

a central role in the resulting hypercholesterolaemia,⁵⁻⁷ and the possibility has been raised of treating the disease with liver transplantation.⁸ The paucity of LDL receptors in the hepatocytes of patients with FH has been thought to be the most important factor in the sluggish catabolism as well as in the heightened total body synthesis of LDL and cholesterol.⁵⁻⁷ If this were true, provision of a normal liver would correct FH because transplanted hepatocytes retain their original metabolic specificity.²

In our patient, the degree of correction has been substantial, at least as judged by serum cholesterol concentrations, but it has not been complete. Serum cholesterol is now about 270 mg/dl. Absorption of cholesterol from rapidly involuting xanthomatous deposits may be contributing to this present level. Repeat metabolic studies in mid-May (to be published in detail elsewhere) will allow quantification of the changes in the synthesis and catabolism of cholesterol and LDL.

ADDENDUM

June 12, 1984: After 6 more weeks of follow-up (total now, 4 months) the patient remains well with normal cardiac and liver function. Plasma cholesterol and triglyceride concentrations remain the same as at the time of the report.

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ISOLATION OF HUMAN T-LYMPHOTROPIC RETROVIRUS (LAV) FROM ZAIRIAN MARRIED COUPLE, ONE WITH AIDS, ONE WITH PRODROMES

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Summary A Zairian married couple had been living in France since 1981. The man had acquired immunodeficiency syndrome (AIDS) and his wife had prodromes of the disorder. Infection with a human T-lymphotropic retrovirus (lymphadenopathy-associated virus) was demonstrated in both by isolation of the virus from their cultured lymphocytes and the detection of specific antibodies in serum samples. Since this virus has been isolated from patients in other AIDS risk categories, the finding of the virus in AIDS patients from the African group adds further support to the hypothesis that this human retrovirus is the AIDS aetiological agent.

INTRODUCTION

EVIDENCE of a role for retroviruses in acquired immunodeficiency syndrome (AIDS) has been supported by the isolation of a new human T-lymphotropic retrovirus (lymphadenopathy-associated virus; LAV) from high-risk populations such as homosexual men with lymphadenopathy syndrome^{1,2} and from AIDS patients²⁻⁴ such as a young haemophiliac.⁵ LAV affects in particular the OKT4-positive helper T-lymphocyte subpopulation³ (and D. Klatzmann et al, unpublished) that is involved in the cellular immune deficiency.^{6,7} Epidemiological surveys on serum antibodies

to LAV^{8,9} also suggest that this virus may have a role in the pathogenesis of AIDS. Many cases of this disorder reported in Europe since 1983 have been in Black patients from central and equatorial Africa¹⁰⁻¹⁴ or Whites who have travelled in this area.¹¹⁻¹⁵ They have none of the usual risk factors. Clearly, the isolation of LAV in AIDS patients from the African group, which has geographical, ethnic, and epidemiological characteristics distinct from those of the other AIDS risk categories, would be strong support for its role in the disease. We report here the isolation of an LAV-related virus from cultured lymphocytes of a Zairian couple living in France. The man had AIDS and prodromal symptoms were recognised in his wife.

CASE-REPORTS

Patient 1

A 26-year-old Black Zairian man was admitted to the Bicêtre hospital in November, 1982, with fever, weight loss, meningeal syndrome, hepatomegaly, splenomegaly, and lymphadenopathy. He had previously been healthy and denied homosexuality and drug abuse. He had never received any blood product transfusion. He and his wife had come from Zaire to France in 1981 and had not returned to Africa since. They had never travelled in the Caribbean or in the USA. The patient had oral thrush and condyloma acuminata. A herpes simplex homini virus was isolated in cultures from a genital ulcer. Severe disseminated cryptococcosis was diagnosed on direct examination and cultures of the cerebrospinal fluid, lymph-node and bone-marrow aspirates, urine, and liver biopsy samples. Examination of faecal samples revealed no parasite. He had serum antibodies to herpes simplex virus, cytomegalovirus, and Epstein-Barr virus, and markers of hepatitis B infection were present (table 1). His lymphocytes expressed the HLA DR5 phenotype. The cryptococcosis was controlled by antifungal agents, and the patient was discharged in April, 1983, on oral flucytosine and ketoconazole. Recently *Mycobacterium kansasii* tenosynovitis of the hand developed and he remains chronically ill.

Patient 2

Patient 1 and his wife, a 23-year-old Black Zairian, had been living together since 1980 and had discontinued sexual relations from November, 1982, until April, 1983. They parted a month later. In

TABLE I—HEPATITIS B MARKERS AND VIRAL SEROLOGY

	Patient 1 Nov, 1982, to Jan, 1983	Patient 2 April, 1983
HBsAg*	+	-
HBsAb*	-	±
HBcAg*	+	ND
HBcAb*	-	ND
HSV†	3200 (IgG)	1600 (IgG)
CMV†	3200 (IgG)	3200 (IgG)
EBV (IgG only)		
VCA‡	1280	320
EA‡	160	<5
EBNA§	320	160

Results expressed as presence (+), absence (-), or doubtful (±) in serum, or as serum antibody titres. HSV=herpes simplex virus; CMV=cytomegalovirus; EBV=Epstein-Barr virus; VCA=viral capsid antigen; EA=early antigen; EBNA=Epstein-Barr virus nuclear antigen; ND=not done.

Measured by: *radioimmunoassay; †enzyme-linked immunosorbent assay; ‡indirect immunofluorescence; §anticomplement immunofluorescence (Dr De Thè, Lyon).

TABLE II—IMMUNOLOGICAL EVALUATION

	Patient 1		Patient 2		Normal values*
	Dec, 1982	Nov, 1983	April, 1983	Feb, 1984	
IgG (g/l)	34.4	..	24.8	..	7-17
IgA (g/l)	4.36	..	4.96	..	0.7-3.5
IgM (g/l)	2.3	..	2.24	..	0.5-3.5
Lymphocytes ($\times 10^9/l$)	0.32	0.53	2.08	1.32	1.4-5.0
OKT3+ cells (%)	51	38.1	53.8	50	68.89±6.45
OKT4+ cells (%)	13	3.08	1.3	26	42.12±5.84
OKT8+ cells (%)	43	44.9	52.2	46	33.13±6.65
OKT4/OKT8	0.3	0.07	0.02	0.57	1.402±0.25
B cells (SIg+ cells)	35	13.20	16	28	11.7±1.6
In-vitro blastogenic responses (cpm)					
PHA	17 264	..	43 320-75 005
Con A	..	24 000	23 264	..	47 708-89 916

*Range or mean±standard deviation. SIg=surface immunoglobulin; PHA=phytohaemagglutinin; Con A=concanavalin A.

April, 1983, patient 2 had lost 11 kg of weight and complained of fatigue. She had oral thrush and chronic herpetic ulcers that had developed before June, 1982. Both were confirmed by culture. She had prurigo, confirmed by a skin biopsy. No parasites were detected in the stools. She had serum antibodies against herpes simplex virus, cytomegalovirus, and Epstein-Barr virus (table 1). Cervical lymphadenopathy developed in February, 1984. She refused further investigation.

IMMUNOLOGICAL EVALUATION

T-cell helper or suppressor-cytotoxic phenotype was determined by indirect immunofluorescence with monoclonal antibodies (Ortho Pharmaceuticals) and goat anti-mouse immunoglobulin (Cappel). B cells were counted by a fluorescence method with goat anti-human immunoglobulin F(ab')₂ fragments conjugated with fluorescein.¹⁶ Blastogenic responses were determined with phytohaemagglutinin (Sigma) 20 µg/ml and concanavalin A (Sigma) 5 µg/ml. Each experiment was done in parallel with lymphocytes from a healthy control from the hospital staff.

Patient 1 had cutaneous anergy as tested with standard tuberculin, candidin intradermal injections, and the 'Multitest' (Institut Merieux, Lyon, France) which contains seven antigens (tetanus, diphtheria, streptococcus, tuberculin, candida, trichophyton, and proteus). His serum IgG and IgA levels were raised (table II). He had absolute lymphopenia with a profound reduction in OKT4-positive cells (helper/inducer phenotype)— $0.042 \times 10^9/l$ on admission gradually falling to $0.003 \times 10^9/l$. The OKT4/OKT8 ratio was 0.3 on admission and fell to 0.02 in

April, 1983. The blastogenic response of peripheral blood lymphocytes to concanavalin A was greatly impaired. Patient 2 had cutaneous anergy to tuberculin and the multitest antigens. Her serum IgG and IgA levels were also high. Her absolute lymphocyte count was normal but she had $0.027 \times 10^9/l$ OKT4-positive cells and the OKT4/OKT8 ratio was 0.02. In October, 1983, this ratio was 0.15. The blastogenic responses to phytohaemagglutinin and concanavalin A were very low.

VIRUS ISOLATION

In November, 1983, T lymphocytes from patient 1's peripheral blood were cultured as previously described.^{1,3} Maximum virus production was obtained on day 15 (fig 1) as measured by reverse transcriptase activity in the cell-free supernatant.^{1,3} The virus was propagated on T lymphocytes from a normal donor, and a similar pattern of virus production was observed. In both cases, the reverse transcriptase peak was followed by a fall in cell growth. The virus was characterised as LAV by indirect immunofluorescence assay;¹ the virus-producing cells were recognised by the serum of the first patient from whom LAV was isolated (positive reference serum),¹ but not by specific antibodies to human T-cell leukaemia virus (HTLV) I p24 or to HTLV I p19. No antibody to HTLV I p24 or HTLV-associated membrane antigens could be detected in patient 1's serum (L. Schaffar). Moreover, an enzyme-linked immunosorbent assay^{3,9} showed that sequential serum samples from patient 1 (from November, 1982, to November, 1983) contained antibodies to LAV but not to HTLV I. These results were confirmed by radioimmunoprecipitation assay;¹ LAV p25 was immunoprecipitated by patient 1's serum (fig 2A). In February, 1984, a similar pattern of virus

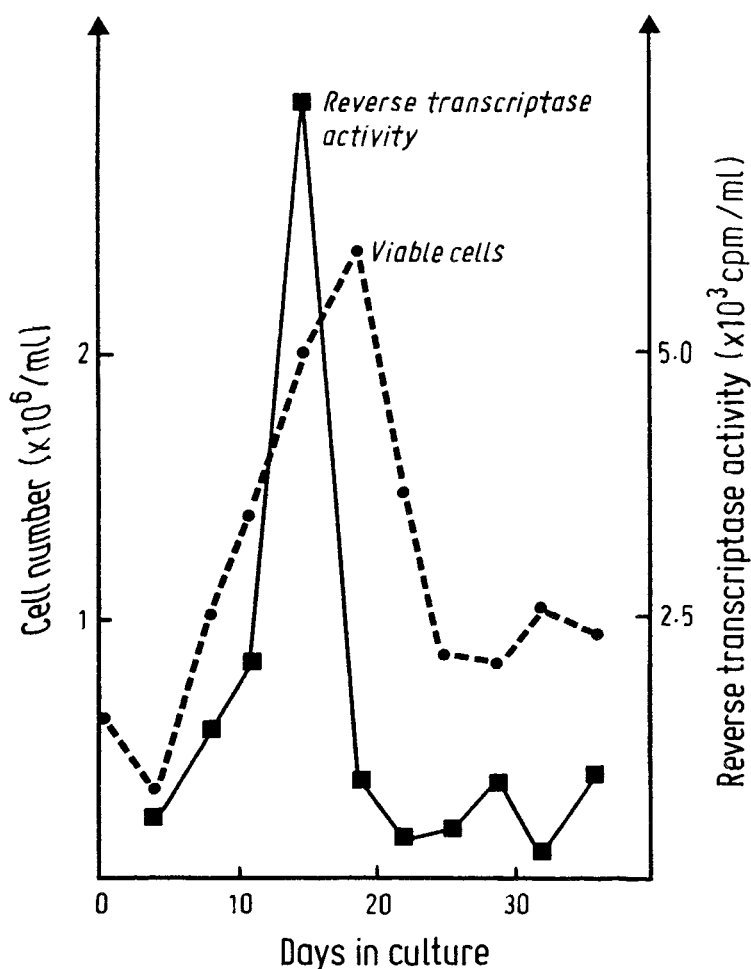


Fig 1—Virus production, measured by reverse transcriptase activity, and cellular growth of lymphocytes from patient 1.

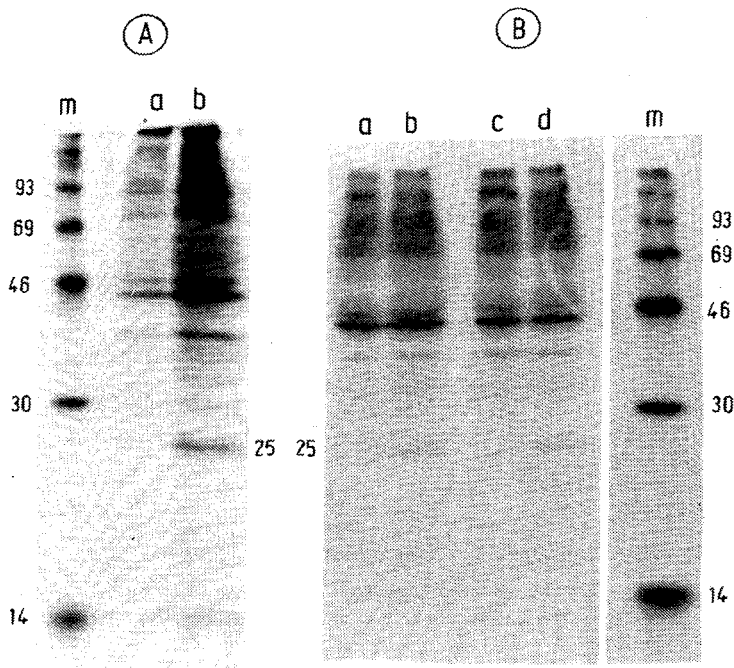


Fig 2—Cell lysates obtained from ^{35}S -methionine-labelled T lymphocytes immunoprecipitated with patients' sera.

A. Immunoprecipitates with patient 1's serum of normal T lymphocytes (lane a), and LAV-infected lymphocytes (lane b). Lane m = molecular weight markers.

B. Immunoprecipitates with patient 2's serum of normal T lymphocytes (lane a) and LAV-infected lymphocytes (lane b) and with positive reference serum of normal T lymphocytes (lane c) and LAV-infected lymphocytes (lane d). Lane m = molecular weight markers.

production was obtained from peripheral blood T lymphocytes of patient 2. At that time, antibodies to LAV were found in her serum by the radioimmunoassay (fig 2B), indicating that she was also infected with LAV. Studies of earlier serum samples from this patient by enzyme-linked immunosorbent assay showed no antibodies to LAV before February, 1984. Thus, LAV antibodies were detected in this patient only after cervical lymphadenopathy had developed.

DISCUSSION

There is strong evidence that AIDS is endemic in central and equatorial Africa.¹⁰⁻¹⁵ The report of Kaposi's sarcoma in Zambia with clinical and biological findings similar to those in AIDS¹⁷ and the likely underestimation of cryptococcosis¹⁸ in Zaire are further evidence. Our patient 1 meets the criteria for the diagnosis of AIDS¹⁹ and his wife has the prodromal symptoms for the disorder²⁰ or AIDS-related complex.¹⁴ They do not differ epidemiologically from other African patients¹⁰ and belong to none of the other AIDS risk categories.¹⁹ AIDS in non-Africans is thought to be caused by an agent transmitted sexually or, less commonly, through needles or blood.¹⁹ Several reports have suggested that a virus from the human retrovirus family might be the aetiological agent.^{1,21-23} The hypothesis of LAV being the agent is supported by its isolation from this couple. In addition, antibodies to LAV have been detected in sera of AIDS patients in Zaire and at a much lower level in a Zairian control population (unpublished). A virus called HTLV III with characteristics similar to those of LAV has been reported²⁴ as a possible aetiological agent of AIDS. Whether or not HTLV III and LAV are the same virus is now under investigation. Since the AIDS incubation period may be as long as 4 years,²⁵ our patients may have acquired the disease in Zaire. We cannot establish whether they acquired the

AIDS causative agent through sexual relations or independently by other modes of transmission. However, heterosexual transmission is seldom documented in non-Africans.^{26,27} The African AIDS risk category is special because of the unknown mode of transmission of the disease and its endemic pattern in Africa. Inoculation of LAV to animals with the reproduction of an AIDS-like disease and seroepidemiological studies, particularly in Africa, will be needed as definitive proof that LAV has an aetiological role.

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