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This study was undertaken to determine whether defects in leukocyte function or in genes at the MHC play a role in the etiology of either localized (LJP) or generalized (GJP) juvenile periodontitis. Thirteen LJP and five GJP patients (ranging in age from 13 to 22 years) and their matched controls were compared with respect to selected leukocyte functions and HLA phenotypic frequencies.

The results of these studies indicated that there were significant decreases in the phagocytic and chemotactic abilities of polymorphonuclear leukocytes (PMN) in both LJP and GJP. All JP patients displayed intrinsic cell defects in chemotaxis compared with controls; in addition, some patients displayed multiple defects, including those which were serum-associated. Also, there appeared to be a significant association between JP and HLA-DR2 and HLA-A33 phenotypes. Fifty percent of the JP patients were HLA-DR2-positive, whereas only six percent of the matched controls were positive. Thirty-six percent of JP patients were HLA-A33-positive, whereas none of the controls was positive. The association seen with DR2 may be due to sampling, since there were no significant differences between the JP cases and a larger unmatched control sample which was not evaluated for periodontal disease.

We conclude from these data that increased susceptibility of some patients to a very aggressive and destructive form of periodontal disease (JP) is based on defects in PMN responsiveness. Further investigations are necessary to determine whether these defects are under genetic control.

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Introduction.

It is widely accepted that bacteria or bacterial substances of the dental plaque are the primary etiologic factor(s) in the initiation of inflammatory periodontal disease (IPD) (Johnson *et al.*, 1962; Löe *et al.*, 1965; Löe, 1966; Ramfjord *et al.*, 1968; Socransky, 1970; Waerhaug, 1971). The specific microflora composition of the periodontal pocket is important in determining the severity and extent of destruction to the periodontium (Johnson *et al.*, 1962; Jordan and Keyes, 1964; Slots, 1976; Newman and Socransky, 1977).

However, an individual's susceptibility may be an additional and important modifying factor in the pathogenesis of IPD (Page and Schroeder, 1976; Glickman, 1972). In the last decade it has been established that increased susceptibility to certain periodontal diseases is associated with decreased leukocyte numbers and/or functional capabilities (Clark and Kimball, 1971; Miller *et al.*, 1971; Lavine *et al.*, 1976; Cianciola *et al.*, 1977; Clark *et al.*, 1977; Lavine *et al.*, 1979; Attstrom and Schroeder, 1979). In addition, there appears to be an association between aggressive forms of IPD and certain hereditary diseases (Fourel, 1972; Jorgenson *et al.*, 1975). A familial pattern is often seen in patients with juvenile periodontitis (JP) (Cohen and Goldman, 1960; Benjamin and Baer, 1967; Rao and Tewani, 1968; Melnick *et al.*, 1976; Kirkham, 1977). Further evidence of the heritable nature of JP can be assumed from the association of ABO blood groups (Kaslick *et al.*, 1971; Malena, 1972), and from the association of specific Human Leukocyte Antigen (HLA) phenotypes in patients with JP (Kaslick *et al.*, 1975; Reinholdt *et al.*, 1977; Kaslick *et al.*, 1980). Most of the reports on the HLA association with JP have involved Caucasians. The report of Cullinan *et al.* (1980) was the only one to report on a Black sample (n = 18). The association of HLA phenotypes with JP is particularly interesting, since this may suggest a role for genes at the major histocompatibility complex (MHC) which influence immune responsiveness, since such genes are thought to be closely linked to the HLA loci in the MHC.

This study was designed to further our understanding of the etiology and pathogenesis of JP by examining the relationship among clinical status, host response mechanisms, and HLA phenotypes in selected subjects with localized juvenile periodontitis (LJP) and generalized juvenile periodontitis (GJP).

Methods.

Subjects. — Unrelated patients were selected from among those who sought treatment at The University of Alabama School of Dentistry. The patients met the following criteria:

(1) no known systemic disease;
(2) under 30 years of age;
(3) evidence of either
  (a) localized (LJP)-destructive periodontal disease bilaterally affecting at least the molars and incisors and not more than two additional teeth ($\leq$ 14 teeth); or
  (b) generalized (GJP)-destructive periodontal disease affecting teeth in addition to incisor-molar regions ($>$ 14 teeth).

Patients taking medication on a regular basis or those who had been on a course of antibiotic therapy in the six months preceding presentation were excluded from the study. Subjects with no known systemic disease or evidence of periodontal disease who were not School of Dentistry patients were chosen as age-race-sex-matched controls for the patients. The study population consisted of 18 Black patients (11 females and seven males ranging in age from 13 to 22 years), and their 18 matched controls. All determinations on each matched pair (patient and control) were accomplished at the same time under identical conditions.

Clinical assessment. — The periodontal examination in all cases was accomplished before any treatment was rendered and included complete medical and dental histories. Also, a plaque index (Pl.I) (Silness and Löe, 1964), gingival index (GI) (Löe and Silness, 1963), pocket depth determination, long cone paralleI radiographs, Schei ruler determination of bone loss on radiographs (Schei *et al.*, 1959), and clinical assessment of mobility on a scale of 0 – III (Miller, 1938) were accomplished on teeth numbers 16, 21, 24, 36, 41, and 44 (Ramfjord, 1959).

Leukocyte function tests. — (1) Polymorphonuclear leuko-

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cytes (PMN) — The PMN were prepared by drawing 20 mL of venous blood into a syringe containing 50 units heparin/mL of blood. The red cells were allowed to sediment at room temperature. After a 30–60-minute period, the leukocyte-rich plasma was delivered into a plastic tube and centrifuged at low speed (210 g) for 10 minutes in the cold (4°C). The cell button was washed in medium 199 (Grand Island Biologic Co., Grand Island, NY) (pH 7.4), and was re-suspended and adjusted to a concentration of 5×10^6 PMN/mL in the same medium.

(a) Leukotactic assay — The method used for leukotactic assay was as previously described (Maderazo and Woronick, 1978). It involved use of a modified Boyden chamber (Ahlco Corp.), which is divided into an upper and lower chamber by a 13-mm-diameter, 5-μm-pore-size micropore filter (Millipore Corp., Bedford, MA). After they were prepared, the chambers were incubated in air at 37° C for 90 minutes. This short incubation period prevented the PMN from reaching the lower surface of the filter, thus avoiding the variability of cell detachment into the fluid of the lower compartment. After incubation, the filters were removed, stained with hematoxylin, cleared with xylene, and mounted on slides. The number of PMN was counted at every 10-μm interval from the original (top) to the distal surface, using 400 × magnification. The Leukotactic Index (LI) is the average distance in μm reached by the PMN in 90 minutes. LI was determined by multiplying the number of PMN per level by the distance of that level from the starting surface. Three fields were counted, and the mean LI for each triplicate filter was calculated. To test for non-stimulated migration (NSM), PMN without serum in the upper compartment were tested in the absence of chemotactic factor in the lower compartment. Chemotaxis was quantified using the same conditions as NSM except for the presence of 10% bacterial chemotactic factor (a filtrate of *Escherichia coli* grown overnight in medium 199) in the lower compartment. Cell-directed inhibitory activity (CDI) of serum was tested by pre-incubating PMN (5×10^5 in 0.1 mL medium 199) with 50 μL of the serum to be studied for 30 minutes at 37° C. The cells thus treated were placed in the upper compartment for assessment of their response to bacterial chemotactic factor in the lower compartment. Chemotactic factor inactivator activity (CFI) of serum was assayed by incubating 150 μL of serum for 30 minutes at 37° C. The mixture was then diluted with medium 199 to a volume of 1.5 mL and was added to the lower compartment. PMN were added to the upper compartment without serum to test remaining activity of the treated bacterial chemotactic factor. Complement-derived chemotactic factor (CDCF) was generated by incubating 0.1 mL of serum with 0.5 mg zymosan for 30 minutes at 37° C. The activated serum was then placed into the lower compartment, and chemotactic activity was assayed using PMN without serum in the upper compartment. The patients' values were compared with those of the simultaneously-tested matched controls, and the significance of the differences determined using the paired Student's *t* test.

(b) Stimulated nitroblue tetrazolium assay (NBT) — The stimulated NBT test is used as a screening test for specific phagocytic impairments (Park *et al.*, 1968). The NBT test actually evaluates a series of functions. These include: adherence of the stimulating particle, its phagocytosis, and then induction of the respiratory burst. If any one of these steps is abnormal, the NBT test will be defective. Although all of the reactions must be intact for the test to be normal, the NBT test in these experiments was used to assess phagocytosis. The method used was described by Park and Good (1970) and was performed by incubating 0.5 mL of heparinized blood at room temperature for 10 minutes with 10 μg endotoxin in 0.5 mL phosphate-buffered saline (PBS), pH 7.2. Next, NBT was added, and after the preparation was incubated at 37° C for 15 minutes, microscope slides were prepared by the smear technique. After being air-dried, smears were stained with Wright's stain, and the PMN which had incorporated NBT crystals (phagocytosis) were enumerated per first 100 PMN counted under oil immersion. Each patient's value was compared with that of his simultaneously-tested matched control, and the significance of the difference was determined using the paired Student's *t* test.

(2) Human leukocyte antigen (HLA) determination — The microdroplet lymphocyte cytotoxicity test described by Terasaki *et al.* (1978) was used for the HLA-A, -B, and -C typing. Antisera were obtained from the National Institutes of Health, from our own serum screening programs, and from Dr. Paul Terasaki, with at least two different antisera used for each antigen tested. For HLA-DR typing, a modified form of the Terasaki procedure was used. B-lymphocytes were enriched by the nylon wool separation techniques using plastic straw columns and were used for typing if the purity was 85% or greater for B-cells. The antisera were obtained from Dr. Paul Terasaki, and at least four sera were used for each specificity tested. The HLA specificities tested were: HLA-A 1, 2, 3, 9, 10, 19, 23, 24, 25, 26, 28, 29, 30, and 33 (N = 14); HLA-B5, 7, 8, 12, 13, 14, 15, 16, 17, 18, 21, 22, 27, 38, 39, 40, 42, 44, 45, 49, 50, 51, 52, 54, 55, 56, 57, 58, 60, 61, 62, and 63 (N = 32); HLA-C1, 2, 3, and 4 (N = 4); and HLA DR 1, 2, 3, 4, 5, 6, 6Y, 7, and 8 (N = 9). The relative risk of disease in the presence of an HLA antigen was estimated *via* the odds ratio (Woolf, 1955). Significance probabilities were derived from Fisher's exact (two-tailed) test. Because of the low number of controls evaluated for HLA and absence of periodontal disease, a second control group was used for comparison with the cases for HLA frequencies. This control group consisted of Black Americans who had not been evaluated for periodontal disease. There were 283 who were HLA-A, -B, and -C-typed, and 137 who were DR-typed.

Results.

The clinical assessment of both LJP and GJP patients when compared with their matched controls can be seen in Table 1. A mean difference in P1.I. of 0.64 ($p < 0.005$) indicated that the controls had significantly higher P1.I. than did LJP subjects. The mean difference in P1.I. of 0.33 for GJP subjects relative to their matched controls was not significant. Similarly, the LJP patients scored lower in the GI than did controls, with a mean difference of 0.75 ($p < 0.005$). However, the mean difference in GI when GJP patients were compared with their matched controls was only 0.06, a non-significant result.

Both the LJP and GJP patients had greater pocket depths, more tooth mobility, and more bone loss as measured on radiographs with the Schei ruler than did their matched controls (Table 1). The mean increase in pocket depth for the LJP subjects compared with controls was 1.86 ($p < 0.005$); for the GJP group, the mean increase was 3.16 ($p < 0.005$). The mean increase in tooth mobility for the LJP group was 0.62 ($p <$

TABLE 1
COMPARISONS OF CLINICAL PARAMETERS

Measure	N	Disease	Control Mean ± SE	Patient Mean ± SE	p Values
Pl.I.	13	LJP	1.8±0.2	1.2±0.1	<0.005
(0-III)	5	GJP	1.9±0.2	1.6±0.3	>0.05
GI	13	LJP	1.6±0.1	0.9±0.1	<0.005
(0-III)	5	GJP	1.6±0.1	1.6±0.2	>0.05
Pocket Depth	13	LJP	2.8±0.1	4.6±0.3	<0.005
(mm)	5	GJP	3.0±0.1	6.2±0.3	<0.005
Mobility	13	LJP	0.0±0.0	0.7±0.1	<0.005
(0-III)	5	GJP	0.1±0.1	1.2±0.2	<0.005
Bone Loss	13	LJP	2.0±0.8	23.5±2.7	<0.005
(%)	5	GJP	1.3±1.3	47.1±2.2	<0.005

TABLE 2
COMPARISON OF SELECTED POLYMORPHONUCLEAR LEUKOCYTE FUNCTION

Measure	N	Disease	Control Mean±SE	Patient Mean±SE	p Values
A. Phagocytosis	13	LJP	54.9±3.0	28.5±3.7	<0.005
(% cells NBT +)	5	GJP	54.0±3.0	42.2±5.1	<0.05
B. Leukotaxis (LI)					
1. Intrinsic Cell-associated	13	LJP	7.4±0.9	4.7±0.7	<0.005
	3	GJP	6.6±2.3	2.9±1.2	<0.05
2. Serum-associated					
a. Chemotactic Factor Investigator (CFI)	13	LJP	6.9±0.9	5.4±0.6	>0.05
	3	GJP	4.5±1.4	4.2±1.5	<0.05
b. Complement-derived Chemotactic Factor (CDCF)	13	LJP	4.5±0.6	3.5±0.5	<0.025
	3	GJP	4.5±1.5	4.3±1.5	>0.05
c. Cell-directed Inhibitor (CDI)	12	LJP	3.2±0.3	3.2±0.3	>0.05
	4	GJP	4.2±0.2	3.7±0.3	>0.05

0.005); for GJP, the difference was 1.10 ($p < 0.005$). The increase in percent radiographic bone loss for LJP was 21.6 ($p < 0.005$) and for GJP 45.9 ($p < 0.005$). These results indicated that both the LJP and GJP patients presented with significantly greater pocket depths, tooth mobility, and radiographic alveolar bone loss than did their matched controls.

Determinations of PMN phagocytosis (NBT test) indicated impairment in both LJP and GJP patients compared with their controls. A mean of 54.9% ± 3.0 control PMN was observed to have incorporated NBT, compared with 28.5% ± 3.7 for LJP patients (Table 2). This resulted in a mean difference (control-LJP patient) of 26.3% ± 1.8 ($p < 0.01$). A mean of 54.0% ± 3.0 of control PMN was observed to have incorporated NBT, compared to a mean of 42.2% ± 5.1 for GJP subjects. This represented a mean difference (control-GJP patient) of 11.8% ± 4.9 ($p < 0.05$). Since the control values (55%) were very close to the expected normal values for the stimulated NBT test, it was arbitrarily assumed that this value represented 100% phagocytosis. Thus, the mean reduction in phagocytosis was calculated to be 48% for LJP patients, and 22% for GJP patients.

The results of assessment of PMN intrinsic cell responsiveness to chemotaxis are illustrated in Table 2. After NSM was subtracted from the LJP patients and their controls, the mean difference in LI (control-LJP patient) was 2.8 ± 0.6 ($p < 0.005$). For the GJP subjects and their controls, the mean difference (control-GJP patient) was 3.7 ± 2.1 ($p < 0.05$). Assay of serum-associated inhibitors of PMN chemotaxis in LJP and GJP compared with their matched controls was also accomplished. As can also be seen in Table 2, the CDCF resulted in a mean reduction of LI in the LJP subjects, compared with their controls' reduction of 1.0 ± 0.4 ($p < 0.025$). The CDCF in the GJP subjects resulted in differences which were not statistically significant. The CFI indicated a mean reduction of LI in the GJP subjects compared with that of their controls [0.3 ± 0.1 ($p < 0.05$)]. The CFI resulted in a non-significant reduction of LJP patients compared with their controls. In addition, the CDI resulted in no significant differences when the LJP and the GJP subjects were compared with their matched controls. The distribution of leukocyte defects within both the test and control groups is illustrated in Table 3. It is of interest that every JP patient, both generalized and localized, had at least one PMN defect, and many had depression of more than one of the PMN functions when compared with the simultaneously-tested matched controls.

The observed significant (uncorrected) associations of LJP and GJP to HLA antigens are illustrated in Table 4. Only two, HLA-A33 and DR2, were significantly different between cases and controls. HLA-A33 was present in 36% of the LJP patients and was not present in any of the matched control subjects (relative risk undefined, $p = 0.04$). HLA-DR2 was present in 42% of the LJP patients, compared with 6% of the matched controls (relative risk = 11.43, $p = 0.06$), and was present in 60% of the GJP patients, compared with 6% of the matched controls (relative risk = 24, $p = 0.05$). There was a non-significant decrease in HLA-A2 (relative risk = 0.23) and a non-significant increase in DR4 (relative risk = 5.33). When the cases were compared with the large unevaluated control groups, the significant increase in A33 persisted (relative risk = 6.00, $p = 0.0135$); however, for DR2 the relative risk dropped to 1.41 and was no longer statistically significant. No

TABLE 3
DISTRIBUTION OF PMN DEFECTS

	Leukotaxis % Depression (C-P)				
		Serum-associated			Phagocytosis
LJP	Cell-associated	CFI	CDCF	CDI	% Depression (C-P)
1	75	0	66	0	43
2	17	69	55	14	50
3	47	(-)77	0	(-)32	51
4	37	0	63	N.D.	27
5	35	39	0	0	48
6	59	66	0	0	55
7	0	0	37	0	36
8	40	0	0	0	84
9	22	0	0	0	41
10	49	64	0	0	33
11	76	(-)10	0	0	37
12	29	29	0	0	100
13	0	0	0	0	51
GJP					
1	28	0	0	0	25
2	73	0	0	0	32
3	46	16	0	0	32
*4	N.D.	N.D.	N.D.	39	33
*5	N.D.	N.D.	N.D.	N.D.	(-)11

(-) Signifies instances in which control values were depressed compared with those of patients.

(*) Subject pairs which were not included in calculations of means and in statistical evaluations because of insufficient data.

N.D. = Not Done.

TABLE 4
HLA AND DISEASE ASSOCIATIONS*

Antigen	Disease	Proportion Among Controls	Proportion Among Patients	Relative Risk Value	p^u	p^c
HLA - A33	LJP	0.00(N=17)	0.36(N=13)	Undefined**	0.04	0.56
HLA - DR2	LJP	0.06(N=17)	0.42(N=12)	11.43	0.06	0.54
	GJP	0.06(N=17)	0.60(N=5)	24.0	0.05	0.45

*Presence of HLA - A, -B, -C, and -D antigens was identified; however, no other associations were near significance and so are not included in this Table.
**R.R. is undefined because this phenotype was not present in any of the controls.
[u]Uncorrected.
[c]Corrected for number of alleles at that locus.

decrease in HLA-A2 was found, but the non-significant increase in DR4 persisted (relative risk = 3.8, p = 0.18). None of the other HLA antigens tested generated uncorrected p-values which were statistically significant.

Discussion.

Classically, JP has been described as a disease in which the amount of periodontal destruction observed is vastly more severe than would have been expected, considering the youth of the patients and the amount of plaque and clinical inflammation present. Presently, histologic evidence clearly indicates the inflammatory nature of the disease. Additionally, the concepts of the specific bacterial etiology (Loesche, 1976) and cyclical nature (Hancock, 1981) of the disease have been described. However, these concepts do not exclude the possibility that host response mechanisms are also operative. It seems reasonable to assume that the quality, location, and invasiveness of the plaque, as well as the nature of the host response, are important co-factors. In this study, the Pl.I. and GI were the same for GJP and their controls, and significantly lower for LJP compared with their controls. On the other hand, the pocket depths, tooth mobilities, and radiographic bone loss were significantly greater in both LJP and GJP patients relative to the observations among controls. These findings are compatible with the expected clinical findings of patients with JP.

Clearly a defect in leukotaxis and phagocytosis is strongly associated with JP. This has been amply demonstrated in this and several previous studies (Lavine *et al.*, 1976; Cianciola *et al.*, 1977; Clark *et al.*, 1977; Lavine *et al.*, 1979; Van Dyke *et al.*, 1980; Genco *et al.*, 1980; Van Dyke *et al.*, 1981; Van Dyke *et al.*, 1982; Ellegard *et al.*, 1984; Suzuki *et al.*, 1984; Suzuki *et al.*, 1985). The present study, in addition, illustrates the occurrence of multiple defects in many JP patients. Every JP patient had depression in at least one of the parameters of leukotaxis. Whereas the overwhelming majority of both LJP and GJP patients displayed an intrinsic cell defect in chemotaxis, a substantial number of LJP (but not GJP) patients displayed a CDCF (serum-associated) defect in leukotaxis as well.

One additional important point regarding the observed depressed leukotaxis is that it was present in both treated and untreated JP patients. Since leukocyte functions were in many instances studied when the patients were apparently not in an active phase, one may infer that the PMN defect is permanent, and may have preceded the infection rather than resulted from it. This is in agreement with the reported high prevalence of leukocyte locomotor dysfunction in JP which occurred in both LJP and GJP, and which was long-lasting and unaffected by treatment of the periodontal condition (Van Dyke *et al.*, 1982; Suzuki *et al.*, 1985).

The majority of both LJP and GJP patients in this study exhibited depression in PMN phagocytosis. This corroborates the findings of Cianciola *et al.* (1977) but conflicts with the report of Lavine *et al.* (1979). It appears that the differences were due to methodology in assessment of phagocytosis. Lavine *et al.* (1979) used the quantitative NBT test for determination of phagocytosis. In the present study, the stimulated NBT test, which may be more sensitive than the quantitative test (Segal, 1974), was used.

Evidence that LJP may have a genetic component in its etiology is supported by the associations found with specific HLA antigens. Terasaki *et al.* (1975), in a U.S. sample (n=19), found a statistically non-significant decreased frequency of HLA-A2 in periodontosis cases (32%) compared with dental controls (61%) and with normal controls (48%). Reinholdt *et al.* (1977), in a Danish sample (n=39), found a non-significant decrease in A2 (43.6% *vs.* 53.6%); also, they reported significant increases in A9, A28, and BW15. Most of these reports on the association of HLA with JP involved Caucasian subjects. Only Cullinan *et al.* (1980) reported on Black subjects.

The studies reported thus far, however, have not demonstrated much consistency in the specific associations. In this study, when the cases were compared with the periodontal disease-free control groups, there were significant increases in A33 and DR2. The A33 increase was not consistent with the only other study of Black cases (Cullinan *et al.*, 1980), which found A33 to be non-significantly decreased among cases. The specific allele (B35) found increased in that study was not evaluated in this study. In this study, the increased HLA-DR2 in cases was not found when the cases were compared with the larger control group, which had not been evaluated for periodontal disease. This may reflect either a significant number of cases among the unevaluated control group, thereby obscuring the association, or simply random sampling differences between the small evaluated control group and the much larger unevaluated control group. The association of specific HLA phenotypes, when considered together with the preponderance of JP occurring among Blacks in our population, suggests that heritable factors play a role in the etiology of the disease. Previous reports on the heritable nature of JP (Fourel, 1972; Jorgenson *et al.*, 1975; Melnick *et al.*, 1976), its familial distribution (Benjamin and Baer, 1967; Kirkham, 1977), and the association with ABO blood groups (Kaslick *et al.*, 1971; Malena, 1972) lend further credence to the hypothesis.

Although this study demonstrates an association between HLA-A33 and LJP as well as HLA-DR2 and both LJP and GJP, it merely suggests a genetic component and does not conclusively prove it. Because of the small number of subjects studied and the lack of consistency in specific allelic associations from study to study, firm conclusions cannot be drawn. Saxen and Koskimies (1984) have recently reported an inability to find evidence of linkage between HLA haplotypes and JP in a small number of multiply-affected families. While there are hypothetical grounds on which there could be a population association not attributable to linkage, the validity of such observations is uncertain. Further studies of correlates of ge-

netics, clinical status, and host response mechanisms in JP should be conducted in order to understand better the etiology and pathogenesis of these types of disease and their interrelationships.

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