was 1:80 to 1:640 (Table 1). Only one of the eight infected animals developed a titer that was as high as any of the six uninfected cats by day 31, and the geometric mean antibody titers were approximately 60 to 120 times higher for the uninfected cats. The antibodies present at the first peak (days 3 to 5) were predominantly immunoglobulin M for both groups, whereas the second peak (after day 10) was primarily immunoglobulin G as determined with ELISA (*5*).

Cats that are naturally infected with FeLV have a greatly increased risk of developing bacterial, viral, and parasitic diseases such as septicemia, stomatitis, peritonitis, pneumonia, haemobartonellosis, and toxoplasmosis (*2*). Presumably, many of these infections, which are usually controlled in part by the humoral immune system, would be subclinical in the absence of immune suppression by FeLV. We observed a delay in the humoral immune response in six of eight FeLV-infected cats and a diminished peak in the antibody response in six of the eight infected animals. These results indicate that FeLV infection causes a severe immune impairment which is expressed as a delayed humoral response and by prolonged depressed concentrations of detectable antibodies in the serum.

The polypeptide (T,G)AL is known to be a T-cell–dependent antigen in rodents (*6*). One would expect it to evoke the same general class of response in cats. That most of the infected cats could, after a certain time, respond to the antigen allows us to speculate that the impairment lies in the T-helper cell function, and that once the B cells are triggered antibodies can be produced. A specific impairment of OKT-4 positive T-helper cells occurs in cells from humans infected with the adult T-cell leukemia virus (*7*).

Little is known about the way in which FeLV causes immunosuppression. Results by Mathes *et al.* implicated a virion structural protein of approximately 15,000 daltons (*8*). In earlier studies, infection with FeLV was associated with prolongation of allograft rejection (*3*), thymic atrophy (*9*), depletion of paracortical lymphoid tissues (*9*), decreased response to T-cell mitogens (*10*), depressed peripheral blood lymphocyte counts (*2*), and diminished mobility of lymphocyte membrane capping (*11*). Despite these results, which appear to reflect both general impairment of lymphoid tissues and specific impairment of T-cell responses, earlier attempts to show that humoral immunity was depressed by FeLV infection were unsuccessful (*3*). Many of these studies were, however, conducted with cats that were inoculated in the laboratory with a particular strain of FeLV. Our results indicate that the humoral antibody response is diminished in cats that are naturally infected with FeLV.

ZE'EV TRAININ
DOROTHEE WERNICKE
Department of Cancer Biology, Harvard School of Public Health, Boston, Massachusetts 02115
HANNAH UNGAR-WARON
Department of Immunology, Kimron Veterinary Institute, Bet-Dagan, Israel
MAX ESSEX
Department of Cancer Biology, Harvard School of Public Health

References and Notes

1. N. Teich, J. Wyke, T. Mark, A. Bernstein, W. D. Hardy, Jr., in *RNA Tumor Viruses*, R. Weiss, N. Teich, H. Varmus, J. Coffin, Eds. (Cold Spring Harbor Press, Cold Spring Harbor, N.Y., 1982), p. 785.
2. M. Essex, W. D. Hardy, Jr., S. M. Cotter, R. M. Jakowski, A. Sliski, *Infect. Immun.* **11**, 470 (1975); R. G. Olsen, L. E. Mathes, S. W. Nichols, in *Feline Leukemia*, R. G. Olsen, Ed. (CRC Press, Boca Raton, Fla., 1981), p. 149; W. D. Hardy, Jr., P. W. Hess, E. G. MacEwen, A. J. McClelland, E. E. Zuckerman, M. Essex, S. M. Cotter, *Cancer Res.* **36**, 582 (1976); L. J. Anderson, O. Jarrett, H. M. Laird, *J. Natl. Cancer Inst.* **47**, 807 (1971); S. M. Cotter, W. D. Hardy, Jr., M. Essex, *J. Am. Vet. Med. Assoc.* **166**, 449 (1975).
3. L. E. Perryman, E. A. Hoover, D. S. Yohn, *J. Natl. Cancer Inst.* **49**, 1357 (1972).
4. W. D. Hardy, Jr., L. J. Old, P. W. Hess, M. Essex, S. M. Cotter, *Nature (London)* **244**, 266 (1973).
5. H. Ungar-Waron, I. Davidson, Z. Trainin, *J. Immunol. Methods* **53**, 175 (1982).
6. E. Mozes and J. Haimovich, *Nature (London)* **278**, 56 (1979).
7. M. Essex, *J. Natl. Cancer Inst.* **69**, 981 (1982).
8. L. E. Mathes, R. G. Olsen, L. C. Hebebrand, E. A. Hoover, J. P. Schaller, P. W. Adams, W. S. Nichols, *Cancer Res.* **39**, 950 (1979).
9. E. A. Hoover, L. E. Perryman, G. J. Kociba, *ibid.* **33**, 145 (1973); L. J. Anderson, O. Jarrett, H. M. Laird, *J. Natl. Cancer Inst.* **47**, 807 (1971).
10. G. L. Cockerell, E. A. Hoover, S. Krakowa, R. G. Olsen, D. S. Yohn, *ibid.* **57**, 1095 (1976).
11. J. E. Dunlap, W. S. Nichols, L. C. Hebebrand, L. E. Mathes, R. G. Olsen, *Cancer Res.* **39**, 956 (1979).
12. We thank M. F. McLane and R. Zuckerman for technical assistance, B. Willkie for providing antisera to cat immunoglobulins M and G, and D. Eardley and W. D. Hardy, Jr., for stimulating discussions. This work was supported by PHS grants CA-13885 and CA-18216.

7 February 1983; revised 11 April 1983

Antibodies to Cell Membrane Antigens Associated with Human T-Cell Leukemia Virus in Patients with AIDS

Abstract. *The acquired immune deficiency syndrome (AIDS), which has recently occurred at increasing rates in homosexual men, intravenous drug users, and others, is characterized by the development of Kaposi's sarcoma and several opportunistic infections including pneumonia caused by* Pneumocystis carinii. *Serum samples from patients with AIDS and from matched and unmatched control subjects were examined for the presence of antibodies to cell membrane antigens associated with human T-cell leukemia virus. Nineteen of 75 of the AIDS patients had antibodies directed to surface antigens of Hut 102, a reference T lymphoid cell line infected with the leukemia virus, as did two of the 336 control subjects.*

The human T-cell leukemia virus (HTLV), initially described in 1980 (*1*), was isolated from an American patient with mycosis fungoides, a form of T-cell lymphoma with extensive skin manifestations. Subsequently, the same virus was found in other individuals with lymphoid malignancies in this country and in various other geographical areas (*2–4*). Two regions of the world where both the virus and T-cell malignancies occur at increased rates are the Caribbean islands (*5–7*) and Southern Japan (*8–10*). In such areas from 4 to 37 percent of the healthy adults have antibodies to HTLV (*6, 7, 10, 11*). This contrasts with less than 1 percent of the healthy adults tested from selected regions of the continental United States, Western Europe, or Northern Japan who have such antibodies (*10–12*).

The acquired immune deficiency syndrome (AIDS) is a newly described disease that has recently been observed in several U.S. cities and in Haiti (*13–15*). The incidence of AIDS has been increasing dramatically. Although the disease was initially seen only in sexually active homosexual men, it has now been recognized in intravenous drug users, patients with hemophilia, Haitian immigrants, and heterosexual contacts of members of other high-risk groups (*15–17*). The syndrome, suspected to be of viral origin (*17*), is characterized by the development of Kaposi's sarcoma (KS), pneumonia caused by *Pneumocystis carinii* (PCP), and infections with various other opportunistic microorganisms. Such infections apparently develop because of an immune dysfunction that is characterized by lymphopenia with an imbalance of the normal ratio of T-helper cells to T-suppressor cells (*14, 16, 18*).

Patients with AIDS have increased titers of antibodies to cytomegalovirus and to the Epstein-Barr virus, and a

Table 1. Presence of antibodies to HTLV-MA in patients with AIDS, in patients with LAS, and in adult male homosexual controls. The Hut 102 and MT 2 cell lines were cultured as described earlier and used at peak phase of logarithmic growth (*1, 8*). The cells (1×10^6 to 2×10^6) were washed twice in phosphate buffered saline (PBS) and exposed to 40 μl of a 1:4 dilution of previously centrifuged serum for 30 minutes at 37°C. Each preparation was then washed twice with PBS and reacted with 40 μl of a 1:20 dilution of fluorescein conjugated $F(ab')_2$ fragment of goat antiserum to human immunoglobulins (IgA + IgG + IgM) (Cappel, Cochranville, Pennsylvania). The samples were again incubated at 37°C for 30 minutes, washed twice with PBS, and examined by fluorescence microscopy. Serum samples were judged as positive if at least 50 percent (or 40 percent when indicated) of the cells showed specific fluorescence. All samples were coded and read in a double-blind manner. A positive and a negative reference human serum sample (*7*) was included in each test.

Category	Cells positive (> 50 percent)		Cells positive (< 40 percent)	
	Hut 102	MT 2	Hut 102	MT 2
AIDS patients				
KS patients	10/34 (29)*	9/34 (27)	14/34 (41)	11/34 (32)
PCP patients	7/30 (23)	6/30 (20)	10/30 (33)	7/30 (23)
Patients with both KS and PCP	2/11 (18)	3/11 (27)	3/11 (27)	4/11 (36)
LAS patients	6/23 (26)	6/23 (26)	7/23 (30)	7/23 (30)
Matched homosexual controls†				
Friends of patients	1/9 (11)	1/9 (11)	1/9 (11)	1/9 (11)
Patients from VD clinic	0/47 (0)	0/47 (0)	0/47 (0)	0/47 (0)
Private practice controls	0/25 (0)	0/25 (0)	0/25 (0)	0/25 (0)

* Number of individuals positive over the total number tested and percent positive. † Matched to 36 of the AIDS patients.

higher prevalence of antibodies to hepatitis A virus and *Treponema pallidum* (*16*). The cytomegalovirus, which was previously considered as a potential cause of the African form of KS (*19*), has also been viewed as a candidate agent for a causative role in the form of KS seen in AIDS patients.

Since individuals with AIDS are probably at greater risk than the normal population for infection with many agents, including those transmitted by blood or by close contact, we decided to determine if they had increased rates of exposure to HTLV. Serum samples examined for antibodies were obtained from 75 patients with AIDS including 72 men (60 homosexual) and 3 women. These included 34 cases of KS, 30 cases of PCP, 11 cases that had both PCP and KS, and 23 homosexual men with lymphadenopathy (LAS), a syndrome that sometimes progresses to AIDS (*20*). These samples were examined, under code, along with samples from three control groups. The control groups were as follows. Group 1, 81 matched homosexual men including 9 friends of AIDS patients, 47 patients from a venereal disease (VD) clinic, and 25 patients of private physicians, all matched to 36 of the AIDS patients for age, race, sexual preference, and place of residence. [For the selection of these cases and the controls, see (*16, 21*)]. Group 2, 118 unmatched homosexual male controls who visited a VD clinic in Chicago in 1978. This series of patients has been described before (*22*). Group 3, 137 first-time volunteer blood donors that gave blood in Philadelphia in 1977. The two last groups were collected before the recognition of AIDS. The samples were classified and coded at the Centers for Disease Control in Atlanta, and sent frozen to Boston for examination.

Several procedures have been used to survey serum samples for evidence of exposure to HTLV. These include radioimmunoassays for antibodies to p24, the major virion core protein (*6–8, 12*), and, with the use of HTLV-infected cells, indirect fixed-cell immunofluorescence (*9, 10, 23*) and indirect living-cell immunofluorescence (*8, 11*). We used the last procedure with two reference HTLV-infected cell cultures, Hut 102 (*1*) and MT 2 (*4*), and two HTLV-uninfected human lymphoid lines, 8402, a T-cell line (*24*), and NC37, a B-cell line that is negative for HTLV and positive for the Epstein-Barr virus genome and lacks surface immunoglobulin (*24*). Hut 102 is the prototype HTLV-infected T-cell culture established from an American patient and MT 2 is a standard HTLV-infected T-cell line established with virus from a Japanese patient. Both are of the OKT 4 phenotype (*3, 25*). When sufficient serum was available, selected samples were also checked by radioimmunoprecipitation with [^{35}S]methionine-labeled HTLV-infected cells or by the lactoperoxidase method with ^{125}I-labeled cells as previously described (*26, 27*).

When samples were judged to be positive on the basis of their ability to cause fluorescence on more than 50 percent of the target cells, 10 of 34 and 9 of 34 of the serum samples from KS patients were positive for the HTLV-associated cell membrane antigen (HTLV-MA) on Hut 102 cells and MT 2 cells, respectively (Tables 1 and 2). Also, 7 of 30 AIDS patients with PCP and 6 of 23 patients with LAS were positive on Hut 102. Overall, 19 of 75 AIDS patients were positive for HTLV-MA at the 50 percent level on Hut 102, compared to only 1 of 81 of the matched control samples, 0 of 118 unmatched homosexual samples, and 1 of 137 of the adult blood donor control samples (Table 2). Twenty-nine samples were tested from patients with chronic active hepatitis and 21 samples were tested from kidney dialysis patients. None of these 50 were positive. Of the 19 serum samples from AIDS patients that were positive for antibodies to HTLV-MA and reacted with 50 percent or more of the Hut 102 cells, all but two reacted with more than 60 percent of the cells and most reacted with more than 70 percent. This range in reactivity is very similar to that seen with positive reference sera obtained from Japanese patients with HTLV-related T-cell leukemia (*11*). The one matched control sample that was positive was from the limited series of nine samples collected as matched friends of AIDS patients. In all categories the results obtained when the MT 2 target cell was used were similar to the results obtained with the Hut 102 target. Of the 27 samples in all categories that were positive at the 50 percent level on Hut 102 cells (Table 2), 19 of 27 or 70 percent were also positive at the 50 percent level on MT 2. No difference was observed in the proportion of antibody positive samples in the 36 matched AIDS cases compared to the 39 unmatched cases. Fourteen serum samples that were positive for antibodies to HTLV-MA were also tested for reactivity with 8402 and NC37 cells. All were negative on both targets.

Twenty positive serum samples from AIDS and LAS patients were available in sufficient quantities to carry out immunoprecipitation of solubilized [^{35}S]-methionine-labeled Hut 102 cells. Of these, 16 (75 percent) precipitated either p24, the major HTLV core protein, or p28, a polyprotein containing p24 (*1, 23, 28*), or both. Examples of these reactions are shown in Fig. 1. Most also precipitated p61, an HTLV-related glycoprotein that is detected at the surface of Hut 102 cells with positive reference sera obtained from Japanese T-cell lymphoma

patients that react with HTLV-MA (*11*). In most cases, however, the reactivity with the serum samples by immunoprecipitation was weak. Four samples from HTLV-MA antibody-negative AIDS patients were also tested by immunoprecipitation and each was negative for all known HTLV-related proteins detected by this technique.

The antigens that make up the HTLV-MA reactivity, which appears to be specific to HTLV-infected cells, include p61 and p28 (*30*). Whether p61 represents the product of a cell gene that is activated by HTLV or a direct product of the HTLV genome has not been established. One histocompatibility antigen, DR5, has been seen more often than expected in patients with KS (*30*). However, it seems very unlikely that HTLV-MA antibodies are directed to DR5 because the reference cells Hut 102 and MT 2 both lack this antigen (*3, 31*).

These results suggest that at least 25 percent of AIDS patients have evidence of exposure to HTLV or a closely related agent. Although another 10 percent or more could be considered weakly positive if a lower cutoff was used for the evaluation (Table 1), about half of the patients were clearly negative for HTLV-MA antibodies. However, the prevalence rate for exposure to HTLV was at least 10- to 40-fold higher in AIDS patients compared with other homosexual controls, a situation that was not seen for other infectious agents evaluated in the same individuals (*16*).

Table 2. Presence of antibodies to HTLV-MA in patients with AIDS, in patients with LAS, in matched and unmatched healthy male homosexual controls, and in blood donors. The procedure used is described in the legend for Table 1.

Category	Greater than 50 percent of cells positive	
	Hut 102	MT 2
AIDS patients	19/75 (25)*	18/75 (24)
LAS patients	6/23 (26)	6/23 (26)
Matched homosexual controls†	1/81 (1)	1/81 (1)
Unmatched homosexual controls	0/118 (0)	0/118 (0)
Blood donors	1/137 (0.7)	2/137 (1.5)
Kidney dialysis patients	0/21 (0)	0/21 (0)
Chronic active hepatitis patients	0/29 (0)	0/29 (0)

*Number of individuals positive over total number tested and percent positive. †All were matched to 36 of the AIDS patients.

Human T-cell leukemia virus is a lymphotropic retrovirus that preferentially infects T-helper cells (*2, 32*). Although most lymphoma cells of the type associated with HTLV are of the helper-cell phenotype, they actually show suppressor rather than helper activity when evaluated in vitro (*33*). Little or nothing is known about whether HTLV ever causes immunosuppression in healthy carriers. However, other naturally occurring retroviruses, such as the feline leukemia virus, cause thymic atrophy (*34*), lymphopenia (*35*), and profound immunosuppression (*36*).

The mechanisms by which HTLV is transmitted is unknown. Transmission by blood transfusion has been considered (*37*), but this could only account for a small proportion of the infections. The rate of infection in spouses of patients with T-cell lymphoma is elevated (*7*), suggesting that HTLV might be transmitted by sexual intercourse or other types of close contact. As mentioned above, two areas where HTLV infection is frequent are Southern Japan and the Caribbean. To our knowledge AIDS has not been reported in Japan. It has, however, been well documented in Haitians (*17*).

Our results indicate that homosexual patients with AIDS and LAS have increased risk for infection with HTLV or a related agent. Such individuals should be monitored to determine rates for de-

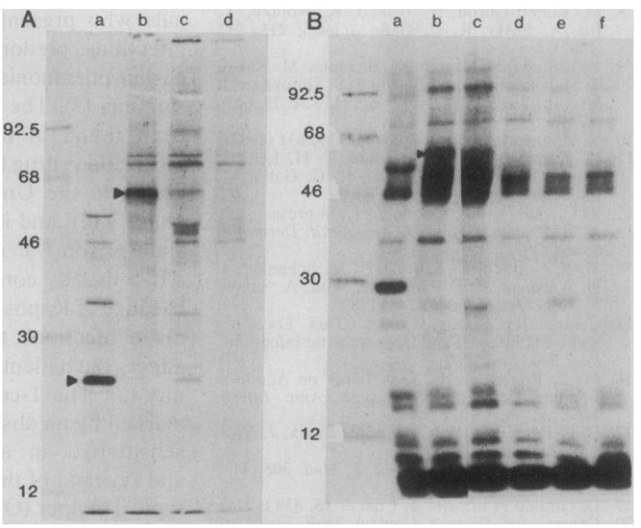

Fig. 1. Reactivity of serum samples from AIDS patients positive for antibodies to HTLV-MA as determined by sodium dodecyl sulfate (SDS)–polyacrylamide gel electrophoresis. (A) Hut 102 cells at their peak log phase of growth were harvested and exposed to [^{35}S]methionine [100 μCi/ml; specific activity 1050 Ci/mmole; New England Nuclear (NEN)], for 2 to 4 hours. A soluble cell lysate was obtained after disruption with RIPA buffer (0.15*M* NaCl, 0.05*M* tris-HCl, *p*H 7.2, 1 percent Triton X-100, 1 percent sodium deoxycholate, and 0.1 percent SDS) and centrifuged for 1 hour at 100,000*g*. The lysate supernatant was cleared once with 10 μl of reference negative control serum bound to Protein-A–Sepharose CL-4B (Protein-A beads) before portions were reacted with 10 μl of the following sera preabsorbed with Protein A beads: (a) reference goat antiserum to purified p24 of HTLV (5 μl) (*8*); (b) representative fluorescence-positive reference serum from a Japanese patient with adult T-cell leukemia (*8*); (c) serum from a representative individual with AIDS that was positive for antibodies to HTLV-MA by membrane immunofluorescence; (d) serum from a representative healthy homosexual control individual that was negative for HTLV-MA by membrane immunofluorescence. Immunoprecipitates were eluted in a sample buffer containing 0.1*M* Cleland's reagent, 2 percent SDS, 0.08*M* tris-HCl, *p*H 6.8, 10 percent glycerol, and 0.2 percent bromophenol blue by boiling at 100°C for 2 minutes. Samples were analyzed in a 12.5 percent acrylamide resolving gel with 3.5 percent stacking gel according to the discontinuous buffer system of Laemmli (*38*). The molecular weight markers, purchased from NEN, were ^{14}C-labeled phosphorylase b (92,500), bovine serum albumin (68,000), ovalbumin (46,000), carbonic anhydrase (30,000), and cytochrome *c* (12,000). (B) Surface-labeling was carried out by lactoperoxidase-catalyzed radioiodination. Three portions of 5 × 10^6 Hut 102 cells with greater than 99 percent viability were iodinated separately with 1 mCi of carrier-free Na^{125}I (NEN) in the presence of 50 μl of Enzymobeads (Bio-Rad) and 25 μl of 1 percent β-D-glucose. After the reaction was terminated, three portions of iodinated cells were pooled and the same procedures as those described in (A) were followed to prepare cell lysates. Portions of cell lysate, after being cleared once, were reacted with 10 μl of each of the following sera: (a) reference goat antiserum to purified p24 of HTLV (*8*); (b) representative serum positive for HTLV-MA by membrane immunofluorescence, from a Japanese patient with T-cell leukemia (*8*); (c) and (d) serum samples from two representative patients with AIDS that were positive for antibodies to HTLV-MA by membrane immunofluorescence [(d) was judged negative by immunoprecipitation]; and (e) and (f) serum samples from two representative healthy homosexual controls that were negative for antibodies to HTLV-MA by membrane immunofluorescence.

velopment of lymphoma, especially those of T-cell origin. Our results also suggest that HTLV should, along with cytomegalovirus and other agents, be studied to determine what role, if any, it might play in the development of AIDS.

M. ESSEX
M. F. MCLANE
T. H. LEE
L. FALK
C. W. S. HOWE
J. I. MULLINS
Department of Cancer Biology, Harvard University School of Public Health, Boston, Massachusetts 02115
C. CABRADILLA
D. P. FRANCIS
Centers for Disease Control, Atlanta, Georgia 30333

References and Notes

1. B. J. Poiesz, F. W. Ruscetti, A. F. Gazdar, P. A. Bunn, J. D. Minna, R. C. Gallo, *Proc. Natl. Acad. Sci. U.S.A.* **77**, 7415 (1980).
2. B. J. Poiesz, F. W. Ruscetti, M. S. Reitz, V. S. Kalyanaraman, R. C. Gallo, *Nature (London)* **294**, 268 (1981); V. S. Kalyanaraman, M. G. Sarngadharan, M. Robert-Guroff, I. Miyoshi, D. Blayney, D. Golde, R. C. Gallo, *Science* **218**, 571 (1982); M. Popovic, P. S. Sarin, M. Robert-Guroff, V. S. Kalyanaraman, D. Mann, J. Minowada, R. C. Gallo, *ibid.* **219**, 856 (1983); I. Miyoshi, I. Kubonishi, S. Yoshimoto, T. Akagi, Y. Ohtsuki, Y. Shiraishi, K. Nagata, Y. Hinuma, *Nature (London)* **294**, 770 (1981).
3. R. C. Gallo, D. Mann, S. Broder, F. W. Ruscetti, M. Maeda, V. S. Kalyanaraman, M. Robert-Guroff, M. S. Reitz, Jr., *Proc. Natl. Acad. Sci. U.S.A.* **79**, 5680 (1982).
4. M. Yoshida, I. Miyoshi, Y. Hinuma, *ibid.*, p. 2031.
5. D. Catovsky *et al.*, *Lancet* **1982-I**, 639 (1982).
6. W. A. Blattner *et al.*, *Int. J. Cancer* **30**, 257 (1982).
7. J. Schüpbach, V. S. Kalyanaraman, M. G. Sarngadharan, W. A. Blattner, R. C. Gallo, *Cancer Res.* **43**, 866 (1983).
8. M. Robert-Guroff, Y. Nakao, K. Notake, Y. Ito, A. Sliski, R. C. Gallo *Science* **215**, 975 (1982).
9. Y. Hinuma, K. Nagata, M. Hanaoka, M. Nakai, T. Matsumoto, K.-I. Kinoshita, S. Shirakawa, I. Miyoshi, *Proc. Natl. Acad. Sci. U.S.A.* **78**, 6476 (1981).
10. Y. Hinuma *et al.*, *Int. J. Cancer* **29**, 631 (1982).
11. N. Tachibana, M. F. McLane, T. H. Lee, C. Howe, V. S. Kalyanaraman, R. C. Gallo, M. Essex, in preparation.
12. R. C. Gallo *et al.*, *Cancer Res.*, in press.
13. A. E. Friedman-Kien, *J. Am. Acad. Dermatol.* **5**, 468 (1971).
14. M. S. Gottlieb, R. Schroff, H. M. Schanker, I. D. Weisman, P. T. Fan, R. A. Wolf, A. Saxon, *N. Engl. J. Med.* **305**, 248 (1982).
15. Centers for Disease Control Task Force on Kaposi's Sarcoma and Opportunistic Infections, *ibid.* **306**, 248 (1982).
16. M. F. Rogers *et al.*, Task Force on Acquired Immune Deficiency Syndrome, *Ann. Intern. Med.*, in press.
17. D. P. Francis, J. W. Curran, M. Essex, *J. Natl. Cancer Inst.* **71**, 1 (1983).
18. F. P. Siegal *et al.*, *N. Engl. J. Med.* **305**, 1439 (1981).
19. G. Giraldo *et al.*, *Int. J. Cancer* **15**, 839 (1975).
20. Centers for Disease Control Task Force on Kaposi's Sarcoma and Opportunistic Infections, *Morbid. Mortal. Weekly Rep.* **31**, 249 (1982).
21. H. W. Jaffee *et al.*, *Ann. Intern. Med.*, in press.
22. M. T. Schreeder *et al.*, *J. Infect. Dis.* **146**, 7 (1982).
23. N. Yamamoto and Y. Hinuma, *Int. J. Cancer* **30**, 289 (1982).
24. J. Azocar and M. Essex, *J. Natl. Cancer Inst.* **63**, 1179 (1979).
25. I. Miyoshi, S. Yoshimoto, I. Kubonishi, H. Taguchi, Y. Shiraishi, Y. Ohtsuki, T. Akagi, *Gann* **72**, 997 (1981).
26. A. P. Chen, M. Essex, M. Kelliher, F. deNoronha, J. A. Shadduck, J. Y. Niederkorn, D. Albert, *Virology* **124**, 274 (1983).
27. J. J. Marchalonis, R. E. Cone, V. Santer, *Biochem. J.* **124**, 921 (1971).
28. V. S. Kalyanaraman, M. G. Sarngadharan, P. A. Bunn, J. D. Minna, R. C. Gallo, *Nature (London)* **294**, 217 (1981).
29. T. H. Lee, M. F. McLane, C. Howe, N. Tachibana, M. Essex, in preparation.
30. N. O'Hara and S. W. Chang, *Ann. Intern. Med.* **97**, 617 (1982).
31. D. L. Mann, M. Popovic, P. Sarin, C. Murray, B. F. Hanes, D. M. Strong, R. C. Gallo, W. A. Blattner, in preparation.
32. M. Essex, *J. Natl. Cancer Inst.* **69**, 981 (1982).
33. Y. Yamada, *Blood* **61**, 192 (1983).
34. E. A. Hoover, L. E. Perryman, G. J. Kociba, *Cancer Res.* **33**, 145 (1973).
35. M. Essex, W. W. Hardy, Jr., S. M. Cotter, R. M. Jakowski, A. Sliski, *Infect. Immun.* **11**, 470 (1975).
36. L. E. Perryman, E. A. Hoover, D. S. Yohn, *J. Natl. Cancer Inst.* **49**, 1357 (1972); Z. Trainin, D. Wernicke, H. Ungar-Waron, M. Essex, *Science* **220**, 858 (1983).
37. I. Miyoshi, M. Fujishita, H. Taquchi, Y. Ohtsuki, T. Akagi, Y. M. Morimoto, A. Nagasaki, *Lancet* **1982-I**, 683 (1982).
38. U. K. Laemmli, *Nature (London)* **227**, 680 (1970).
39. Supported by grant RD-173 from the American Cancer Society and NIH grants CA 18216, 2T32CA09031 and 5T32HL07523. C.W.S.H. is also a member of the Department of Hematology at Brigham-Women's Hospital. We thank R. Gallo for stimulating discussions, reference reagents, and the exchange of information prior to publication.

24 March 1983; revised 11 April 1983

Proviral DNA of a Retrovirus, Human T-Cell Leukemia Virus, in Two Patients with AIDS

Abstract. *The acquired immune deficiency syndrome (AIDS) is characterized by T-lymphocyte dysfunction and is frequently accompanied by opportunistic infections and Kaposi's sarcoma. Human T-cell leukemia virus (HTLV) is associated with T-cell malignancies and can transform T lymphocytes in vitro. In an attempt to find evidence of HTLV infection in patients with AIDS, DNA from samples of peripheral blood lymphocytes from 33 AIDS patients was analyzed by Southern blot-hybridization with a radiolabeled cloned HTLV DNA probe. Analysis of DNA from both the fresh (uncultured) lymphocytes and from T cells cultured with T-cell growth factor revealed the presence of integrated HTLV proviral sequences in lymphocytes from two of the patients, both of whom had antibody to HTLV. The proviral sequences could not be detected in blood samples obtained from these individuals at a later date, consistent with the possibility that the population of infected cells had become depleted.*

Acquired immune deficiency syndrome (AIDS) is a new disease whose incidence in the United States has increased steadily since 1979 (*1*). The disorder was first noted in male homosexuals who presented with opportunistic infections, predominantly *Pneumocystis carinii* pneumonia (*2*), or with Kaposi's sarcoma (*3*). The syndrome has recently been found in other groups including intravenous drug users (*4*), Haitian immigrants to the United States (*5*), hemophiliacs (*6*), and inmates at a New York state prison (*7*). Although patients with AIDS usually come to medical attention because of Kaposi's sarcoma or opportunistic infections, the underlying disorder affects the patients' cell-mediated immunity (*8*). The T-cell dysfunction is often marked by an absence of delayed hypersensitivity, an absolute lymphopenia, and reversal of the usual ratio of phenotypic T-helper ($OKT4^+$) to T-suppressor ($OKT8^+$) cells whereby the latter come to predominate among circulating lymphocytes (*8*). Although the epidemiologic data suggest an infectious, possibly viral, etiology for AIDS, no agent has been linked etiologically to the disease. Many of the patients have chronic infection with cytomegalovirus (*9*) or hepatitis B virus, but the presence of these agents may be characteristic of the social history of the patients and may have preceded the disease or may represent infections permitted by the immune deficit.

We have been testing the hypothesis that AIDS is caused by a human retrovirus related to the human T-cell leukemia virus, HTLV (*10*). Retrovirus infection, known to cause leukemias, lymphomas, and solid tumors in several species of animals and T-cell malignancies in man, has also been shown to result in immune deficiency in some cats infected with feline leukemia virus (*11*). The target cell for the putative AIDS agent may be the T cell or a T-cell subset. Since HTLV is a T-cell tropic retrovirus (*12*), it can be linked hypothetically to other human T-cell disorders. The finding of AIDS in Haitians who may not have been exposed to other risk factors for the disease may be important since HTLV appears to be endemic in the West Indies (*13*). The search for evidence of retrovirus infection poses many problems. Several of the hallmarks of such infection, namely virus production, complete provirus integration into the host DNA, and antibody response to viral antigens have not been found in retrovirus-induced neoplasms. In a disease characterized by cellular depletion, as AIDS appears to be, it may be difficult to sample a pa-