

The diagnosis of PCP in 51% of AIDS cases reported in this paper is similar to the national figure of 58%.

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CYCLOSPORIN IMMUNOSUPPRESSION AS THE POSSIBLE CAUSE OF AIDS

Many investigators have suggested that AIDS is caused by a transmissible infectious agent, most probably a virus (Curran J: *N Engl J Med.*, 1983, 309:609-610). We propose that a non-viral infectious agent may act either as the primary causative agent of AIDS or as a secondary agent responsible for maintaining the disease state. Our hypothesis suggests that the severe impairment of the immune system and the subsequent fatal opportunistic infections in AIDS result from the systemic release of a potent cyclosporin-like immunosuppressive molecule from a fungal infectious agent.

Three different strains of the same fungal species have been isolated from long-term monocyte cultures of three AIDS patients. Simultaneous culture and examination of six normal human control monocyte cultures in the same culture plate showed no fungal growth or contamination. The fungal strains have been identified as atypical isolates of Thermoascus crustaceus (Dactylomyces crustaceus). Unlike the majority of soil or plant fungi, their optimum growth temperature is 37°C. Such fungi, including other species of Thermoascus, have never previously been isolated at the National

Institutes of Health from either patients or normal individuals. They are unique isolates from clinical material from patients with AIDS.

The mycelia of these isolates contain a cyclosporin-like compound (CyAIDS) as detected by high-pressure liquid chromatography (HPLC) analyses. CyAIDS was found in high concentration near the reference peaks for cyclosporin A (CyA) and cyclosporin D standards (provided by Sandoz, Ltd). Mass spectrographic analyses of these samples are underway.

CyAIDS was also found in plasma samples studied by HPLC. Four out of four samples from patients with AIDS had CyAIDS peaks. The level of CyAIDS in the plasma of one patient was estimated to exceed 1,000 ng/ml. Two control blood samples failed to show significant levels of cyclosporin-like peaks. In contrast to these findings, no significant plasma cyclosporin levels could be measured in a radioimmunoassay for cyclosporin using a polyclonal sheep anticyclosporin antibody (provided by Sandoz, Ltd) (A. Palestine, personal communication). It is possible that CyAIDS produced by the fungi isolated from AIDS patients is sufficiently distinct immunologically that it cannot be detected by the sheep antibody. (Several different types of cyclosporins have been identified so far.) It is also possible that the AIDS patients produce antibodies against CyAIDS, and these could interfere with the radioimmunoassay.

The cyclosporins are hydrophobic, cyclical, neutral peptides containing 11 amino acids and having molecular weights of approximately 1,200 daltons (Wenger R: in White DJG (Ed): Cyclosporin A: Proc Int Conf CyA, Elsevier Biomed Press, 1982, 19-34). The CyA currently licensed by Sandoz for use in

transplantation (see below) is produced from a soil fungus strain originally classified as Trichoderma polysporum Rifai and now identified as Tolipocladium inflatum Gams (Borel J: in White DJG (Ed): Cyclosporin A: Proc Int Conf CyA, Elsevier Biomed Press, 1982, 5-17).

CyA is well known as a potent immunosuppressive substance. The mycelial extracts from Sabouraud broth cultures were observed to have an immunosuppressive effect in the mixed leukocyte culture assay. CyA has been shown to cause immunosuppression by inhibiting the production of interleukin-2 (IL-2) (Wagner H: Transplant Proc., 1983, 15:523-526) and by inhibiting the expression of IL-2 receptors on T helper cells (Palacios R, Moller G: Nature, 1981, 290:792-794). CyA also inhibits synthesis of gamma interferon (Reem G, Cook L, Vilcek J: Science, 1983, 221:63-65). When T cells are co-cultured with antigen or mitogen in the presence of CyA, they will not be transformed into activated cells. However, once a T cell expresses cytotoxic activity, it becomes resistant to the action of CyA. T suppressor functions are apparently not affected by CyA (Borel J: Transplant Proc., 1983, 15:1881-1885).

Cyclosporin is used to induce immunosuppression following transplantation. Two to 13% of patients immunosuppressed in this way develop opportunistic infections and malignancies. In some cases, these effects may represent reactivation of Epstein-Barr virus (Sheil AGR: Transplant Proc., 1977, 9:1133-1138; Bird AG: in White DJG (Ed): Cyclosporin A: Proc Int Conf CyA, Elsevier Biomed Press, 1982, 307-315). One known effect of CyA therapy in man is the reversal of the T helper to T suppressor ratio through depletion of the number of T helper cells (Kerman RH, Van Buren CT, Flechner S,

et al: Transplant Proc., 1983, 15:1971-1973). CyA therapy in dogs causes lassitude, fatigue, weight loss, diarrhea, and elevated globulin levels (Ryffel B: in White DJG (Ed): Cyclosporin A: Proc Int Conf CyA, Elsevier Biomed Press, 1982, 45-75).

Plasma from AIDS patients exerts an inhibitory effect on normal lymphocytes. It prevents such cells from responding to mitogens or to allogeneic lymphocytes (Cunningham-Rundles S, Michelis M, Masur H: J Clin Immunol., 1983, 3:156-165). An inhibitory factor in plasma from AIDS patients has been purified and has been shown to be a low molecular weight compound. This compound impairs the production of IL-2 (G. Quinnan, personal communication). Typically, the T cells from AIDS patients fail to develop IL-2 receptors (J. Fahey, personal communication). In vitro, IL-2 can restore the cytotoxic response of lymphocytes from AIDS patients (Rook A, Masur H, Lane C, et al: J Clin Invest., 1983, 72:1-6).

The isolates of T. crustaceus were obtained from monocyte cultures. It seems unlikely that monocytes are the primary targets of infection in AIDS patients. However, if the fungi can grow in monocytes, their transmission would be possible from one individual to another through a needle stick or through blood components.

These results are extremely preliminary. The fungi may simply be contaminants of the monocyte cultures or opportunistic infectious agents in the AIDS patients. More isolations are needed. Further studies of the CyAIDS compounds isolated from both blood from patients with AIDS and mycelia of the fungus will be needed to determine whether the immunosuppressive activity will have any consequence in vivo. The fungus and the CyAIDS may simply be cofactors which,

along with other infectious agents, are necessary for inducing the full impairment of the immune system characteristic of AIDS. However, the types of immunologic impairments typical of AIDS and many of the immunosuppressive activities produced by the cyclosporins are comparable and would be consistent with an active role for a cyclosporin-like molecule in the immune suppression characteristic of AIDS.

This fungus may not prove on further evaluation to be the etiologic agent of AIDS. It is important, however, to consider a wide range of infections and infectious agents which might be responsible for the immunodeficiencies seen in the AIDS patients. It is also important to consider etiologic factors other than infectious agents as possible cofactors or initiators of AIDS.

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HISTOLOGIC OBSERVATIONS IN AIDS AND KAPOSI'S SARCOMA (KS)

An etiologic role for bacteria has not been systematically explored in AIDS and KS. This report describes histologic observations made on biopsy materials from a 29-year-old white homosexual man with AIDS and KS. Permission for

autopsy could not be obtained in this case.

A lymph node showing reactive hyperplasia was excised and examined with a Fite stain 2 months before the patient's death. Intracellular, purple coccoid forms and large Russell bodies were seen within a stained, acid-fast section of the node. The Russell bodies appeared to develop from the coccoid forms. Staphylococcus epidermidis was cultured from the node. Similar structures were seen in the surrounding connective tissue. Intracellular coccoid forms were seen within liver cells in liver biopsy sections characterized as showing non-specific inflammation.

The patient developed multiple KS skin lesions on his face 2 weeks before death. Both intracellular and extracellular purple coccoid forms (Fite stain) and very rare pink coccoid forms (Gram stain) were observed throughout the dermis. These coccoid forms resembled some of the coccal forms of beta-Streptococcus, group G, which were isolated from a blood culture obtained 1 day before death. Some aberrant "large forms" of streptococci were similar in size to some of the Russell bodies observed in vivo within the lymph nodes.

The histopathological finding of coccoid forms in vivo in AIDS and KS is not a syndrome-specific finding. Similar structures have been observed in forms of cancer, collagen diseases, lymphoproliferative diseases, and in "normal" tissue (Cantwell AR, Jr: in Domingue GJ (Ed): Cell Wall Deficient Bacteria: Basic Principles and Clinical Significance. Addison-Wesley Publishing Company, Reading, Massachusetts, 1982, 321-360). However, other studies from this and other laboratories have also shown intracellular and extracellular coccoid forms associated with AIDS and KS. They have

been seen within enlarged lymph nodes of one suspected AIDS patient and within the skin lesions in two homosexual men with AIDS (Cantwell AR, Jr: Growth, 1982, 46:331-336; Cantwell AR, Jr: Cutis, 1983, 32:58-64, 68). Cell wall deficient bacteria (CWDB) have been detected in necroscopic analyses of sections of the heart, lungs, intestines, and in KS skin lesions of a 74-year-old Jewish man who died without clinical evidence of ante-mortem infection. Various bacteria--Corynebacterium sp. and Propionibacterium acnes from one case and Staphylococcus epidermidis and Streptococcus viridans from another--were cultured from the skin lesions of two of three elderly, heterosexual Jewish men with KS (Cantwell AR, Jr: Growth, 1981, 45:79-89). In eight of nine patients with AIDS and KS, acid-fast Mycobacterium avium-intracellulare have been detected at autopsy (Zakowski P, Fligiel S, Berlin GW, et al: J Am Med Assoc., 1982, 248:2980-2982). The Russell bodies and other bacterial forms seen in in vivo sections might be related to cell wall deficient and acid-fast forms of staphylococci, streptococci, and corynebacteria-like organisms which have been observed and cultured from samples of blood of both healthy and diseased individuals (Wuerthele-Caspe Livingston V, Livingston AM: Trans NY Acad Sci., 1972, 34:433-453).

Further studies are necessary to establish a link between histologic observations and clinical isolates. "Occult" bacteria were finally determined to cause "legionnaires' disease"; they may, likewise, prove to have more than an opportunistic role in AIDS.

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AIDS FROM CENTRAL AFRICA IN A HETEROSEXUAL DANISH MALE

The second Danish patient with AIDS of probable African origin recently died in Copenhagen at age 31. He was a previously healthy businessman who moved to central Africa in 1974. From 1974 to 1976 he lived mostly in Rwanda and from 1976 to 1980 in neighboring Burundi. During this time he paid short visits to Kenya; he also spent 2 days in Zaire. Between 1979 and 1981 he visited the Ivory Coast for 1 month and Canada for 1 week (crossing briefly into the United States). In December 1981 he left Burundi. From then until his death, he lived in France, the Ivory Coast, and Denmark.

The patient had never received a blood transfusion, and he denied homosexuality and intravenous drug abuse.

While in Rwanda in 1974, he contracted infectious mononucleosis. The diagnosis was confirmed in Denmark. In 1976 he developed bilateral orchitis of unknown origin. He was treated for gonorrhoea on several occasions in Burundi and for syphilis once in France after his last visit to Burundi. The venereal diseases were probably acquired from native (Watutsi) bar girls in Bujumbura, the capital of Burundi.

The patient was slightly obese but otherwise in good health until his return to Europe from Burundi in January 1982. He developed fatigue and fever and possibly lymphadenopathy. He was treated for toxoplasmosis in France, but a firm diagnosis was never established; and serological tests performed in 1983 for toxoplasmosis were negative. He had episodes of fever, and his general level of health gradually deteriorated. In November 1982, while taking anti-malarials for fever, a long-lasting skin

AIDS Memorandum, Vol. 1(2), 1983

eruption appeared. He was hospitalized in December of that year with a bleeding nose.

The patient suffered from functional dyspnoea and weight loss during 1983. He was examined for malaria because of recurrent fever. Malaria was not confirmed. By August of that year, he had lost 25 kg and was dyspnoeic even when at rest.

On August 12 he was rehospitalized. He required artificial respiration, as the initial discrete bilateral pulmonary infiltrates rapidly progressed despite high-dose erythromycin, sulfamethoxazol-trimethoprim, and prednisone therapies. An open lung biopsy revealed *Pneumocystis carinii* (PC) and cytomegalovirus (CMV) infections. Pentamidine and acyclovir therapies were started, but pneumothorax, progressive respiratory insufficiency, and later hypotension with anuria supervened. He died on August 31. An autopsy was not performed.

Lymphocyte counts of cells in peripheral blood showed severe lymphopenia ($0.14 \times 10^9/l$). No proliferative responses could be measured to mitogens and antigens in vitro. The T helper/T suppressor ratio was low (0.09), and NK cell activity was moderately decreased. (Lymphocyte studies were performed by the Tissue Type Laboratory, Rigshospitalet.) The S-IgA level was above normal; IgG and IgM levels were normal. Antinuclear antibodies and lymphocytotoxic antibodies were not found. The anti-CMV antibody titer was positive (1:128) as was the Epstein-Barr IgG antibody titer.

The patient fulfills the AIDS criteria but does not fit into any of the risk groups defined to date. We suggest that "Africans" be included in the list of risk groups. In addition, since this

patient is suspected of having acquired his immune deficiency syndrome from heterosexual contact with Africans, we suggest that such contact would constitute another risk factor for AIDS.

In certain central African countries Kaposi's sarcoma (KS) is common. The highest prevalence of KS--about 12% of all cancers--is found in Zaire (Hutt MSR: *Antibiot Chemother.*, 1981, 29:3-8).

The first case of an AIDS-like disease of probable African origin occurred in 1976 in a 46-year-old Danish woman surgeon who had been working in Zaire. She died of PC pneumonia in 1977 (Bygbjerg IC: *Lancet*, 1983, 1:925). Reports from Belgium (Clumeck N, Mascart-Lemone F, de Maubeuge J, et al: *Lancet*, 1983, 1:642) and France (Brunet JB, Bouvet E, Chaperon J, et al: *Lancet*, 1983, 1:700-701) point to Zaire and Chad as risk areas for AIDS. Next to Zaire, Burundi has the highest prevalence of African KS (Hutt, 1981). Other cases of AIDS are expected to develop in African immigrants to Europe and among Europeans who visit or live in Africa. Cases probably have occurred but may simply have been overlooked in the past. The case of AIDS described in this report reinforces the connection between KS and AIDS in the central African area.

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A PERSPECTIVE ON AIDS CASES AMONG HEALTH CARE WORKERS

It has been common knowledge at least since early 1982 that the epidemiology of AIDS is similar in many ways to that of hepatitis B. As a result, the