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HUMAN T CELL LYMPHOTROPIC VIRUS INFECTION IN GUAYMI INDIANS FROM PANAMA

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Abstract. Preliminary studies found that 9% of Guaymi Indians from Bocas del Toro province have antibody to human T cell lymphotropic virus (HTLV-I/II). The present study enrolled 317 (21% of the population) Guaymi Indians from Changuinola, the capital of Bocas del Toro province and 333 (70% of the population) from Canquintu, an isolated rural village. Demographic information and family relationships were ascertained and subjects were screened for neurologic diseases. Serum specimens were screened by an enzyme-linked immunosorbent assay for HTLV-I/II antibody and positives were confirmed according to U.S. Public Health Service criteria. Twenty-five (8%) Guaymi residing in Changuinola and 7 (2.1%) from Canquintu were confirmed seropositive. In Changuinola, antibody was virtually limited to residents ≥ 15 years of age (24 [16%] of 153) and rates were slightly higher in males than in females; in Canquintu, antibody rates did not increase significantly with age and appeared higher in females than in males. In Changuinola, there was no evidence for household clustering of infection. In contrast, HTLV antibody among Canquintu residents clustered significantly by household. HTLV-associated neurologic disease was not detected in either population. The atypical seroepidemiology observed in both locations might be explained if the virus endemic to the Guaymi differed from HTLV-I previously described in the Caribbean basin and Japan.

The human T cell lymphotropic virus type I (HTLV-I) is etiologically associated with adult T cell leukemia/lymphoma (ATL)[1] and with a chronic degenerative neurologic disease,[2] currently termed HTLV-I associated myelopathy/tropical spastic paraparesis (HAM/TSP).[3] Several studies have reported that HTLV-I infection, ATL, and HAM/TSP are endemic in the Caribbean basin.[4]

The Republic of Panama geographically and culturally links Central America, South America, and the Caribbean. HTLV-I/II antibody prevalence in Panamanian metropolitan populations is similar to that in other cities in the region.[5] Seroepidemiologic studies of a representative sample of the Republic's population found that ~1% had HTLV-I/II antibody and that Panamanians of West Indian and African ancestry had the same antibody prevalence as the other major racial/ethnic groups.[6] These studies also indicated an unusually high HTLV-I/II seropositivity rate (9%) among Guaymi Indians from Bocas del Toro province, an area near the Panama/Costa Rica Caribbean border.

Clinical epidemiology studies in well-defined populations have documented the presence of both ATL and HAM/TSP in Panama and suggest that the incidence of HAM/TSP is considerably greater than that of ATL.[7,8] The extent to which variant HTLV strains may account for these observed clinical patterns is not yet known. The high prevalence of HTLV-I/II infection in an isolated Amerind group has important implications concerning the epidemiology of HTLV in the New World and may help to explain the disease patterns in Panama.

The objectives of the present study were to determine the prevalence of HTLV infection in a representative sample of Guaymi Indians from Bocas del Toro province, identify some potential risk factors for infection, and explore possible associations between HTLV seropositivity and neurologic disease. The study verified that infection clustered in Guaymi from urban Bocas del Toro, but similarly high rates were not found in a rural population. There are a variety of possible explanations for our findings, including endemic foci of unique HTLV types.

FIGURE 1. Map of Panama showing area inhabited by Guaymi Indians.

MATERIALS AND METHODS

Study populations

Guaymi Indians inhabit isolated segments of Chiriqui, Veraguas, and Bocas del Toro provinces in Panama and portions of Puntarenas province, Costa Rica. The present Guaymi people are descendants from Indians who retreated to the mountains during Spanish colonization. Relative isolation in this extremely rugged, nearly inaccessible area has persisted for ~300 years, and the Guaymi remain largely unadmixed with people of European or African descent.[9] However, acculturation is occurring. Many residents migrate to urban areas to seek salaried employment, usually at banana plantations in Changuinola. In general, entire nuclear families migrate and establish long-term residences on the plantations. Housing, medical care, education, and other amenities are provided during employment. The present study surveyed the Guaymi populations of urban Changuinola and rural Canquintu (Fig. 1).

Changuinola. Changuinola, the capital of Bocas del Toro province, is a typical Caribbean urban center with paved streets, city water and electricity, government operated primary and secondary schools, and a secondary level hospital. Changuinola is the center of Panama's Caribbean banana industry, which provides the major source of employment. There were ~18, 911 Changuinola residents enumerated in the 1980 census (35% of the provincial population), of whom 1,498 (8%) were Guaymi Indians. Our study population consisted of Guaymi (≥1 year of age) who resided in randomly selected households in Chiriqui Land Company housing areas during April, 1988. We used Census Bureau estimates of average household size to determine the number of houses to sample to confirm a 9% seroprevalence of HTLV-I/II (allowing for a 5% difference from the true population rate at a 5% significance level) and then used random numbers to select houses from census maps.

Three hundred ninety-five Guaymi Indians resided in selected homes. Of these, 366 (93%) were contacted, 337 subjects were ≥1 year old, and blood specimens were obtained from 317 (21% of the estimated Changuinola Guaymi population). No subject refused to participate. Twenty-nine subjects could not be located at the time of the survey. Sufficient blood specimens for testing could not be obtained from 20 individuals, mostly children <5 years old.

Canquintu. The majority of Guaymi in Changuinola have migrated from the Canquintu corregimiento (county), of which Canquintu is one of the largest Guaymi communities. Canquintu consists of traditional wooden dwellings along the Cricamola River, about a day's journey by jeep, dug-out canoe, and foot from Changuinola. The economy is based on subsistence agriculture. Facilities found in the village include a government health center staffed by a physician, a government primary school, a church-operated women's vocational school, and a church.

We visited Canquintu in March 1989, mapped all dwellings, and enumerated 478 residents >1 year of age in 51 households. The Canquintu study was conducted during April 1989 and at-

tempted to enroll all residents identified the previous month. A third trip was made in July 1989 to sample residents not present in March. We contacted 399 (83%) eligible residents from 49 (96%) households and obtained blood specimens from 333 (70% of the total population). Blood specimens could not be obtained from 66 subjects interviewed, mostly children ≤9 years of age (53%, compared to 36% of the overall population). No subject contacted refused to participate. The 79 subjects counted in the census but not included in the survey were absent from Canquintu during both study trips.

Data and specimen collection

In Changuinola, Guaymi Indian labor union representatives visited the selected houses to assure that the occupants were Guaymi, explain the study, and enumerate eligible participants. The following week, study teams conducted the survey. In Canquintu, a study physician and regional health official met with community leaders to explain the study and then visited each dwelling to enumerate residents and advise them of the study. The following month, study teams worked 1 week to collect data and specimens. Study teams for both sites consisted of a neurologist, 2 nurses, and a Guaymi Indian translator. Study teams carried out interviews, examinations, and specimen collections in the subjects' homes after obtaining oral informed consent from each subject or, for children, their guardians.

Team members received formal training in interview techniques, performing a standard neurologic screening exam, and recording data. Basic data, including name, age, sex, race, birth place, residence history, and family relationships, were ascertained by interviewing competent adults. The standard World Health Organization neurologic screening history and physical examination was administered to all participants.[10] All persons with an abnormality noted on the neurologic screening history or exam were further evaluated by a study neurologist.

We collected 10 ml of venous blood for serologic assays and, in Changuinola, a second heparinized specimen for hematologic morphology studies. Serum specimens were separated, aliquoted, and stored in liquid nitrogen the same evening they were collected and subsequently stored at −20°C until tested. In Changuinola, peripheral blood smears were prepared the evening of collection, and morphologic studies were later performed by Marciaq Altafulla, Chief of Hematology at the Social Security Medical Center, Panama City.

Laboratory methods

HTLV antibody assays. All serum specimens were screened for HTLV-I/II antibody in the Dupont HTLV-I enzyme-linked immunosorbent assay (ELISA) kit (Dupont de Nemours, Wilmington, DE) at the Centers for Disease Control, Atlanta, GA according to the manufacturer's instructions. This test, as well as the confirmatory assays, detects antibody to both HTLV-I and HTLV-II.

Specimens repeatedly reactive by ELISA were tested in a modified Western blot.[11] HTLV-I antigen, purified from a lysate of the HTLV-I-infected cell line MT-2,[12] was obtained from a commercial source (Hillcrest Biologicals, Cypress, CA). HTLV-I antigen was suspended in sample buffer, heated at 95°C for 4 min, electrophoresed in a single well of a 10% polyacrylamide gel (0.1 A overnight then 0.2 A for 4 hr), and then transferred by electroblotting to nitrocellulose sheets. Washed sheets were blocked to reduce nonspecific reactivity (PBS, pH 7.4, with 0.5% Tween 20, 0.2% sodium azide, and 5 g/100 ml nonfat dry milk) and cut into 3 mm strips. Individual strips were incubated overnight at room temperature with 1:100 dilutions of serum, washed, and incubated for 60 min at room temperature with 5 μg/ml biotinylated goat anti-human IgG (heavy and light chain) (Vector Laboratories, Burlingame, CA). Strips were washed again and then incubated with avidin-biotin-peroxidase conjugate (Vector Laboratories) according to manufacturer's instructions. Immune reactions were visualized with 3, 3' diaminobenzidine, nickel chloride, and hydrogen peroxide substrate (Sigma Chemical Co., St. Louis, MO). In each test run, banding patterns were compared with those of a known positive serum (a patient with HAM/TSP) and with monoclonal antibodies against HTLV-I specific proteins (p19, p24, and gp68). Negative control serum specimens were used in each test.

Specimens that reacted to at least one HTLV-I gene product but that could not be classified as seropositive for HTLV-I/II by Western blot alone were tested in a radioimmunoprecipitation assay

TABLE 1

Age-sex specific HTLV-I/II antibody prevalence among Guaymi Indians residing in Changuinola

Age (years)	Males		Females		Total	
	No./total	Percent	No./total	Percent	No./total	Percent
1–9	0/59		0/57		0/116	
10–14	0/19		1/24	4.2	1/43	2.3
15–19	1/11	9.1	2/20	10	3/31	9.7
20–24	3/23	13	0/12		3/35	8.6
25–29	5/16	31.3	2/9	22.2	7/25	28
30–34	3/11	27.3	3/14	21.4	6/25	24
≥35	4/30	13.3	1/7	14.3	5/37	13.5
Unknown			0/5		0/5	
Total	16/169	9.5	9/148	6.1	25/317	7.9

(RIPA).[11] HTLV-I-infected MT-2 cells were metabolically labeled (200 μCi of each nucleotide/ml/10^7 cells) with ^{35}S cysteine and ^{35}S methionine (New England Nuclear, Boston, MA), disrupted with RIPA lysing buffer, and centrifuged. Lysate supernatants were then reacted with each serum (20 μl) for 16 hr at 4°C. Immune complexes were precipitated with protein A-sepharose CL-4B (Sigma Chemical Co.) for 1.5 hr at 4°C. Bound immune complexes were washed with RIPA lysing buffer and eluted in sample buffer by boiling for 4 min. Samples were analyzed in a discontinuous buffer system[13] with 10% acrylamide resolving gels; gels were dried and antibody patterns visualized by autoradiography.

As specified by a U.S. Public Health Service (USPHS) working group,[14] a specimen was considered positive for HTLV-I/II antibody if it demonstrated reactivity to the *gag*-encoded protein p24 and to an *env*-encoded glycoprotein (gp46 or precursor gp61/68) on Western blot or RIPA. Specimens demonstrating antibody to at least 1 suspected HTLV-I gene product but not satisfying the criteria for positive were designated indeterminate. All remaining specimens, including those not repeatedly reactive in the screening test, were designated negative.

Hepatitis assays. We used Abbott Laboratories kits to test serum specimens for evidence of hepatitis B virus (HBV) infection. Hepatitis B surface antigen (HBsAg) was measured by using the AUSZYME qualitative enzyme immunoassay. Anti-HBsAg was measured by AUSAB, an ELISA test for qualitative determination of antibody to subtypes ad and ay of HBsAg. Antibody to the HBV core antigen (anti-HBc) was measured by CORZYME.

Statistical analyses

Statistical comparisons utilized the Mantel-Haenszel χ^2 statistic, χ^2 for linear trend, or Fisher's exact test. The distribution of seropositive pairs within households was analyzed as described by Walter.[15]

RESULTS

HTLV seroprevalence

Changuinola. Thirty-three (10.4%) of 317 individuals tested had repeatedly reactive ELISA screening tests and 25 (7.9% of the total) were seropositive for HTLV-I/II according to USPHS criteria (Table 1). When compared with Western blot band patterns of Japanese HTLV-I seropositive samples, the Western blot patterns of the Guaymi from Changuinola showed equally strong reactivity at *gag* p24, but weaker *env* gp68 and *gag* p19 reactivity (Fig. 2). This pattern resembled the reactivity of pedigreed HTLV-II-positive specimens when tested on HTLV-I antigen strips. Eight of the repeatedly reactive specimens were indeterminate by Western blot and negative by RIPA and were considered seronegative in the remainder of the analyses.

With the exception of an 11-year-old girl (whose parents were seronegative), HTLV-I/II antibody was limited to subjects ≥15 years of age, of whom 24 (15.7%) of 153 were seropositive (Table 1). Antibody prevalence increased significantly with age in males (χ^2 for trend = 12.7, $P < 0.001$) and in females (χ^2 for trend = 10.3, $P < 0.001$). Antibody rates were slightly higher among males than females, but the difference was not statistically significant. Three

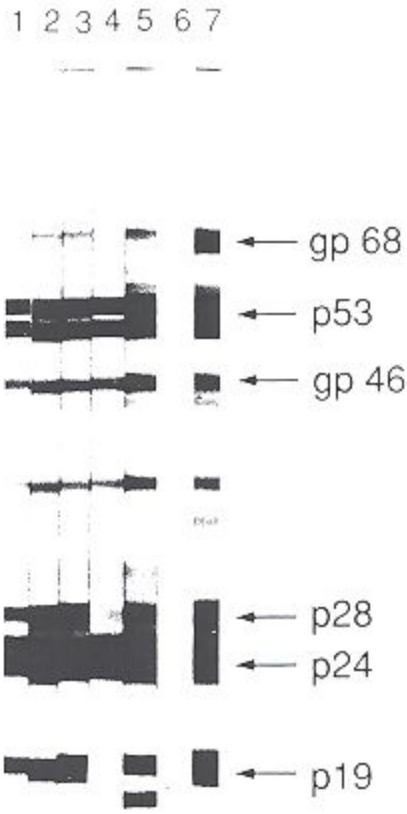

FIGURE 2. HTLV-I Western immunoblot patterns of Guaymi Indians. Lanes 1–5 are seropositive Guaymi Indians; lane 6 is an antibody-negative control; lane 7 is an antibody-positive Japanese HAM/TSP patient. Seropositive Guaymi typically demonstrated weaker p19 (*gag*) and gp68 (*env*) reactivity than the positive control. Western immunoblot strips were prepared using HTLV-I-infected MT-2 cells.

hundred fourteen (99%) of 317 Guaymi from whom serum specimens were collected, including the 24 seropositive adults, were born in traditional villages in Bocas del Toro and had migrated to Changuinola; the seropositive 11-year-old girl was born in Chiriqui province and had migrated to Changuinola with her family. Seropositivity was not associated with district or village of birth.

Analysis of seropositive pairs did not suggest household clustering of HTLV-I/II infection. Of the 34 households sampled, 2 contained 3 seropositive persons, 6 contained 2 seropositive persons, 7 contained 1 seropositive person, and 19 had none. The observed number of seropositive "pairs" (12) did not differ significantly from the expected number (10.4). Analysis of family units similarly failed to reveal evidence of associations between spouses or between parents and children (Table 2). None of the 29 children with a seropositive parent had antibody, and none of 6 wives of seropositive men and 6 husbands of seropositive women had antibody.

Canguinola. Fifteen (4.5%) of 333 residents tested had repeatedly reactive HTLV-I/II ELISA screening tests and 7 (2.1% of the total) were seropositive according to USPHS criteria. Four of the repeatable reactive specimens were indeterminate by Western blot and negative by RIPA and were considered seronegative in the remainder of the analyses. Western blot patterns from positive subjects were similar to those from Changuinola. In contrast to the results from Changuinola, antibody was found in younger persons. Prevalence appeared to increase with age, and females were more likely to be seropositive than males, although differences were not statistically significant at the 5% level (Table 2).

Five of the 7 HTLV-I/II seropositive subjects were from 2 families, and the remaining 2 were from separate families and households. A 56-year-old man, his 50-year-old wife, and their 18-year-old daughter had HTLV-I/II antibody; 3 seronegative sons aged 8, 14, and 16 years also resided in this household. Two seropositive sisters (10 and 6 years old) lived with a seronegative 12-year-old maternal half-brother and a 54-year-old seronegative grandfather; their mother and father were not enrolled. The other 2 seropositive subjects were unrelated 23-year-old women who were associated with 13 and 12 seronegative household/family members, respectively.

Analysis of seropositive pairs suggested household clustering of infection. Forty-nine households were sampled; 1 contained 3 seropositive persons, another contained 2, 2 contained 1 seropositive person, and 45 had none. The observed number of seropositive "pairs" in the same household (4) differed from the expected number (0.46) ($Z = 5.3$, P [one-tailed] < 0.0001). Analysis of family units also revealed associations

TABLE 2

Age/sex specific HTLV-I/II antibody prevalence among Guaymi Indians residing in Canquintu

Age (years)	Males		Females		Total	
	No.	Percent	No.	Percent	No.	Percent
1–9	0/68		1/51	2	1/119	0.8
10–14	0/32		1/33	3	1/65	1.5
15–19	0/14		1/20	5	1/34	2.9
20–24	0/13		2/9	22.2	2/22	9.1
25–29	0/3		0/11		0/14	
30–34	0/6		0/8		0/14	
≥35	1/31	3	1/29	3.5	2/60	3.3
Unknown	0/1		0/4		0/5	
Total	1/168	0.6	6/165	3.6	7/333	2.1

between spouses and among parents and children (Table 3).

HTLV-associated diseases

One hundred six (31%) of 337 Changuinola residents were detected in the screening history and exam as possibly having neurologic disease; of these, 101 were evaluated by a study neurologist and 38 (38%) had neurologic abnormalities. Epilepsy, the most common diagnosis, was noted in 30 subjects (9%).[16] In Canquintu, 41 (14%) of 302 study subjects (neurologic screening was only done on the first trip) were detected as possibly having neurologic disease, including 29 (71%) who had neurologic abnormalities diagnosed, and 20 (7% of the total population) had epilepsy. We did not detect gait disturbances or neurologic disease compatible with HAM/TSP in either population. Abnormal neurologic screening exams or epilepsy were not associated with HTLV-I/II antibody in either population. Finally, no particular hematologic changes were associated with the presence of HTLV-I/II antibody in subjects from Changuinola; specifically, rosette-like lymphocytic nuclei were not seen.

TABLE 3

Analysis of HTLV-I/II seropositivity in Canquintu family units

Family relationship	No. seropositive/total
Children of:	
seropositive mother	1/6
seronegative mother	1/194
seropositive father	1/5
seronegative father	0/144
Wife of:	
seropositive man	1/1
seronegative man	1/40
Husband of:	
seropositive woman	1/2
seronegative woman	0/39

Hepatitis B infection

Serum specimens from both locations were tested for HBV markers. For Canquintu, only the 287 serum specimens collected during the April field trip were tested; of these, only 271 had sufficient volume to test for all markers.

Markers of HBV infection were found at high levels in both Changuinola and Canquintu (Table 4). The prevalence of HBV infection was significantly higher in Canquintu than in Changuinola (60% vs. 50%), as was the prevalence of chronic HBs antigenemia (25% vs. 11%). Since only 5 Canquintu residents (from the first trip) had HTLV antibody, we combined the populations to assess possible associations between HTLV and HBV infection (the 5 HTLV-seropositive Canquintu residents detected on the April trip had some HBV marker) (Table 5). The frequency of HBV infection was significantly higher in subjects with HTLV-I/II antibody (23 out of 30, 77%) than in those who were seronegative (298 out of 556, 54%), but HBs antigenemia did not vary significantly (23% and 18%, respectively).

DISCUSSION

This study sampled defined populations, used serologic assays to detect antibody against HTLV *gag* and *env* proteins, and confirmed our hypothesis that HTLV infection is unusually common among Guaymi Indians from Bocas del Toro. However, disparate prevalence rates and

TABLE 4

Hepatitis B virus markers in Guaymi Indians from Changuinola and Canquintu

	HBV infect*		HBsAg		anti-HBs		anti-HBc	
	No.	Percent	No.	Percent	No.	Percent	No.	Percent
Changuinola								
n = 315†	159	50	36	11	89	28	144	46
Canquintu								
n = 271†	162	60	69	25	74	27	108	40
Changuinola vs. Canquintu								
χ^2	4.7		18.6					
P =	0.03		<0.001					
r =	1.5		2.6					
95% CI	1–2.1		1.7–4.2					

* Presence of any marker of hepatitis B virus infection.

† Number of sera tested, this may vary from total population because insufficient quantities were available to measure all markers and definitely exclude infection. In Canquintu, only sera from the first trip (April) were tested for hepatitis B markers.

atypical epidemiologic patterns were observed in urban and rural populations.

Eight percent of the urban Changuinola and 2% of the rural Canquintu Guaymi populations reacted serologically to HTLV. In Changuinola, infection occurred in adults (15% of those ≥ 15 years of age were seropositive). Unlike other endemic populations, antibody prevalence was greater in males than in females[4, 17–19] and infection did not cluster within families or in households.[18, 20, 21] In Canquintu, seroprevalence was higher in females than in males and clustering of infection within family units and within households was observed. Yet, infection rates did not increase with age beyond the 20–24 year age group, as it did in other endemic populations.

The apparent differences in seroprevalence between the 2 regions should be interpreted with caution. It is possible that the HTLV infection rates observed in Canquintu are more representative of the Guaymi population and that the patterns observed in Changuinola reflect risk factors unique to migrants living in an urban environment. For example, transmission by parenteral exposure might occur more frequently in such a setting. However, HBV, known to be hyperendemic among the Guaymi,[22, 23] was strongly associated with HTLV seroreactivity in both populations and HBV infection rates were somewhat higher in the rural setting, which would argue against increased parenteral or sexual exposure in Changuinola. In addition, Guaymi Indians do not practice ritual scarification or tattooing, disposable needles and syringes are almost universally used throughout Panama by health practitioners, and major surgeries or other med-

TABLE 5

HTLV-I/II seropositive vs. seronegative (Changuinola/Canquintu)

	HBV infect*		HBsAg		anti-HBs		anti-HBc	
	No.	Percent	No.	Percent	No.	Percent	No.	Percent
Both populations								
n = 586†	321	55	105	18	163	28	252	43
HTLV-pos								
n = 30	23	77	7	23	13	43	20	67
HTLV-neg								
n = 556	298	54	98	18	150	27	232	42
HTLV-pos vs. HTLV-neg								
χ^2	5.2							
P =	0.02							
r =	2.8							
95% CI	1.1–7.4							

* Presence of any marker of hepatitis B virus infection.

† Number of sera tested; this may vary from total population because insufficient quantities were available to measure all markers and definitely exclude infection. In Canquintu, only sera from the first trip (April) were tested for hepatitis B markers; this included 5 of the 7 seropositives shown in Table 2.

ical interventions resulting in transfusions are rare in Bocas del Toro.

There was no indication as to possible mechanisms by which HTLV is maintained at high levels in the Changuinola Guaymi population. Lack of evidence for co-infection among spouses argues against sexual transmission.[15, 24] The virtual absence of antibody in the 159 children < 15 years of age suggests that mother-child transmission did not occur either in utero or peripartum[25–27] or through breast milk[28, 29] (breast-feeding is almost universally practiced in this population). It is possible that mother-child and sexual transmission are major risk factors for HTLV infection among Guaymi, and that infected children (or, less likely, spouses) may not yet have developed circulating antibody. To address this question, we have initiated studies to detect proviral DNA in the lymphocytes of seronegative high-risk family members.

Finally, the atypical seroepidemiology we observed in both locations might be explained if the virus responsible for the HTLV-I/II seropositivity in the Guaymi is not the same as the virus endemic elsewhere in the Caribbean and in Japan. The atypical Western blot patterns of seropositive specimens, the unusual distribution of seropositivity in the population, and the extremely low incidence of ATL in Panama all suggest the presence of a retrovirus closely related, but not identical, to HTLV-I. HTLV-II proviral DNA has been found in the lymphocytes of 3 HTLV-I/II seropositive Guaymi Indians from Changuinola (M. D. Lairmore, personal communication), and further studies to clarify the nature of the retrovirus endemic in this population are in progress.

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