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Idiopathic Production of Interleukin-1 in Acquired Immune Deficiency Syndrome

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We determined the capacity of peripheral blood monocytes from 19 patients with acquired immune deficiency syndrome (AIDS) or related conditions (1 with lymphadenopathy, 8 with AIDS-related complex, and 10 with AIDS) to produce intracellular and extracellular interleukin-1 (IL-1) spontaneously and upon stimulation with bacterial endotoxin. All patients were anti-human T-cell lymphotropic virus type III antibody positive. Results were compared with those obtained with 10 normal controls of similar age. A subset of patients who spontaneously produced high amounts of intracellular and extracellular IL-1 was identified. Total production of IL-1 in this subset was an average of 2.9 times that of controls. It is suggested that spontaneous production of IL-1 in this group represents an in vivo phenomenon since it was associated with more than 3 g of globulins per deciliter of serum, more than 2,300 mg of immunoglobulins per deciliter of serum, higher IgA values, higher titers of anti-Epstein-Barr virus antibodies, and lower neutrophil counts in peripheral blood. The role of Epstein-Barr virus, human immunodeficiency virus itself, or other infectious agents in spontaneous IL-1 production by these patients remains to be determined. Stimulation with endotoxin induced intracellular and extracellular IL-1 production to similar levels in patients and controls. These results show that AIDS patients are able to produce and release IL-1. High idiopathic production of IL-1 identified in some patients can help to explain the hypergammaglobulinemia seen in AIDS patients and might also be related to progression and severity of the disease.

Acquired immune deficiency syndrome (AIDS) is a recently recognized disease of the immune system in which a number of altered immune parameters have been described (33, 35). Since its earliest description, it was clear that one of the prominent features of AIDS was a decrease in the absolute number of T helper ($OKT4^+$) lymphocytes. The diminished number of these cells determined not only a decreased T helper/suppressor ratio but also was central to most of the immune alterations observed in vitro and in vivo (33, 35). Subsequently, lack of B-cell response to mitogens, B-cell polyclonal activation, and deficiency in natural killer function were also demonstrated (14, 18, 25). The involvement of other host defense components has been less well characterized. Quantitative defects of mononuclear phagocytes do not seem to be common (33, 38). However, functional alterations of mononuclear phagocytes either primary, such as defective chemotaxis and adherence (15, 37), or secondary, such as lymphokine-induced phagocytosis (27), to the T-cell defect are more common. Mononuclear phagocytes have a crucial role in the induction of immune responses by presenting antigens to the T and B cells (7, 39) and by delivering signals via monokines to the same cells, which allows them to expand clonally (29, 36). The best-characterized monokine is interleukin-1 (IL-1), formerly known as lymphocyte-activating factor (12). Recent studies have shown that monocytes from patients with AIDS release normal levels of IL-1 (1, 6). The released IL-1 could play a major role in the systemic manifestations seen in AIDS, like fever and the wasting syndrome (5, 12). On the other hand, when human monocytes are stimulated by biological agents like bacterial lipopolysaccharides (LPS), most of the IL-1 produced is retained within the cells (19). This intracellular IL-1 fraction is probably more related to the in situ immune function of monocytes (12, 17). Since no assessment of the intracellular IL-1 compartment in AIDS has been conducted, we determined the in vitro capacity of peripheral blood monocytes from patients to produce intracellular IL-1 and to release it upon stimulation with LPS. During the course of these studies, a subset of patients was identified that produced and released IL-1 without intentional in vitro stimulation. As the laboratory data showed, this subset of patients might represent a group with a more profound alteration of the immune system.

MATERIALS AND METHODS

Patients and controls. Of 19 patients at the AIDS clinic at the M. D. Anderson Hospital and Tumor Institute between August and November 1985 who were studied, 18 were male homosexuals between 22 and 49 years of age and the remaining patient was a 30-year-old woman with transfusion-related AIDS. Four males were also intravenous drug abusers.

All patients were anti-human T-cell lymphotropic virus type III antibody positive by enzyme-linked immunosorbent assay and had been referred by physicians for treatment of an AIDS-related condition. The patients were studied before any form of immunorestorative treatment. Whereas 1 patient had lymphadenopathy, 8 had AIDS-related complex, and 10 had AIDS. Of the AIDS patients, five had opportunistic infections (OI), three had Kaposi's sarcoma, and two had both Kaposi's sarcoma and OI. Of the AIDS-OI patients, one had active *Pneumocystis carinii* pneumonia and active anal herpes, and four patients had a history of *P. carinii* pneumonia. Of the AIDS-OI patients with Kaposi's sarcoma, one had active disseminated candidiasis and gastro-

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TABLE 1. Spontaneous production of IL-1 in AIDS patients

Subjects (no.)	Mean (± SE) IL-1 production (U/ml)			Intra-/extracellular ratio
	Extracellular	Intracellular	Total	
Controls (10)	3.4 ± 0.73	24.5 ± 7.1	27.3 ± 7.6	8.5 ± 1.7
AIDS patients (19)	11.6 ± 2.6[a]	42.0 ± 8.4	54.1 ± 10.7	6.9 ± 1.6
NrP[b] (8)	2.4 ± 0.65	18.3 ± 3.6	20.5 ± 3.9	10.2 ± 3.3
SpP[b] (11)	18.4 ± 3.1[a]	59.4 ± 11.9[a]	78.6 ± 14.2[a]	3.4 ± 0.6[a]

[a] $P < 0.05$ by nonpaired t test when compared with controls. All others, $P > 0.05$.
[b] Subgroups NrP and SpP were based on spontaneous release of <7 or >7 U of IL-1 per ml, respectively.

intestinal tuberculosis, and one had a history of *P. carinii* pneumonia and candidiasis.

Controls were 10 healthy heterosexual males and females of similar ages from hospital personnel.

Cell cultures. The general recommendations for handling blood products from AIDS patients were followed (Centers for Disease Control, Morbid. Mortal. Weekly Rep. **31**:1–6, 1982). Patients and normal controls were assayed at the same time. Peripheral blood monocyte cultures for the assessment of IL-1 production were performed as described previously (19), with modifications. Peripheral blood mononuclear cells obtained by Ficoll-Hypaque density gradient centrifugation from normal controls were washed with balanced salt solution and adjusted to 6×10^6 cells per ml in RPMI 1640 medium with 10% heat-inactivated human AB serum from a single normal donor. Because of relative monocytosis observed in patients, mononuclear cells from patients were obtained and washed in the same way for the controls but adjusted to 4×10^6 cells per ml to contain a comparable number of monocytes. All solutions were endotoxin free as determined by the *Limulus* assay. Samples (0.5 ml) of cell suspensions from either patients or controls were dispensed in 24-well plastic culture plates (Limbro, New Haven, Conn.) and allowed to adhere for 1 h at 37°C in a 5% CO_2 incubator. The nonadherent cells were then removed by gentle washing. The remaining monolayer consisted of more than 98% nonspecific esterase-positive cells morphologically identifiable as monocytes. The cells adhering to one replicate well were counted by the method of Nakagawara and Nathan (28) with cetavlon and a Coulter Counter (model Zf; Coulter Electronics, Inc., Hialeah, Fla.). Amplification and threshold settings were adjusted to give readings comparable to those obtained with a hemacytometer. The monocytes adhering in the remaining replicate wells were further incubated with culture medium RPMI 1640 and 5% human serum with or without 1 μg of LPS from *Salmonella typhimurium* (Difco Laboratories, Detroit, Mich.) per ml. The cells were cultured for 20 h at 37°C in 5% CO_2 in air. The supernatants were harvested, centrifuged, separated, and frozen until tested. Samples (0.5 ml) of RPMI 1640 and 5% human serum were added to the cells remaining, and the culture plates were frozen at −20°C until further preparation.

On the day of testing for IL-1, the supernatants and monolayers were allowed to thaw and the cell lysates were scraped off the wells and transferred to a test tube. Both supernatant and lysate aggregates were dispersed in an ultrasonic cleaning bath and tested.

IL-1 assay. For determination of IL-1 activity, the thymocyte costimulatory assay was used (11, 19). The assay is based on the capacity of IL-1 to potentiate the mitogenic response of mouse thymocytes to suboptimal doses of phytohemagglutinin. C3H/HeJ mice (Jackson Laboratory, Bar Harbor, Maine) were the source of thymocytes. Samples were assayed at dilutions of 1:5, 1:25, and 1:125 to minimize the effect of potential inhibitors. Samples (0.1 ml) of each dilution were mixed in triplicate with the same volume of thymocyte suspension (15×10^6 cells per ml) to which phytohemagglutinin (10 μg/ml) and 2-mercaptoethanol (5×10^{-5} M) had been added. The cultures were incubated at 37°C for 72 h. At 6 h before termination, 1 μCi of tritiated thymidine (specific activity, 2 Ci/mmol) was added to each culture in a volume of 10 μl. The cultures were harvested in filter paper with a cell harvester, and thymidine incorporation was measured in a scintillation counter. The results in counts per minutes were plotted and compared with those of a reference preparation tested at the same dilutions and arbitrarily assigned the value of 100 U/ml (standard); thus, the results are given in units per milliliter, calculated as described previously (32). The standard was a mixture of intra- and extracellular IL-1 produced by normal human monocytes stimulated with LPS (5 μg/ml) for 20 h, and it was kept in aliquots frozen at −70°C until its use. The same standard was used throughout the entire study.

Other tests performed. The following studies were also performed on all of the patients as part of their initial immunological evaluation: complete blood count; mononuclear cell marker T11, T3, T4, T8, T10 (Ortho Diagnostics, Raritan, N.J.), B-1 (Coulter), and Ia (Becton Dickinson, Mountain View, Calif.) counts with a laser flow cytometer (Ortho); delayed-hypersensitivity skin tests with the multitest CMI unit (Merieux Institute Inc., Miami, Fla.); immunoglobulin assay by immune nephelometry; cytomegalovirus and Epstein-Barr virus (EBV) serology by enzyme immunoassay.

Statistics. Simple linear correlation, the chi-square test, and Student's t test for nonpaired samples were used for statistical evaluations.

RESULTS

Production of IL-1. (i) Nonstimulated cultures. Regardless of the number of cells per culture, nonstimulated cultures from normal controls released very little IL-1 into the medium (<7 U/ml), while showing significant intracellular accumulation (average of 24.5 U/ml or 8.5 times the activity released (Table 1). Intracellular IL-1 activity correlated with the number of cells cultured ($r = 0.673$, $P < 0.05$). This pattern of spontaneous production is consistent with our previous observations (19). Compared with those from controls, nonstimulated cultures from AIDS patients released more IL-1 spontaneously (mean ± standard error [SE], 11.6 ± 2.6 versus 3.4 ± 0.73 U/ml; $t = 2.43$, $P < 0.05$ [Table 1]). The amount of IL-1 released by patients was independent of the number of cells per culture ($r = 0.069$, $P > 0.05$). The distribution of the values showed that the difference between patients and controls was mainly due to a subset of patients

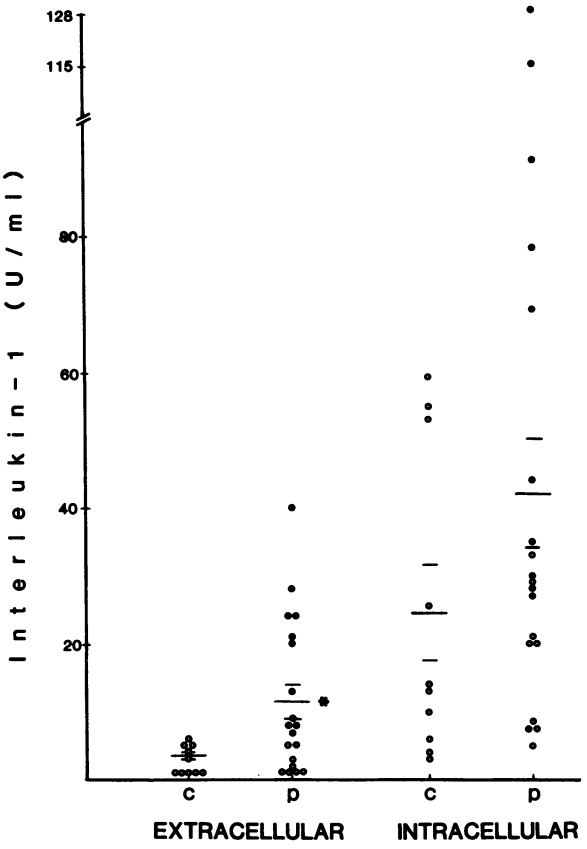

FIG. 1. Spontaneous production of extracellular and intracellular IL-1. Distribution of values obtained in controls (c) and patients (p). Filled circles correspond to patients who produced more than 7 U of extracellular IL-1 per ml. Bars indicate means ± SE. *, $P < 0.05$ compared with controls.

(11 of 19) that released more than two standard deviations of IL-1 above the mean of the controls (>7 U/ml), while the remaining cases, (8 of 19) behaved as did the controls (Fig. 1). Patients who released IL-1 activity comparable to that of controls (normal producers [NrP]) also had intracellular IL-1 activity at a level similar to that of controls (Table 1). On the other hand, patients who released more than 7 U of IL-1 per ml (spontaneous producers [SpP]) also accumulated significantly more intracellular IL-1 activity than did controls (mean ± SE, 59.4 ± 11.9 versus 24.5 ± 7.1 U/ml; $P < 0.05$), and there was no correlation of IL-1 activity and the number of cells cultured ($r = 0.03$, $P > 0.05$). In the subgroup of SpP, the ratio of intra- to extracellular IL-1 was significantly lower than in controls because of relatively higher extracellular activity (Table 1). There was no difference in the number of cells per well cultured between subgroups NrP and SpP (625,763 ± 83,840 versus 703,957 ± 83,388; $t = 0.645$, $P > 0.05$) or between all patients and controls (671,033 ± 58,909 versus 491,341 ± 78,738; $t = 1.809$, $P > 0.05$). The total spontaneous production of IL-1 (extracellular plus intracellular) by SpP was an average of 2.9 times that of controls and 3.8 times that of NrP.

(ii) LPS-stimulated cultures. In control cultures, IL-1 activity released upon LPS stimulation was an average of 15.4 times higher than that seen in nonstimulated cultures. Under the same conditions, intracellular IL-1 activity rose by an average of 5.4 times (Table 2). In all patients, LPS stimulation enhanced the production of intra- and extracellular IL-1. The increment of production was, however, related to the levels observed without stimulation. Thus, the increment of intra- and extracellular IL-1 activity seen in NrP was comparable to that seen in control cases (17.2 times for extracellular IL-1 and 4.6 times for intracellular IL-1; Table 2), whereas the increment of production of IL-1 in SpP was significantly smaller (3.5 times for extracellular IL-1 and 2.2 times for intracellular IL-1; $P < 0.05$ when compared with controls and NrP; Table 2). The net result was that, upon LPS stimulation, both intra- and extracellular IL-1 activities in all patients were comparable to those of controls.

Typical results in the thymocyte costimulatory assay obtained in representative cases from each group with or without LPS stimulation are presented in Table 3.

In three SpP patients, the IL-1 determination was repeated 1 to 3 months after the first assay. In two patients, increased spontaneous release was again observed; the third patient showed a normal pattern. This last patient also showed general improvement of his symptomatology, whereas the first two did not.

Clinical correlation. An attempt was made to correlate the IL-1 data with the diagnosis, number of symptoms, temperature at the time of the study, absolute number of lymphocytes, T cells, immunoglobulins, and other clinical and laboratory parameters by linear correlation analysis. We were unable to find a significant linear correlation with any of the variables studied.

Since a difference in spontaneous production was detected among the patients, the clinical and laboratory parameters in subgroups NrP and SpP were compared by either the Student t test, considering absolute values, or the chi-square test, considering normal and abnormal values. In the SpP subgroup, the number of patients with more than 3 g of globulins per dl of serum, the number with immunoglobulins above 2,300 mg/dl of serum, immunoglobulin A levels, and titers of anti-EBV antibodies were significantly higher, whereas the number of neutrophils in peripheral blood was significantly lower (Table 4). Statistical significance was not

TABLE 2. LPS-stimulated production of IL-1 in AIDS patients

Subjects (no.)	Mean (± SE) IL-1 production (U/ml)			Intra-/extracellular ratio	Induced/spontaneous ratio	
	Extracellular	Intracellular	Total		Extracellular	Intracellular
Controls (10)	40.7 ± 11.4	76.3 ± 16.8	117 ± 22.6	3.5 ± 1.4	15.4 ± 2.4	5.4 ± 1.4
AIDS patients (19)	41.6 ± 6.4	82.1 ± 10.2	124 ± 14.9	2.6 ± 0.49	9.2 ± 2.8	3.2 ± 0.7
NrP[a] (8)	26.9 ± 5.8	60.4 ± 13.1	87 ± 17.6	2.8 ± 0.6	17.2 ± 5.7	4.6 ± 1.5
SpP[a] (11)	52.3 ± 9.0	97.9 ± 13.2	150 ± 19.3	2.6 ± 0.75	3.5 ± 0.7[b]	2.2 ± 0.5[b]

[a] Subgroups NrP and SpP were based on spontaneous release of <7 or >7 U of IL-1 ml, respectively.
[b] $P < 0.05$ by nonpaired t test when compared with controls. All others, $P < 0.05$.

TABLE 3. Thymocyte costimulatory assay: results of spontaneous and LPS-induced release of IL-1 by monocyte cultures in representative AIDS patients from subgroups NrP and SpP[a]

Stimulus added to monocyte cultures (concn)	Supernatant dilution	Avg cpm (U/ml) produced by[b]:		
		Control	NrP AIDS patient	SpP AIDS patient
None	1:5	6,764 (1)[c]	6,912 (1)	61,397 (22)
	1:25	3,651	3,465	11,323
	1:125	2,484	2,352	6,633
LPS (1 μg/ml)	1:5	49,769 (60)	47,846 (38)	42,861 (114)
	1:25	35,388	22,094	50,379
	1:125	13,727	10,887	20,378

[a] Patients and control were studied and assayed for IL-1 production on the same days.
[b] Average counts per minute in triplicate cultures. The average counts per minute for the IL-1 standard (100 U/ml) were 99,183 (1:5), 47,923 (1:25), 17,049 (1:125), and 4,171 (1:625). For LPS medium alone the value was 2,067 cpm, and for culture medium alone it was 1,476 cpm. SE, <10% in all cases. The number of monocytes per culture was 363,950 for control, 387,825 for NrP, and 465,750 for SpP.
[c] Units per milliliter were calculated from the counts obtained in all three dilutions.

seen in other parameters analyzed by either test, including cell markers (T11, T3, T10, B-1, and Ia).

DISCUSSION

Mononuclear phagocytes are central to defense against infections in humans. As mentioned, some monocyte functions seem to be affected in patients with AIDS (15, 27, 37). The possibility of defective production of IL-1 by monocytes in AIDS has also been raised (13, 34). However, the results presented here confirm recent reports by Alcocer-Varela et al. (1) and Enk et al. (6) that monocytes from AIDS patients release significant amounts of IL-1 upon stimulation with LPS. The results can explain why addition of IL-1 in vitro failed to improve the proliferative responses of lymphocytes from AIDS patients to viral antigens and mitogens and in the autologous mixed-lymphocyte reaction in the studies of Sheridan et al. (34) and Gupta et al. (13), respectively. The present studies clearly demonstrate that the entire spectrum of AIDS patients produces not only extracellular IL-1 but intracellular IL-1 as well. The production follows the same pattern as in normal individuals in response to stimulation with LPS. Measurement of the intracellular fraction, in addition to extracellular IL-1, was incorporated since knowledge of both fractions provides an accurate estimate of total IL-1 production (19). Also, it has recently been shown that intra- and extracellular fractions can be distinguished physicochemically (20, 21) and are probably produced by different genes (2, 23), suggesting that their biological roles could also be different. The capacity of monocytes from AIDS patients to produce IL-1 upon stimulation with LPS could also be relevant for immunorestorative attempts based on stimulation of IL-1 production as a way to induce T4 cell expansion.

IL-1 production is an important component of the mononuclear phagocyte role during the induction of immune responses. Another important part, expression of Ia determinants, essential for antigen presentation to T and B cells, is probably normal (Y. Sei, R. J. Petrella, P. Tsang, and J. G. Bekesi, N. Engl. J. Med. **315**:1611, 1986), even though other related cells, like epidermal Langerhans cells, have been shown to express this antigen poorly in AIDS patients (3). On the other hand, processing and expression of antigens (31) have been difficult to assess because of a lack of T helper cells capable of recognizing the antigens processed.

The results in unstimulated cultures are particularly interesting. Human monocytes from normal adults, when cultured under controlled conditions, including LPS-free culture medium and serum and the least handling possible, release very small amounts of IL-1 into the culture medium but produce significant amounts of intracellular IL-1. This minimal stimulation is probably related to cell handling, adherence to the culture plates, and minimal amounts of LPS in serum or culture medium not detected by the *Limulus* assay (19). Under these conditions, monocytes from about half of the patients studied behaved as expected (NrP), whereas monocytes from the remaining patients (SpP) produced and released high IL-1 activity. Since differences in production could be related to specific patterns of the

TABLE 4. Clinical and laboratory features of NrP SpP AIDS patients

Patients (no.)	No. with:			Mean ± SE[a]						No. positive/no. studied with[a]:	
	AIDS-related complex	OI	Fever (>37°C)	No. of T4 cells/μl	No. of T8 cells/μl	T4/T8 ratio	Immunoglobulin A concn (mg/dl)	EBV titer	No. of polymorphonuclear leukocytes/μl	>3 g of globulins/dl	>2.3 g of immunoglobulins/dl
AIDS-NrP (8)	5[b]	1[b]	2[b]	262 ± 74[b]	512 ± 99[b]	0.52 ± 0.15[b]	251 ± 32[c]	373 ± 89[c]	2,998 ± 320[c]	3/8[c]	1/8[c]
AIDS-SpP (11)	4[b]	6[b]	6[b]	136 ± 50[b]	566 ± 133[b]	0.28 ± 0.09[b]	487 ± 92[c]	1,226 ± 314[c]	2,151 ± 235[c]	9/11[c]	6/9[c]

[a] For 192 normal controls, the 95% confidence limits were as follows: 950 to 1,094 T4 cells per μl, 581 to 675 T8 cells per μl, a T4/T8 ratio of 1.69 to 1.99, 30 to 225 mg of immunoglobulin A per dl, an EBV titer of <320, a polymorphonuclear leukocyte count of 1,500 to 7,000, 2 to 3 g of globulins per dl, and 0.75 to 2.3 g of immunoglobulins per dl.
[b] No significant difference between NrP and SpP AIDS patients.
[c] $P < 0.05$ by either the nonpaired t test or the chi-square test.

disease, patients in both groups were compared in diagnosis and in a series of clinical and laboratory features. Even though the most severe cases were among the SpP of IL-1, as evidenced by more OI, higher fever, lower T4 cell numbers, and lower T4/T8 ratios, the values of these parameters did not reach significant differences when compared with those of NrP, suggesting that other factors also relate to the symptomatology and severity of the disease. On the other hand, subgroup SpP was significantly associated with higher levels of immunoglobulins, specifically, higher immunoglobulin A levels, and higher titers of anti-EBV antibodies. These findings might be relevant because IL-1 and EBV have an important role in the stimulation of immunoglobulin production (8, 22, 30) and could help to explain the high levels of these proteins observed in AIDS patients.

The finding that peripheral blood mononuclear phagocytes from some AIDS patients spontaneously produced high levels of IL-1 in vitro, whereas the same cells from some other AIDS patients or normal controls did not, suggests that the cells from SpP had been stimulated before culturing or in vivo. If this were the case, spontaneous IL-1 production in AIDS patients would then be a sign of the disease related to its infectious complications. Any infectious agents known to induce IL-1 production and affect AIDS patients could have been responsible. Among others, the observed relationship with EBV was notable, but any gram-negative bacteria or some fungi could have played the same role. Alternatively, the enhanced production of IL-1 could be an idiosyncratic response to the retroviral infection itself affecting monocytes. In this case, spontaneous production of IL-1 might be a marker of a specific subgroup of AIDS patients.

Regardless of its ultimate cause, idiopathic production of IL-1 in AIDS might have an important role in its pathophysiology and prognosis. Indeed, production of IL-1 could be a link between the acute retroviral self-limited infection and a chronic active disease that leads eventually to full-blown immunodeficiency. It has been shown in vitro that activation of normal T4 cells by phytohemagglutinin facilitates infection by human T-cell lymphotropic virus type III (9). It is conceivable that in vivo a similar state of activation also provides a convenient setting for the replication of the virus. This could help to explain why homosexuals and transfusion recipients are the main affected populations; both groups have high numbers of circulating T cells activated by stimulation with alloantigens of the major histocompatibility complex (10, 24). IL-1 is one of the molecular mediators that participate in the activation of T helper cells in the presence of antigen (26). IL-1 induces the appearance of IL-2 receptors in T4 cells and induces the release of IL-2 by the same cells (4, 16). It is, therefore, possible that in vivo IL-1 production keeps the T4 pool activated and hence more susceptible to human T-cell lymphotropic virus type III, perpetuating the infection that progressively kills the antigen-recognizing T cells.

In this context, it is conceivable that patients in whom production of IL-1 is induced after the initial human T-cell lymphotropic virus type III infection (because of an inherent response to the virus or because of other infections) are those likely to develop a progressive disease. This is suggested by the fact that, 1 year after this study, three of five SpP patients with AIDS-related complex developed AIDS, compared with one of four in the NrP group. However, future analysis of a larger cohort of cases is necessary to determine comparative prognoses in these cases.

IL-1 is a molecule with a wide range of biological activities that probably participates actively in several immunological and inflammatory diseases (5). Clinical assessment of its production will help us understand its exact clinical and pathophysiological role and may help us to design better therapeutic approaches for those ailments in which its participation can be demonstrated.

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