1982, he was hospitalized for herpes zoster and a 17-kg weight loss. Hepatosplenomegaly was noted. The absolute lymphocyte count was 450/mm^3. Liver enzymes were elevated; antibodies to hepatitis B core and surface antigens were present. A liver biopsy showed changes consistent with persistent hepatitis. Evaluation for an occult malignancy was negative. The zoster resolved following 5 days of adenosine arabinoside therapy.

In early June, he was readmitted with fever and respiratory symptoms. Chest x-ray showed bibasilar infiltrates. No causative organism was identified, but clinical improvement occurred coincident with administration of broad spectrum antibiotics. Laboratory studies as an outpatient documented transient thrombocytopenia (63,000/mm^3) and persistent inver-

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sion of his T-helper/T-suppressor ratio (T_H/T_S =0.2). He was readmitted for the third time in early September with fever, chills and nonproductive cough. His cumulative weight loss was now 47 kg. Chest x-ray demonstrated bilateral pneumonia, and open lung biopsy showed infection with *P. carinii*. He responded to sulfamethoxazole/trimethoprim (SMZ/TMP). His T-cell defects persist.

Case 2: A 10-year-old severe hemophiliac from Pennsylvania had been treated with Factor VIII concentrate on a home care program. He had never required blood transfusion. He had been remarkably healthy until September 1982 when he experienced intermittent episodes of fever and vomiting. Approximately 2 weeks later, he also developed persistent anorexia, fatigue, sore throat, and nonproductive cough. On October 20, he was admitted to a hospital with a temperature of 38.4 C (101.2 F) and a respiratory rate of 60/min. Physical examination revealed cervical adenopathy but no splenomegaly. The absolute number of circulating lymphocytes was low (580/mm^3) and the T-helper/T-suppressor ratio was markedly reduced (T_H/T_S = 0.1). His platelet count was 171,000/mm^3. Serum levels of IgG, IgA, and IgM were markedly elevated. Chest x-rays showed bilateral pneumonia and an open lung biopsy revealed massive infiltration with *P. carinii* and *Cryptococcus neoformans*. Intravenous SMZ/TMP and amphotericin B have led to marked clinical improvement, but the T-cell abnormalities persist.

Case 3: A 49-year-old patient from Ohio with mild hemophilia had been treated relatively infrequently with Factor VIII concentrate. During the summer of 1982, he noted dysphagia and a weight loss of approximately 7 kg. In October, he was treated for cellulitis of the right hand. Two weeks later, he was observed by a close relative to be dyspneic. He was admitted in November with progressive dyspnea and diaphoresis. Chest x-rays suggested diffuse pneumonitis. His WBC count was 11,000/mm^3 with 9% lymphocytes (absolute lymphocyte number 990/mm^3). The T_H/T_S ratio was 0.25. Open lung biopsy revealed *P. carinii*. The patient was treated with SMZ/TMP for 6 days with no improvement, and pentamidine isethionate was added. Virus cultures of sputum and chest tube drainage revealed herpes simplex virus. He died on November 22.

Case 4: A 52-year-old severe hemophiliac from Missouri was admitted to a hospital in April 1982 with fever, lymphadenopathy, and abdominal pain. Persistently low numbers of circulating lymphocytes were noted (480/mm^3). Granulomata were seen on histopathologic examination of a bone marrow aspirate. Cultures were positive for *Histoplasma capsulatum*. The patient improved after therapy with amphotericin B. During the following summer and early fall, he developed fever, increased weight loss, and difficulty thinking. On readmission in early November, he had esophageal candidiasis. Laboratory tests showed profound leukopenia and lymphopenia. A brain scan showed a left frontal mass, which was found to be an organizing hematoma at the time of craniotomy. A chest x-ray showed "fluffy" pulmonary infiltrates. Therapy with SMZ/TMP was begun. Exploratory laparotomy revealed no malignancy. A splenectomy was performed. Biopsies of liver, spleen, and lymph node tissues were negative for *H capsulatum* granulomata. The lymphoid tissue including the spleen showed an absence of lymphocytes. His total WBC declined to 400/mm^3 and the T_H/T_S cell ratio was 0.1. He died shortly thereafter.

Suspect Case: Described below is an additional highly suspect case that does not meet the strict criteria defining AIDS. A 7-year-old severe hemophiliac from Los Angeles had mild mediastinal adenopathy on chest x-ray in September 1981. In March 1982, he developed a spontaneous subdural hematoma requiring surgical evacuation. In July, he developed parotitis. In August, he developed pharyngitis and an associated anterior and posterior cervical adenopathy, which has not resolved. In late September, he developed herpes zoster over the right thigh and buttock, and oral candidiasis . Chest x-rays revealed an increase of the mediastinal adenopathy and the appearance of new perihilar infiltrates. In late October, enlargement of the cervical nodes led to a lymph node biopsy. Architectural features of the node were grossly altered, with depletion of lymphocytes. Heterophile tests were negative. IgG, IgA, and IgM levels were all elevated. He has a marked reduction in T-helper cells and a T_H/T_S ratio equal to 0.4. Recent progressive adenoid enlargement has caused significant upper airway obstruction and resultant sleep apnea.

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Editorial Note: These additional cases of AIDS among hemophilia A patients share several features with the three previously reported cases. All but one are severe hemophiliacs, requiring large amounts of Factor VIII concentrate. None had experienced prior opportunistic infections. All have been profoundly lymphopenic (< 1000 lymphocytes/mm^3) and have had irreversible deficiencies in T-lymphocytes. Clinical improvement of opportunistic infections with medical therapy has been short lived. Two of the five have died.

In most instances, these patients have been the first AIDS cases in their cities, states, or regions. They have had no known common medications, occupations, habits, types of pets, or any uniform antecedent history of personal or family illnesses with immunological relevance.

Although complete information is not available on brands and lot numbers for the Factor VIII concentrate used by these additional five patients during the past few years, efforts to collect and compare these data with information obtained from the earlier three cases are under way. No common lot number has been found among the lots of Factor VIII given to the five patients from whom such information is currently available.

These additional cases provide important perspectives on AIDS in U.S. hemophiliacs. Two of the patients described here are 10 years of age or less, and children with hemophilia must now be considered at risk for the disease. In addition, the number of cases continues to increase, and the illness may pose a significant risk for patients with hemophilia.

The National Hemophilia Foundation and CDC are now conducting a national survey of hemophilia treatment centers to estimate the prevalence of AIDS-associated diseases during the past 5 years and to provide active surveillance of AIDS among patients with hemophilia.

Physicians are encouraged to continue to report AIDS-suspect diseases among hemophilia patients to the CDC through local and state health departments.

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Possible Transfusion-Associated Acquired Immune Deficiency Syndrome (AIDS) — California

CDC has received a report of a 20-month old infant from the San Francisco area who developed unexplained cellular immunodeficiency and opportunistic infection. This occurred after multiple transfusions, including a transfusion of platelets derived from the blood of a male subsequently found to have the acquired immune deficiency syndrome (AIDS).

The infant, a white male, was delivered by caesarian section on March 3, 1981. The estimated duration of pregnancy was 33 weeks; and the infant weighed 2850 g. The mother was known to have developed Rh sensitization during her first pregnancy, and amniocentesis done during this, her second, pregnancy showed the fetus had erythroblastosis fetalis. The infant had asphyxia at birth and required endotracheal intubation. Because of hyperbilirubinemia, six double-volume exchange transfusions were given over a 4-day period. During the 1-month hospitalization following birth, the infant received blood products, including whole blood, packed red blood cells, and platelets from 19 donors. All blood products were irradiated.

After discharge in April 1981, the infant appeared well, although hepatosplenomegaly was noted at age 4 months. At 7 months, he was hospitalized for treatment of severe otitis media. Oral candidiasis developed following antibiotic therapy and persisted. At 9 months of age, he developed anorexia, vomiting, and then jaundice. Transaminase levels were elevated, and serologic tests for hepatitis A and B viruses and cytomegalovirus were negative; non-A non-B hepatitis was diagnosed.

At 14 months of age, the infant developed neutropenia and an autoimmune hemolytic anemia and thrombocytopenia. Immunologic studies showed elevated serum concentrations of IgG, IgA, and IgM, decreased numbers of T-lymphocytes, and impaired T-cell function in vitro. Following these studies, he was begun on systemic corticosteroid therapy for his hematologic disease. Three months later, a bone marrow sample, taken before steroid therapy began, was positive for *Mycobacterium avium-intracellulare*. Cultures of urine and gastric aspirate, taken while the infant received steroids, also grew *M. avium-intracellulare*. The infant is now receiving chemotherapy for his mycobacterial infection. He continues to have thrombocytopenia.

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The parents and brother of the infant are in good health. The parents are heterosexual non-Haitians and do not have a history of intravenous drug abuse. The infant had no known personal contact with an AIDS patient.

Investigation of the blood products received by the infant during his first month of life has revealed that one of the 19 donors was subsequently reported to have AIDS. The donor, a 48-year-old white male resident of San Francisco, was in apparently good health when he donated blood on March 10, 1981. Platelets derived from this blood were given to the infant on March 11. Eight months later, the donor complained of fatigue and decreased appetite. On examination, he had right axillary lymphadenopathy, and cotton-wool spots were seen in the retina of the left eye. During the next month, December 1981, he developed fever and severe tachypnea and was hospitalized with biopsy-proven *Pneumocystis carinii* pneumonia.

Although he improved on antimicrobial therapy and was discharged after a 1-month hospitalization, immunologic studies done in March 1982 showed severe cellular immune dysfunction typical of AIDS. In April 1982, he developed fever and oral candidiasis, and began to lose weight. A second hospitalization, beginning in June 1982, was complicated by *Salmonella* sepsis, perianal herpes simplex virus infection, encephalitis of unknown etiology, and disseminated cytomegalovirus infection. He died in August 1982.

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Editorial Note: The etiology of AIDS remains unknown, but its reported occurrence among homosexual men, intravenous drug abusers, and persons with hemophilia A (*1*) suggests it may be caused by an infectious agent transmitted sexually or through exposure to blood or blood products. If the infant's illness described in this report is AIDS, its occurrence following receipt of blood products from a known AIDS case adds support to the infectious-agent hypothesis.

Several features of the infant's illness resemble those seen among adults with AIDS. Hypergammaglobulinemia with T-cell depletion and dysfunction are not typical of any of the well-characterized congenital immunodeficiency syndromes (*2*), but are similar to abnormalities described in AIDS (*3*). Disseminated *M. avium-intracellulare* infection, seen in this infant, is a reported manifestation of AIDS (*4*). Autoimmune thrombocytopenia, also seen in this infant, has been described among several homosexual men with immune dysfunction typical of AIDS (*5*). Nonetheless, since there is no definitive laboratory test for AIDS, any interpretation of this infant's illness must be made with caution.

If the platelet transfusion contained an etiologic agent for AIDS, one must assume that the agent can be present in the blood of a donor before onset of symptomatic illness and that the incubation period for such illness can be relatively long. This model for AIDS transmission is consistent with findings described in an investigation of a cluster of sexually related AIDS cases among homosexual men in southern California (*6*).

Of the 788 definite AIDS cases among adults reported thus far to CDC, 42 (5.3%) belong to no known risk group (i.e., they are not known to be homosexually active men, intravenous drug abusers, Haitians, or hemophiliacs). Two cases received blood products within 2 years of the onset of their illnesses and are currently under investigation.

This report and continuing reports of AIDS among persons with hemophilia A (*7*) raise serious questions about the possible transmission of AIDS through blood and blood products. The Assistant Secretary for Health is convening an advisory committee to address these questions.

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