Effect of *Strongyloides stercoralis* Infection and Eosinophilia on Age at Onset and Prognosis of Adult T-Cell Leukemia

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Onset of adult T-cell leukemia (ATL) usually follows a long period of viral latency. *Strongyloides stercoralis* infection has been considered a cofactor of leukemogenesis. Hypereosinophilia (HE) is also observed and could be associated with either the presence of parasites or the leukemic process. In non-Hodgkin's lymphoma, eosinophilia may or may not affect prognosis. To determine whether infection with *S stercoralis* and therefore eosinophilia has a significant effect on the development of ATL, we studied two variables in 38 patients: age at onset and median survival rate. Infected (Ss+) patients (n = 19) were younger (P=.0002) and survived longer (P=.0006) than uninfected (Ss–) patients (n = 19) (median age, 39 *vs* 70 years; median survival, 167 *vs* 30 days). Mean survival of patients with hypereosinophilia (HE+) was not significantly different from that of patients without hypereosinophilia (HE–) (P=.57). However, overall survival was longer for Ss+HE+ patients than for Ss–HE– patients (P=.01; 180 *vs* 30 days) or Ss–HE+ patients (P=.03; 180 *vs* 45 days). Among patients with mean survival more than 180 days, Ss+HE+ patients survived longer (P= .028). Our data confirm that cofactors related to the environment, such as *S stercoralis* and hypereosinophilia associated with *S stercoralis* or human T-cell leukemia virus, type 1 (HTLV-1) might be important in HTLV-1–associated leukemogenesis and suggest that hypereosinophilia affects the prognosis of HTLV-1–associated leukemia. (Key words: Adult T-cell leukemia; Eosinophilia; *Strongyloides stercoralis*; Viral latency) Am J Clin Pathol 1997;107:81–87.

A high prevalence of infection with *Strongyloides stercoralis* is noted in healthy carriers of human T-cell leukemia virus, type 1 (HTLV-1).[1,2] That *S stercoralis* infection is found more often in patients with adult T-cell leukemia (ATL)[3,4] emphasizes that *S stercoralis* is a cofactor of leukemogenesis induced by HTLV-1.[1,5–7] Some authors have reported that hypereosinophilia (HE) is also frequently found in HTLV-1 carriers[8]; others disagree.[9,10] HE is frequently observed in patients with peripheral T-cell lymphomas.[11] Conflicting data have been reported regarding the association of HE with development of non-Hodgkin's T-cell lymphomas, particularly in ATL.[11–18] HE-associated parasite infection was not reported in any publications reviewed.

To determine whether *S stercoralis* infection and eosinophilia, separately or in conjunction, are important factors in development of ATL, we studied their relation to age at onset and median survival rate in patients with clinical ATL.

MATERIALS AND METHODS

Diagnostic Criteria

Between 1983 and 1995 in Martinique, ATL was diagnosed in 38 patients (18 women, 20 men), 26 of whom have been described previously[4] (Table 1, patients 1 to 26). Diagnostic criteria for ATL in the group studied included absolute lymphocyte count (>4×10^9/L) with at least 5% abnormal lymphocytes, peripheral lymphadenopathy, positive antibody to HTLV-1 at enzyme-linked immunosorbent assay and Western blot analysis, and an immunophenotypic profile (CD2+, CD3+, CD4+, CD25+, and CD7−) consistent with ATL. In addition, monoclonal integration of HTLV-1 virus in tumor cells, similar to that

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TABLE 1. FINDINGS IN 38 PATIENTS WITH ADULT T-CELL LEUKEMIA

Patient No.	*Sex*	*Age (y)*	*LN*	*HM*	*SM*	*CL*	*Ss*	*HE*	*Survival (d)*
9	M	48	+	+	+	+	+	+	46
26	M	57	+	–	–	+	+	+	72
20	F	52	+	+	–	+	+	+	100
10	F	23	+	+	+	+	+	+	180
23	M	36	+	–	–	–	+	+	180
32	M	53	+	–	–	–	+	+	360
3	F	39	+	–	+	–	+	+	418
15	M	38	+	–	–	–	+	–	8
8	M	41	+	+	+	+	+	–	27
16	M	39	+	–	–	–	+	–	60
33	M	32	+	–	–	–	+	–	80
24	F	35	+	+	+	+	+	–	97
6	M	54	+	+	+	+	+	–	113
37	F	42	+	–	–	+	+	–	167
35	F	39	+	–	–	–	+	–	270
34*	F	46	+	–	–	–	+	–	>300
28	M	39	+	+	+	+	+	–	457
25	M	35	+	+	+	+	+	–	515
13	F	42	–	–	–	+	+	–	720
27	F	84	+	–	–	–	–	+	3
11	F	95	+	–	–	–	–	+	30
29	M	70	+	–	–	–	–	+	60
21	M	46	+	+	–	–	–	+	160
7	F	48	–	–	–	+	–	+	2,550
4	M	75	+	–	–	+	–	–	11
2	M	31	+	–	–	+	–	–	16
38	F	78	+	–	–	–	–	–	16
1	M	81	+	–	–	–	–	–	20
5	F	49	+	+	+	–	–	–	20
18	F	90	–	–	–	–	–	–	25
22	F	43	+	+	+	–	–	–	30
31	F	46	+	–	–	–	–	–	30
14	F	57	–	–	–	–	–	–	37
19	F	74	+	+	+	–	–	–	43
30	M	49	+	–	+	+	–	–	60
12	M	49	+	–	–	–	–	–	90
17	M	83	+	–	–	–	–	–	150
36*	M	73	+	+	+	–	–	–	>210

LN = lymphadenopathy; HM = hepatomegaly; SM = splenomegaly; CL = cutaneous lesions; Ss = Strongyloides stercoralis; HE = hypereosinophilia; + = >1×10⁹/L.
* Still alive.

reported in the literature,[19] was confirmed in 9 patients. The Baermann test was used to detect *S stercoralis* in at least three fecal samples from each patient. Eosinophils were counted with a Coulter/STKS cell counter (Coulter; Miami). As a control, May-Grünwald–Giemsa stained smears were examined under a microscope. An eosinophil count >1×10⁹/L was reported as positive for HE.

Patients

Age at onset of ATL was compared in two groups: *S stercoralis*–infected (Ss+) patients and infection-free (Ss–) patients. In addition, we compared a group of patients with hypereosinophilia (HE+) with a group without this hematologic feature (HE–).

To assess the effects of *S stercoralis* infection on survival rate, we compared the following groups of patients: Ss+ *vs* Ss–, HE–Ss+ *vs* HE–Ss–, and HE+Ss+ *vs* HE+Ss–. The effect of HE on survival rate also was compared, in the following patient groups: HE+ *vs* HE–, Ss–HE+ *vs* Ss–HE–, and Ss+HE+ *vs* Ss+HE–. In addition, Ss+HE+ *vs* Ss–HE– patient groups and Ss+HE– *vs* Ss–HE+ groups were compared. The number of patients included in each group is indicated in Table 2. There was no difference in treatment between groups.

Statistical Analysis

To evaluate the effects of *S stercoralis* infection or eosinophilia on age at onset of ATL, we used the Mann-Whitney *U* test. Survival time was calculated from the time of diagnosis to death. Survival curves were obtained according to the method of Kaplan and Meier. The degree of statistical significance among survival curves was analyzed with the log-rank test for the various hypereosinophilia and *S stercoralis* subgroups. Independence of these factors with regard to patient age was determined with the Cox proportional hazards model. The difference was considered significant at $P<.05$. The relative mortality risk was given for each group. Statistical analysis took the number of survivors into account. Patient 7 was excluded from statistical computations of survival because of unusually long survival (7 years). Results from the HE+Ss– patient group (n = 4) were too small for meaningful analysis and therefore are reported

TABLE 2. NUMBER OF PATIENTS STUDIED

ATL	*HE+*	*HE–*	*Total*
SS+	7	12	19
SS–	5 (4*)	14	19 (18*)
Total	12 (11*)	26	38 (37*)

ATL = adult T-cell leukemia; HE = hypereosinophilia.
**Number of patients included in analysis of survival rate.*

here for information only. Computations were performed with the Statview 4.5 statistical program (Abacus Concepts, Berkeley, Calif, 1994).

RESULTS

Clinical data for the 38 patients are reported in Table 1. Nineteen patients (8 women, 11 men) were infected with *S stercoralis*. Patients younger than 40 years were more often infected (10 of 11; 4 women, 6 men) than those older than 40 years. Infection was usually diagnosed several years before onset of ATL (average, 6.5 years; range, 1 to 27 years) and was resistant to treatment with tiabendazole or albendazole. At onset of disease, 12 patients had eosinophil counts $>1\times10^9$/L (range, 1.1 to 6.5×10^9/L); 7 were infected with *S stercoralis*.

Statistical Analysis

Effects of* S stercoralis *infection and presence of hypereosinophilia on age at disease onset.—Median age of patients in all groups was 48 years (range, 23 to 95 years). Difference in age between the Ss+ and Ss– groups was significant (P=.0002): Ss+ patients were younger (median age, 39 years; range, 23 to 57 years) than Ss– patients (median, 70 years; range, 31 to 95 years). No significant difference was found between HE+ and HE– patients (median age, 50 *vs* 46 years; P=.57).

Effects of* S stercoralis *infection and presence of hypereosinophilia on survival.—Median survival time in the 37 patients followed up was 72 days (range, 3 to 720 days) and varied according to the age of the patient (P=.01) (Fig 1, A). Survival curves for the four patient groups (Fig 1, B) demonstrate that infected patients (ie, Ss+HE– or Ss+HE+) survived longer than noninfected patients (Ss–HE– or Ss–HE+) (P=.0009).

Infection With S stercoralis *and Survival*

Analysis of survival curves demonstrated a statistically significant difference between the Ss+ and Ss– groups (Fig 2, A). Patients infected with *S stercoralis* survived longer than noninfected patients (median survival, 167 *vs* 30 days; P=.0006), and survival was independent of patient age (P'=.618). SS+HE– patient groups clearly survived significantly longer (P=.008) (Fig 2, B). No correlation was found with patient age (P'=.200). Presence of infection seemed to increase survival time in the HE+ group as well (P=.033). Pertinent statistical data are summarized in Table 3.

Hypereosinophilia and Survival

In terms of overall survival, no significant difference was observed between HE+ and HE– groups (median survival, 100 *vs* 60 days; P=.96) (Fig 3, A). The presence of eosinophilia had no significant effect on survival in either Ss+ or Ss– patient groups (P=.48 and .75, respectively) (Fig 3, B; Table 4). However, of the patients who survived 180 days or longer (9 of 10 Ss+ patients), those without HE survived longer (412 *vs* 284 days; P=.028)

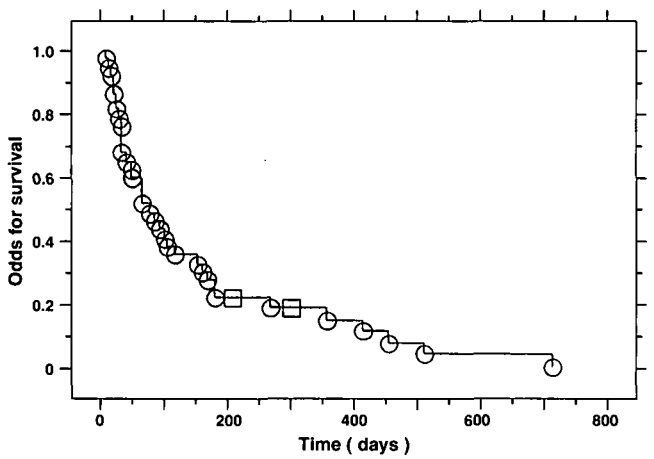
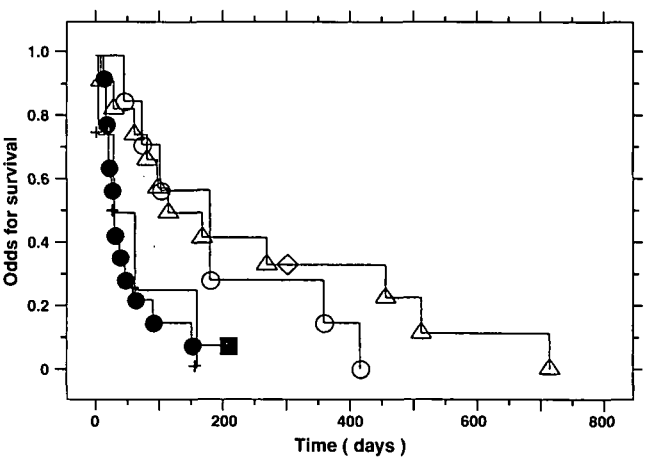


FIG 1. A, Survival time in 37 patients with ATL. □ = Excluded patients.



B, Survival curves for four groups of patients. Δ = Ss+HE–, ○ = Ss+HE+, + = Ss–HE+, ● = SS–HE–, ■ and ◇ = excluded patients.

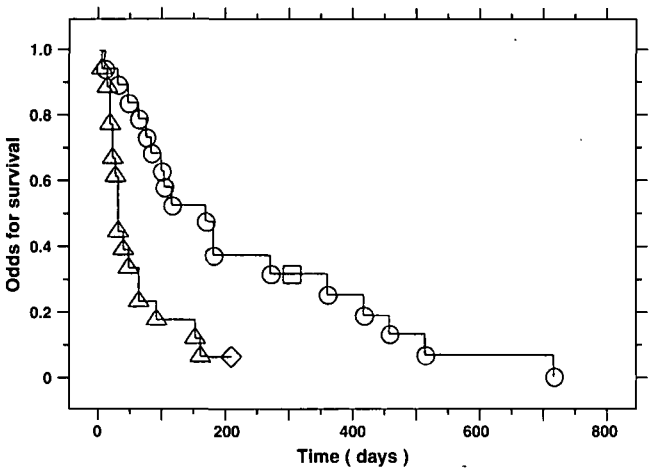
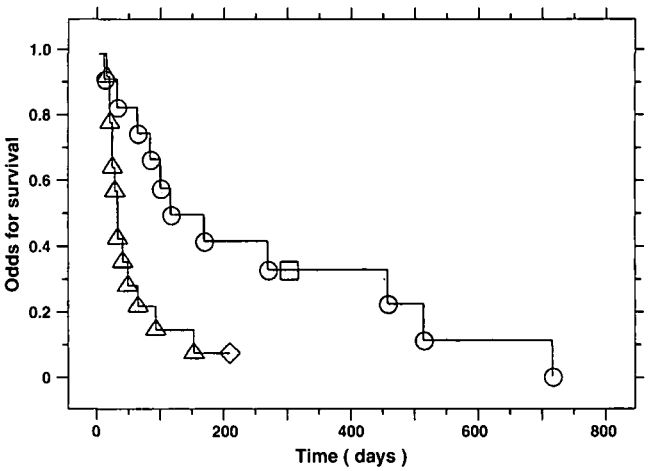


FIG 2. Effects of *S stercoralis* infection on survival with ATL. A, Survival curves for Ss+ (○) and Ss- (Δ) patient groups (P=.0006). □ and ◇ = excluded patients.



B, Survival curves for Ss+HE- (○) and Ss-HE- (Δ) patient groups (P=.008). □ and ◇ = excluded patients.

(Table 5). A significant difference was also noted between Ss+HE+ compared with Ss-HE- patient groups (median survival, 180 *vs* 30 days; P=.014). The mortality relative risk for Ss-HE- patients was 3.7 times that in SS+HE+ patients. Intergroup comparison demonstrated that Ss+HE- patients survived longer than SS-HE+ patients (P=.053) (Table 6).

DISCUSSION

HTLV-1, human immunodeficiency virus, and *S stercoralis* are all endemic in Martinique. *S stercoralis* infection is found frequently in patients with ATL, with an infection rate of 50% *vs* 1% in the overall population of Martinique. For example, a 3% infection rate is found in banana plantation workers and their families, a group that has been much studied for *S stercoralis*.[4,20] In contrast, patients with acquired immune deficiency syndrome have moderate rates of *S stercoralis* infection.[20]

TABLE 3. EFFECTS OF INFECTION WITH *S STERCORALIS* ON SURVIVAL

Patient Group	*No. of Patients*	*Median Survival (d)*	P*	P'†	*RR‡*
SS+	19	167	.0006	.618	2.3
SS-	18	30			
SS+HE-	12	140	.008	.200	2.8
SS-HE-	14	30			
SS+HE+	7	180	.033	.128	
SS-HE+	4	45			

HE+ = eosinophilia (>1×10⁹/L).
* Log rank test.
† Regression analysis of survival as a function of age.
‡ Relative risk for mortality, HE- *vs* HE+ patient groups.

The main route of transmission of HTLV-1 is from mother to child during breast-feeding. Infection during childhood appears to be a prerequisite for the development of ATL in adulthood. These findings, published in the literature,[21] seem to indicate that latency begins at birth, when the child is infected from maternal milk.

Our study shows that the period of latency preceding the onset of ATL is substantially shorter in Ss+ patients than in Ss- patients. *S stercoralis* infection causes a specific polyclonal expansion of CD4+-activated lymphocytes (Th1 type),[22,23] which might lead to the appearance of a malignant clone.[5,6] A high level of monoclonal integration of HTLV-1 proviral DNA is found in those HTLV-1 carriers who are also Ss+.[5] The results of our study suggest that patients infected with HTLV-1 at birth and later in life with *S stercoralis* present preferentially with a monoclonal proliferation of CD4+ cells, compared with other patients with HTLV-1. No data are currently available regarding the prevalence of ATL in HTLV-1+Ss+ patients compared with HTLV-1+Ss- patients; a prospective study is in progress, however.

Patients infected with *S stercoralis* frequently have eosinophil counts above 1×10⁹/L. Some findings emphasize that a clonal expansion of type 2 helper T

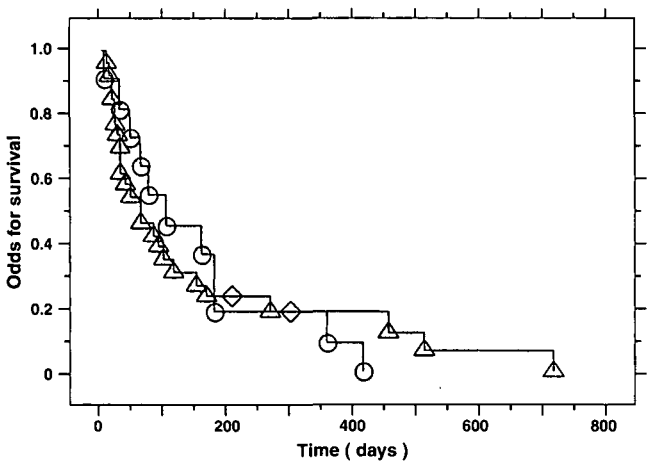
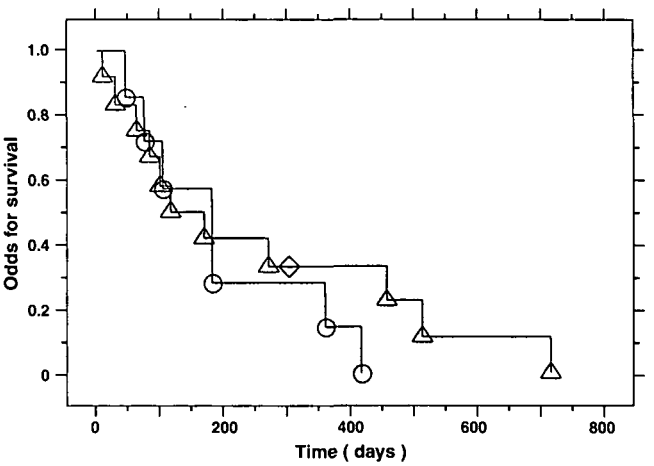


FIG 3. Effects of hypereosinophilia on survival with ATL. A, Survival curves for HE+ (○) and HE− (Δ) patient groups (P=.96). ◇ = excluded patients.



B, Survival curves for Ss+HE+ (○) and Ss+HE− (Δ) patient groups (P=.48). ◇ = excluded patient.

cells associated with HE may represent a premalignant condition.[24,25] These data confirm the hypothesis that specific links exist between HTLV-1–associated leukemia and the presence of *S stercoralis*.

TABLE 4. EFFECTS OF HYPEREOSINOPHILIA ON SURVIVAL

Patient Group	*No. of Patients*	*Median Survival (d)*	P*	P'†	*RR‡*
HE+	11	100	.96	.014	1.4
HE−	26	60			
SS−HE+	4	45	.75	.764	
SS−HE−	14	30			
SS+HE+	7	180	.48	.980	1.1
SS+HE−	12	140			

HE+ = eosinophilia (>1×10⁹/L).
* Log rank test.
† Regression analysis of survival as a function of age.
‡ Relative risk for mortality, HE− *vs* HE+ patient groups.

TABLE 5. EFFECTS OF HYPEREOSINOPHILIA ON SURVIVAL >180 DAYS

Patient Group	*No. of Patients*	*Median Survival (d)*	P*	P'†
HE+	4	284	.028	.44
HE−	6	412		

* Log rank test.
† Regression analysis of survival as a function of age.

ATL carries a poor prognosis. In our series, mean survival was less than 3 months in more than 50% of patients. In studies performed in Japan,[26] poor prognostic indicators included age 40 years or older, hypercalcemia, high lactic dehydrogenase level, and advanced performans status. Our results clearly indicate that Ss+ patients survive longer than the others and that this survival is independent of age.

HE is frequently noted in peripheral T-cell lymphomas,[11] but overall survival rate, especially in ATL, may or may not be associated with the presence of HE.[11–18] Analysis of our statistical data, in terms of the effect of HE on survival, did not yield unequivocal results. Rather, our findings suggest that HE alone has no influence on the evolution of ATL (see Table 4). They indicate, however, that the presence of HE, when associated with *S stercoralis* (Ss+HE+), may

TABLE 6. EFFECTS OF INFECTION WITH *S STERCORALIS* AND HYPEREOSINOPHILIA ON SURVIVAL

Patient Group	*Median No. of Patients*	*Survival (d)*	P*	P'†	*RR‡*
SS+HE+	7	180	.014	.887	3.74
SS+HE−	14	30			
SS+HE-	12	140	.053	.127	
SS−HE+	4	45			

* Log rank test.
† Regression analysis of survival as a function of age.
‡ Relative risk for mortality, HE− *vs* HE+ patient groups.

carry a better prognosis in ATL (see Table 6). Among patients who survived longer than 180 days, however, those who did not develop eosinophilia (Ss+HE–) survived longer (see Table 5). Thus the presence of *S stercoralis* infection without associated eosinophilia would indicate a better prognosis compared with other situations.

Eosinophil production is controlled by activated T lymphocytes, through production of granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin 3 (IL-3), and IL-5. Eosinophilia in patients with T-cell lymphomas has been correlated with GM-CSF, IL-3, or IL-5 production by the lymphomatous cells.[27,28] In addition, HTLV-1–infected CD4-lymphocytes seem to produce one or several lymphokines that may stimulate eosinophilopoiesis.[12,29,30] HE may be either beneficial or harmful to patients with *S stercoralis* infection or lymphoma, depending on specific conditions.[31] Eosinophil function could differ in non-complicated ATL compared with ATL with *S stercoralis* infection. The cytokine response, with subsequent effect on eosinophilopoiesis, could be different, depending on the primary pathologic event. Hence, intrinsic secretion of GM-CSF, tumor necrosis factor, and IL-4 occurs naturally in ATL cells,[12,29,30] whereas IL-5 and IL-3 can be produced by lymphocytes in response to helminthic antigens. Eosinophils found in malignant disease are also more sensitive to glucocorticoid treatment than others are. This confirms the hypothesis that a functionally different population is involved.[31,32]

Work on eosinophilia in asymptomatic HTLV-1 carriers[8–10] or patients with ATL[12–15] did not address the question of parasites, particularly helminths. This could explain certain discrepancies observed among studies relative to the frequency of eosinophilia in asymptomatic HTLV-1 carriers[9,10] and the effect of this on the prognosis of lymphomas.[13–17]

The results of our study confirm the hypothesis that cofactors related to the environment play an important, although not exclusive, role in the development of HTLV-1–associated leukemogenesis. Among these, infection with *S stercoralis* and the eosinophilic response of the infected host to *S stercoralis* or HTLV-1 may prove to be key elements. Further studies in a larger group of patients will be necessary to confirm these results. In particular, future studies should evaluate the role of cytokines and the kinetics of the population of lymphocyte clones in asymptomatic HTLV-1 carriers both with and without *S stercoralis*.

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