ACQUIRED IMMUNODEFICIENCY SYNDROME IN AFRICAN PATIENTS

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Abstract Between May 1979 and April 1983, 18 previously healthy African patients were hospitalized in Belgium with opportunistic infections (cryptococcosis, *Pneumocystis carinii* pneumonia, central-nervous-system toxoplasmosis, progressive cutaneous herpes simplex virus infection, disseminated cytomegalovirus infection, candidiasis, or cryptosporidiosis) or Kaposi's sarcoma, or with both. Ten of them died. During the same period five other patients were hospitalized with an illness consistent with a prodrome of the acquired immunodeficiency syndrome (chronic lymphadenopathy, fever, weight loss, and diarrhea). All patients tested had a marked decrease in helper T cells, an inversion of the normal ratio of helper to suppressor T cells, and a decreased or absent blastogenic response of lymphocytes to mitogens. Twenty patients had anergy. There was no evidence of an underlying immunosuppressive disease and no history of blood-product transfusion, homosexuality, or intravenous-drug abuse. This syndrome in patients originating in Central Africa is similar to the acquired immunodeficiency syndrome reported in American patients. (N Engl J Med 1984; 310:492-7.)

THE acquired immunodeficiency syndrome (AIDS) is known to occur among homosexual or bisexual men, intravenous-drug abusers and their infants, female sexual partners of men with the syndrome, Haitians, and patients with hemophilia.[1] In a preliminary report we suggested that black Africans from Equatorial Africa might be another high-risk group.[2] In this paper we extend our observations and describe demographic, clinical, immunologic, and serologic characteristics of 22 black Africans and one white man who had been living in Zaïre. Eighteen had opportunistic infections or Kaposi's sarcoma, and five had symptoms consistent with a prodromal phase of AIDS.

METHODS

In Belgium between May 1979 and April 1983, we studied 17 previously healthy Africans with no clinical or pathologic evidence of any underlying immunosuppressive disease or history of immunosuppressive therapy who presented with evidence of cellular immune deficiency and severe opportunistic infection or Kaposi's sarcoma (or both). Five of the patients have been partially described elsewhere.[2] One with candida stomatitis and idiopathic pneumonia was considered to have probable AIDS on the basis of cutaneous anergy and a decreased ratio of helper to suppressor T cells. Also included in the study were five patients considered to be in a prodromal phase of AIDS, with illness characterized by at least two of the following signs: loss of more than 10 per cent of body weight, diarrhea for at least two months with no pathogens isolated, and lymphadenopathy together with a decreased ratio of helper to suppressor T cells. Generalized lymphadenopathy was defined as the presence of palpable lymph nodes larger than 1 cm at two or more extrainguinal sites.

Starting in 1981, 20 patients (15 with AIDS and 5 with prodromal illness) were studied prospectively by at least one of us and were questioned with the detailed standardized questionnaire developed by the Centers for Disease Control. The records of the other three patients were reviewed after their deaths.

The control group for in vitro mononuclear-cell studies and serum immunoglobulin levels consisted of 20 healthy black African volunteers (matched for age and sex) living in Belgium who were not known to be drug abusers or homosexuals and were not taking any medications. Control subjects were excluded if they had an acute illness during the month before testing.

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Immunologic Studies

Patients evaluated prospectively were tested for cutaneous anergy by intradermal injections of candida, mumps, and tuberculin (purified protein derivative) antigens. In vitro studies included identification of T-lymphocyte subpopulations by indirect immunofluorescence, using commercially available monoclonal antibodies (OKT3 for T cells, OKT4 for helper/inducer T cells, and OKT8 for suppressor/cytotoxic T cells; Ortho Diagnostic Systems, Raritan, N.J.).

Lymphocyte-transformation responses to the mitogens phytohemagglutinin (PHA-P, Burroughs Wellcome, Research Triangle Park, N.C.), concanavalin A (Miles, West Haven, Conn.), and pokeweed mitogen (Gibco-Biocult, Chagrin Fall, Ohio) were quantitated by a micromethod.[3] Serum immunoglobulin levels and absolute lymphocyte counts were evaluated by routine methods.

Serologic Studies

Antibody titers to cytomegalovirus and herpes simplex virus were determined with the complement-fixation test.[4] IgG antibody titers to Epstein–Barr viral capsid antigen were measured by immunofluorescence.[5] Hepatitis B surface antigen and antibodies to hepatitis B surface and core antigens were measured by radioimmunoassay. Antibody titers to *Toxoplasma gondii* were determined by the IgM indirect-fluorescence method and the Sabin–Feldman dye test. Treponemal antibodies were also evaluated.[6]

RESULTS

Demographic Data

It is estimated that 6000 to 8000 people from Central Africa are currently living in Belgium. Most of them are Zaïrian tradesmen, students, or diplomats with their families. No change in migration patterns has occurred within the past few years.

From May 1979 to April 1983, 17 black Africans and 1 white Greek who had lived for 20 years in Zaïre had evidence of opportunistic infections or Kaposi's sarcoma on the basis of cultures or histologic studies (Table 1). With the exception of tuberculosis, which occurred in Patients 2, 14, and 18, no patients had evidence of previous severe or recurrent opportunistic infections. Extensive investigations did not reveal any

Table 1. Opportunistic Infections and Kaposi's Sarcoma in 18 Africans.*

Patient No.	Age/Sex	Date of Diagnosis	Country of Origin	Diagnosis	Outcome
Patients studied prospectively					
1	28/M	1/81	Zaïre	Visceral generalized Kaposi's sarcoma, *Candida albicans* pneumonia	Died
2	46/M	4/81	Zaïre	*C. albicans* esophagitis, *Pneumocystis carinii* pneumonia, pulmonary tuberculosis	Died
3	56/M	12/82	Zaïre	Cutaneous disseminated Kaposi's sarcoma, generalized cryptococcal infection with meningitis, genital herpes infection, *P. carinii* pneumonia	Died
4	39/M	5/82	Zaïre	Kaposi's sarcoma of the large bowel, *C. albicans* stomatitis and lung abscesses, relapsing salmonella septicemia	Died
5	39/M	5/82	Zaïre	Relapsing cryptococcal meningitis, generalized cytomegalovirus infection	Alive (ill)
6	36/M	6/82	Chad	Generalized cryptococcal infection with meningitis, *Salmonella typhimurium* septicemia	Died
7	33/F	6/82	Zaïre	*C. albicans* esophagitis and stomatitis, genital herpes infection, cryptosporidium enteritis, generalized cytomegalovirus infection, herpetic pneumonia	Died
8	24/F	9/82	Zaïre	Mucocutaneous genital herpes infection, *C. albicans* stomatitis	Alive
9	37/F	12/82	Zaïre	Relapsing *Toxoplasma gondii* brain abscesses	Alive (ill)
10	28/F	2/83	Burundi	*C. albicans* stomatitis, *P. carinii* pneumonia	Alive (ill)
11	23/F	3/83	Zaïre	*T. gondii* meningoencephalitis, genital herpes infection, *C. albicans* stomatitis and vaginitis	Alive (ill)
12	48/M	4/83	Zaïre	Genital herpes infection, generalized cytomegalovirus infection	Alive
13 †	46/M	4/83	Zaïre	Idiopathic pneumonia (unidentified pathogen), *C. albicans* stomatitis	Died
14	33/M	4/83	Zaïre	Pulmonary tuberculosis, *T. gondii* brain abscesses	Alive
15	42/M	12/82	Zaïre	Aseptic meningitis, generalized cytomegalovirus infection	Alive (ill)
Patients studied retrospectively					
16	24/F	5/79	Zaïre	*P. carinii* pneumonia, generalized cryptococcal infection with meningitis	Died
17	47/M	10/81	Zaïre	*P. carinii* pneumonia, generalized cryptococcal infection with meningitis	Died
18	37/M	7/82	Zaïre	*Myobacterium tuberculosis* adenitis, generalized cryptococcal infection with meningitis	Died

*All patients were black except Patient 18. †Patient with probable AIDS.

underlying immunosuppressive disease or a history of immunosuppressive therapy to account for opportunistic infections in any of the patients. Nine had had parasitic infections (Patients 1, 2, 7, 8, 11, 12, and 15 through 17), including ankylostomiasis (two cases), schistosomiasis (*Schistosoma mansoni* [two]), amebiasis (four), ascaridiasis (one), and filariasis (one). Only Patient 11 had active helminthiasis (*Loa loa*) when AIDS was diagnosed. After therapy with diethylcarbamazine no change occurred in her immunologic status. In all other patients, extensive serologic studies, including the indirect-immunofluorescence test for antibody to *Trypanosoma brucei*, were negative. In addition, a thick-drop examination for plasmodium species was negative in all patients.

Twelve of the 18 patients were men (mean age, 38 years; range, 28 to 56) and 6 were women (mean age, 28 years; range, 23 to 37). All patients stated that they were heterosexual and had not used parenteral or inhalational drugs. None had received any blood transfusions during the previous five years. The families of the three patients studied retrospectively reported that there had been no history of homosexuality or illicit drug use. All patients were of upper socioeconomic status. Eight had been living in Zaïre and came to Belgium because of unexplained weight loss and chronic diarrhea. The other 10 had been living in Belgium for 4 to 48 months (median, 17) at diagnosis but had frequently returned to Africa for familial or business purposes. In family members of three patients (Patients 7, 12, and 14) there had been similar clinical illness during the previous three years.

Of the five Africans with the prodrome of AIDS, three were women (mean age, 28 years) and two were men (mean age, 47 years). All were heterosexual and reported that they did not use illicit drugs and had not received any blood transfusions during the previous five years. Extensive investigations and the medical history did not reveal any underlying disease or previous or ongoing parasitic infections. Three of the patients came to Belgium for medical investigations, another had been living in Belgium for six years, and the fifth had been in Belgium for one year. Retrospectively, it was found that the husband of Patient 21 had died in 1976 in Belgium, at the age of 27, from *Salmonella enteritidis* and *Candida albicans* pneumonia — a picture consistent with AIDS.

Clinical Presentation

Patients with Opportunistic Infections or Kaposi's Sarcoma or Both

Ten of the 18 patients died. Autopsies performed in seven patients with opportunistic infections did not reveal any evidence of malignant disease. Patient 4, who had *C. albicans* lung abscesses and salmonella septicemia, was found at autopsy to have had previously unrecognized Kaposi's sarcoma of the large bowel. Five of the surviving patients remained ill and three

had minor symptoms at three to eight months after the initial studies. All patients presented with fever and weight loss. The mean duration of these symptoms was 7 months (range, 2 to 15). Thirteen patients also had chronic diarrhea. Eleven (Patients 1, 2, 4 through 8, 10, 12, 13, and 16) had generalized lymphadenopathy, which was due to *Cryptococcus neoformans* in three. Patient 11 had axillary adenopathy, and Patients 15 and 18 had cervical adenopathy. *Mycobacterium tuberculosis* was isolated from a lymph node in Patient 18. Six patients had cryptococcal meningitis, with cryptococcemia in five. They died in spite of treatment with amphotericin and 5-fluorocytosine. At autopsy, *Pneumocystis carinii* pneumonia was found in three cases. In two of the three patients with intracerebral lesions due to *T. gondii* the only symptom was headache. Five weeks after the end of two months of successful therapy with pyrimethamine–sulfadiazine, Patient 9 presented with a relapse of *T. gondii*–associated brain abscess, which responded well to a new course of pyrimethamine–sulfadiazine.

Table 2. Clinical Data in Patients without Opportunistic Infections.

Patient No.	Age/Sex	Country of Origin	Onset of Symptoms	Fever	Diarrhea	Weight Loss (kg)	Lymphadenopathy	Previous Infections
19	60/M	Rwanda	12/82	No	No	10	Yes	None
20	24/F	Zaïre	1/83	No	Yes	5	Yes	None
21	30/F	Zaïre	12/79	No	Yes	10	Yes	None
22	38/M	Burundi	1/83	Yes	Yes	6	Yes	Staphylococcal Perianal abscess
23	29/F	Rwanda	Unknown	Yes	No	8	Yes	Syphilis

Kaposi's sarcoma occurred in three patients. It was generalized and involved the skin, the lymph nodes, and the mucosa of the whole digestive tract in Patient 1, who died from persistent *Bacteroides fragilis* septicemia. Patient 3 had disseminated cutaneous lesions (on the legs, chest, and toes) without visceral involvement. Patient 4 had asymptomatic Kaposi's sarcoma of the large bowel, which was discovered at autopsy. All 15 patients studied prospectively were anergic to skin-test antigens.

Patients without Opportunistic Infections

Clinical data in five patients with lymphadenopathy but no opportunistic infections are summarized in Table 2. Weight loss and lymphadenopathy were constant features. Chronic lymphadenopathy (of more than two months' duration) was generalized in three patients and was localized in cervical and axillary sites in Patients 20 and 21, respectively. In all five patients a lymph-node biopsy showed nonspecific intense follicular hyperplasia with marginal plasmacytosis, and delayed skin hypersensitivity to three antigens was suppressed. Patient 21 had symptoms for three years, without any opportunistic infection occurring until now.

Immunologic and Serologic Data

Table 3 summarizes the findings of the lymphocyte-subset analysis, proliferative studies, and IgG determinations in specimens from patients with AIDS and opportunistic infections and from those without infections.

Twelve of 15 patients with AIDS and opportunistic infections and 1 of 5 with lymphadenopathy had a decreased total T-lymphocyte count (OKT3). All patients had a marked depression in the number of helper/inducer T cells (OKT4) and an inversion of the normal ratio of helper/inducer (OKT4) to suppressor/cytotoxic (OKT8) T lymphocytes, with values ranging from 0 to 0.37. Blastogenic responses of peripheral-blood lymphocytes to the three mitogens were decreased or absent in all patients tested. These immunologic abnormalities persisted in all subjects.

Polyclonal hypergammaglobulinemia was present in most patients whether they were infected or not. The IgG level was elevated in 14 patients, and the IgA and IgM levels were elevated in Patient 3 and in Patients 10, 15, 19, and 23, respectively.

Serologic markers for previous infection with hepatitis B virus were positive in 15 of 18 patients tested (Table 4). Antibodies to cytomegalovirus, herpes simplex virus, Epstein–Barr virus, and *T. gondii* were present in several patients. Of the three with an active infection from *T. gondii*, only one (Patient 11) had IgM antibodies against it. The fluorescent-treponemal-antibody test was negative in all subjects except Patients 19 and 23.

Discussion

Our 23 African patients with AIDS reported that there was no history of homosexuality or drug addiction, and none had received blood transfusions in the previous five years. The infections seen were similar to those described in other groups of patients with AIDS and included generalized cryptococcosis, central-nervous-system toxoplasmosis, *P. carinii* pneumonia, progressive cutaneous herpes simplex viral infection, disseminated cytomegalovirus infection, and cryptosporidiosis. The mortality rate was 55 per cent. Immunologic features were associated with AIDS and were found to be persistent in all patients studied. There was a severe T-cell defect characterized by cutaneous anergy, decreased T-cell responses to mitogens, and inversion of the normal ratio of helper/inducer to suppressor/cytotoxic T cells.

In patients who had clinical signs compatible with the prodrome of AIDS[7] (those with lymphadenopathy), the total lymphocyte count and the percentage of T lymphocytes (OKT3) were in the normal range. Nevertheless, these patients also presented with a severe defect in T-cell function. It is not known whether this group of patients with lymphadenopathy but without opportunistic infections had a distinct syndrome with a better prognosis or whether they were in

Table 3. Peripheral-Blood Lymphocyte Populations and Responses to Mitogens and Serum Immunoglobulins in the Patients.*

Patient No.	Cell Counts *					Mitogen Stimulation †			IgG
	Lymphocytes	OKT3	OKT4	OKT8	OKT4/OKT8	PHA	CONA	PWM	
	cells/mm³	%	%	%		%	%	%	*mg/dl*
Patients with opportunistic infections									
1	972	74 (719)	21 (204)	56 (544)	0.37	59	52	47	2750
2	300	48 (144)	8 (24)	52 (156)	0.15	12	NA	21	2160
3	672	40 (269)	1 (7)	25 (168)	0.04	3.8	10.3	8.3	1680
4	1728	47 (812)	3 (52)	42 (726)	0.07	NA	NA	NA	2080
5	446	53 (236)	1 (4.5)	49 (219)	0.02	NA	NA	NA	3250
6	80	29 (23)	2 (1.6)	45 (36)	0.04	0.5	2	6	2036
7	396	31 (123)	0 (0)	26 (103)	0	0	2.3	0	2203
8	1143	49 (560)	3 (34)	53 (606)	0.06	16	14	6	4580
9	224	42 (94)	2 (4.5)	41 (92)	0.05	0.1	0.7	6.4	3216
10	4138	32 (1324)	10 (414)	28 (1159)	0.32	NA	NA	NA	3576
11	207	45 (93)	1 (2)	39 (81)	0.02	0.7	7.1	15.4	1849
12	1728	66 (1140)	12 (207)	50 (864)	0.24	0.5	21.1	20.9	4300
13	1819	62 (1128)	4 (73)	60 (1091)	0.06	NA	NA	NA	2486
14	440	71 (312)	13 (57)	63 (277)	0.2	13	17.6	4.2	1715
15	1399	46 (644)	13 (182)	67 (937)	0.19	NA	NA	NA	4400
Patients with lymphadenopathy									
19	1872	68 (1273)	9 (168)	57 (1067)	0.16	12	4.6	9	5970
20	1800	67 (1206)	0.5 (9)	49 (882)	0.01	28.5	32.7	93.5	2936
21	676	72 (487)	5 (34)	65 (439)	0.07	0	0	11.1	2730
22	2650	70 (1855)	14 (371)	67 (1775)	0.21	29	16	11	1928
23	5380	76 (4089)	8 (430)	69 (3712)	0.12	9.8	9.7	6	6360
Normal range	1330–4500	52–80 (869-1799)	27–65 (398-1680)	12–40 (189-912)	1.12–2.25	62–200	67–200	62–185	777–2150

*The total lymphocyte count was determined by multiplying the leukocyte count by the number of lymphocytes in the differential cell count. Numbers in parentheses represent absolute counts.

†The normalized mitogen response was calculated with the following formula:

$$\frac{(\text{cpm stimulated} - \text{cpm unstimulated})\ \text{patient}}{(\text{cpm stimulated} - \text{cpm unstimulated})\ \text{control}} \times 100.$$

PHA denotes phytohemagglutin, CONA concanavalin A, PWM pokeweed mitogen, and NA not available.

a prodromal stage of the classic AIDS syndrome with severe opportunistic infection or Kaposi's sarcoma or both.

Parasitic diseases and malnutrition are two possible causes of immunodepression in Africa. A wide range of prevalent protozoal and helminthic infestations have been reported to induce immunodeficiency. In malaria the number of T lymphocytes is reduced,[8] but cell-mediated immunity seems to be unaffected, and only humoral immunity is impaired.[9] African trypanosomiasis has been shown to be associated with several T-cell dysfunctions.[10] Diffuse cutaneous leishmaniasis is known to induce immunosuppression, but it is restricted to parasite-specific antigens.[11] Schistosomiasis and filariasis are also able to impair the immune responses to parasite-unrelated antigens.[12] On the basis of repeated examinations of blood and stool specimens, as well as serologic tests, we were able to exclude active parasitic infestations as a possible cause of the impaired cell-mediated immunity in all our subjects except Patient 11, who had loiasis. Protein malnutrition has been described as a cause of T-cell immunodeficiency. The proportion and absolute number of T lymphocytes are markedly decreased, and the thymus has been found to be atrophic and depleted in postmortem studies.[13] This immunodeficiency is usually observed in children with extreme malnutrition. Our patients were previously healthy adults in an upper socioeconomic class. Thus, it is unlikely that malnutrition was the primary cause of their syndrome. However, since most of them presented with severe weight loss during their illness, it is possible that malnutrition was an aggravating factor.

All these features suggest that the clinical syndrome in our African patients was similar to AIDS observed in the United States. Recent studies have supported the hypothesis of an etiologic relation between human T-cell leukemia virus and AIDS.[14-16] However, the low frequency with which the virus or its nucleic acid sequences have been detected and the prevalence of antibodies in only one quarter of patients with AIDS are disturbing.[15,16] Cytomegalovirus has also been implicated as a causative agent.[17] The low seroreactivity to cytomegalovirus that we observed in our African patients is not consistent with such a hypothesis. However, the complement-fixation test that we used is relatively insensitive.

The occurrence of AIDS in black Africans who lived in Belgium or in Central Africa and who had not been exposed to other risk factors for the disease may signify

Table 4. Serologic Data in the Patients.*

Patient No.	Cytomegalovirus	Epstein–Barr Virus	Herpes Simplex Virus	HBsAg	Antibody to HBsAg	Antibody to HBcAg	Toxoplasma Gondii †
Patients with opportunistic infections							
1	1:16	1:32	0	NA	NA	NA	NA
2	1:8	1:32	1:64	0	+	+	0
3	0	1:64	1:1024	NA	NA	+	0
4	NA	1:1024	NA	NA	NA	NA	NA
5	0	1:1024	1:128	0	+	+	1:1000
6	0	NA	0	0	+	NA	0
7	1:8	NA	1:64	+	NA	+	0
8	1:1024	1:64	1:1024	0	0	0	1:1500
9	0	1:128	0	0	+	+	1:1000
10	1:8	1:80	NA	0	0	0	1:500
11	0	0	0	0	+	NA	1:1000
12	1:32	0	0	0	+	NA	0
13	1:16	1:128	1:16	0	+	+	0
14	0	0	0	0	+	+	1:2000
15	1:16	1:512	1:128	0	+	+	0
Patients with lymphadenopathy							
19	NA	1:80	1:128	0	0	+	1:32
20	0	NA	0	0	+	0	1:32
21	1:16	1:64	0	0	0	+	0
22	1:64	0	1:128	0	+	+	NA
23	1:128	0	1:128	0	0	0	0

*HbsAg denotes hepatitis B surface antigen, HbcAg hepatitis B core antigen, and NA not available.

†Determined by the Sabin–Feldman dye test.

that the putative agent of AIDS is endemic both in Europe and in Africa. However, a European reservoir is unlikely. Indeed, until now, all reported European cases occurred in high-risk subjects (homosexual men, patients with hemophilia, and those who had had blood transfusions) who had traveled in the United States or the Caribbean region or had received blood products from these countries.[18,19] All our African patients living in Belgium traveled regularly to their country of origin and may have acquired the syndrome there, since it occurred in those who later came to Belgium for medical care.

It is not known how the agent of AIDS is transmitted in the African population. The occurrence of the syndrome in young to middle-aged men and women suggests that heterosexual contact may be a mode of transmission. Serologic markers of past infection with hepatitis B virus were present in 15 of 18 patients tested. In tropical areas, hepatitis B virus represents one of the major public-health problems, and active or past infection from the virus has been noted in 90 per cent of the adult population in Senegal.[20] Since the distribution of AIDS seems to be parallel with that of hepatitis B viral infection, one may expect an extension of the syndrome in Central Africa.

Whether or not AIDS is a new disease in Africa remains difficult to determine, but data on Kaposi's sarcoma or opportunistic infections provide some indirect information. Kaposi's sarcoma is known to occur along the equatorial region, and its highest prevalence has been noted in Eastern Zaïre and Western Uganda, with annual incidence rates approximating 8 per 100,000 adult men.[21] The tumor occurs with greatest frequency among the black male population in Africa, with a much lower incidence among the Europeans residing in this area. In most cases, the disease is indolent or slowly progressive and is limited to the skin, at least clinically. However, rapidly progressive and fatal evolution is reported in children and young adults who have involvement of lymph nodes and visceral organs.[22] Impairment of cell-mediated immunity has been demonstrated in such patients.[23] This presentation and course are similar to those associated with Kaposi's sarcoma in homosexual men with AIDS. No epidemiologic data exist on a recent change in the pattern of the disease in Central Africa, and there is an urgent need for such information. Concerning cryptococcosis, from 1953 to 1967, only 14 cases were reported from Zaïre,[24] whereas in 1981 and 1982 15 cases of fatal cryptococcal meningitis occurring in young Zaïrians were diagnosed in the Mama Yemo Hospital of Kinshasa.[25] Whether these cases reflect an increasing incidence of this opportunistic infection in the Zaïrian population needs to be confirmed by further studies. The current incidence of *P. carinii* pneumonia is unknown, although in 1963 this type of disease was described in debilitated children in Zaïre.[26]

It is possible that AIDS has always been present but unrecognized in Africa. However, we are struck by the increasing number of patients who have come from

Zaïre or Rwanda to Belgium during the past four years to seek medical care. We believe that AIDS is a new disease that is spreading in Central Africa.

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References

1. Fauci AS. The acquired immune deficiency syndrome: the ever-broadening clinical spectrum. JAMA 1983; 249:2375-6.
2. Clumeck N, Mascart-Lemone F, de Maubeuge J, Brenez D, Marcelis L. Acquired immune deficiency syndrome in Black Africans. Lancet 1983; 1:642.
3. Mascart-Lemone F, Delespesse G, Servais G, Kunstler M. Characterization of immunoregulatory T lymphocytes during ageing by monoclonal antibodies. Clin Exp Immunol 1982; 48:148-54.
4. Zissis G, Clinet G. Viral-antibody detection by a more sensitive complement-fixation reaction. Lancet 1974; 1:754-5.
5. Lamy ME, Favart AM, Burtonboy G, Arana A. Epstein–Barr virus viral capsid antigen titer by immunofluorescence: new semiautomated method based on the microtiter system. J Clin Microbiol 1977; 6:66-71.
6. Deacon WE, Lucas JB, Price EV. Fluorescent treponemal antibody-absorption (FTA-Abs) test for syphilis. JAMA 1966; 198:624-8.
7. Centers for Disease Control Task Force on Kaposi's Sarcoma and Opportunistic Infections. Epidemiologic aspects of the current outbreak of Kaposi's sarcoma and opportunistic infections. N Engl J Med 1982; 306:248-52.
8. Wyler DJ. Peripheral lymphocyte subpopulations in human *falciparum* malaria. Clin Exp Immunol 1976; 23:471-6.
9. Clayton CE. Immunosuppression in trypanosomiasis and malaria. In: The role of the spleen in the immunology of parasitic diseases. (Tropical Diseases research series no. 1.) Basel: Schwabe, 1979:97-115.
10. Askonas BA, Corsini AC, Clayton CE, Ogilvie BM. Functional depletion of T- and B-memory cells and other lymphoid cell subpopulations during trypanosomiasis. Immunology 1979; 36:313-21.
11. Petersen EA, Neva FA, Oster CN, Diaz HB. Specific inhibition of lymphocyte-proliferation responses by adherent suppressor cells in diffuse cutaneous leishmaniasis. N Engl J Med 1982; 306:387-92.
12. Wilkins HA, Brown J. *Schistosoma haematobium* in a Gambian community. II. Impaired cell-mediated immunity and other immunological abnormalities. Ann Trop Med Parasitol 1977; 71:59-66.
13. Smythe PM, Breton-Stiles GG, Grace HJ, et al. Thymolymphatic deficiency and depression of cell-mediated immunity in protein-caloric malnutrition. Lancet 1971; 2:939-43.
14. Gallo R, Sarin PS, Gelmann EP. Isolation of human T-cell leukemia virus in acquired immune deficiency syndrome (AIDS). Science 1983; 220:865-7.
15. Essex M, McLane MF, Lee TH, Falk L, Howe CWS, Mullins JI. Antibodies to cell membrane antigens associated with human T-cell leukemia virus in patients with AIDS. Science 1983; 220:859-62.
16. Gelmann E, Popovic M, Blayney D, et al. Proviral DNA of a retrovirus, human T-cell leukemia virus, in two patients with AIDS. Science 1983; 220:862-5.
17. Brennan RO, Durack DT. Gay compromise syndrome. Lancet 1981; 2:1338-9.
18. Lissen E, Wichmann I, Jimenez JM, Andreu-Kern F. AIDS in haemophilia patients in Spain. Lancet 1983; 1:992-3.
19. Brunet JB, Bouvet E, Leibowitch J, et al. Acquired immunodeficiency syndrome in France. Lancet 1983; 1:700-1.
20. Barin F, Perrin J, Chotard J. Cross-sectional and longitudinal epidemiology of hepatitis B in Senegal. Prog Med Virol 1981; 27:148-62.
21. Oettle AG. Geographical and racial differences in the frequency of Kaposi's sarcoma as evidence of environmental or genetic causes. Acta Un Int Cancer 1962; 18:330-63.
22. Taylor JF, Templeton AC, Vogel CL, Ziegler JL, Kyalwazi SK. Kaposi's sarcoma in Uganda: a clinico-pathological study. Int J Cancer 1971; 8:122-35.
23. Taylor JF. Lymphocyte transformation in Kaposi's sarcoma. Lancet 1973; 1:883-4.
24. Renoirte R, Michaux JL, Gatti F, et al. Nouveaux cas d'histoplasmose africaine et de cryptococcose observés en République Démocratique du Congo. Bull Acad Roy Med Belg 1967; 7:465-527.
25. Lamey B, Melameka N. Aspects cliniques et épidémiologiques de la cryptococcose à Kinshasa: à propos de 15 cas personnels. Med Trop 1982; 42:507-11.
26. Thijs A, Janssens PG. Pneumocystosis in Congolese infants. Trop Geogr Med 1963; 15:158-72.

AN EFFICACY TRIAL OF DOXYCYCLINE CHEMOPROPHYLAXIS AGAINST LEPTOSPIROSIS

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Abstract Because leptospirosis has been an important cause of morbidity in U.S. soldiers training in the Republic of Panama, we conducted a randomized, double-blind, placebo-controlled field trial during the fall of 1982 to determine whether doxycycline was an effective chemoprophylactic agent against this infection. Doxycycline (200 mg) or placebo was administered orally on a weekly basis and at the completion of training to 940 volunteers from two U.S. Army units deployed in Panama for approximately three weeks of jungle training. Twenty cases of leptospirosis occurred in the placebo group (an attack rate of 4.2 per cent), as compared with only one case in the doxycycline group (attack rate, 0.2 per cent, $P<0.001$), yielding an efficacy of 95.0 per cent. This study demonstrated the value of doxycycline as a prophylactic drug against leptospirosis. (N Engl J Med 1984; 310:497-500.)

FOR many years leptospirosis has been recognized as an occupational hazard of U.S. soldiers training in the Republic of Panama.[1] In 1981 and 1982, several large outbreaks of this disease occurred among soldiers training during the fall. Attack rates ranging from 2 to 8 per cent in military units were documented (Takafuji ET: unpublished data).

Preventive measures against leptospirosis have been unsatisfactory. Vaccines directed against prevalent serovars (serovarieties of *Leptospira interrogans*) are currently used in domestic animals,[2-5] but serovar-specific vaccines have limited usefulness in tropical environments with numerous serovars. Environmental control measures and the wearing of protective clothing have not been practical.[2,6,7] Field trials conducted

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