

## Leg Ulcers in Patients With Sickle Cell Disease

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During the entry examination, leg ulcers were present in 2.5% of 2,075 patients 10 years of age and older with sickle cell disease who entered into the Cooperative Study of Sickle Cell Disease (CSSCD) between 1979 and 1986. Prevalence rates were highest among patients with sickle cell anemia and sickle cell anemia with thalassemia genotypes. Among sickle cell anemia patients free of ulcers at entry, the overall incidence was 5.73 per 100 person years in those having associated  $\alpha$ -thalassemia and 9.97 for those without. Among sickle cell anemia patients with two  $\alpha$  genes, the estimated incidence of leg ulcers is 2.38 per 100 person years and 6.12 per 100 person years among

sickle cell anemia patients with three  $\alpha$  genes ( $P < .05$ ). In both groups, the incidence was highest among those patients over 20 years of age and considerably higher among males than females ( $P < .001$ ). Leg ulcers were nonexistent in patients with sickle  $\beta$  plus thalassemia and sickle hemoglobin C disease. Low steady-state hemoglobin is associated with a higher incidence of ulcer formation ( $P < .0001$ ) in sickle cell anemia patients. The protective effect of hemoglobin F is apparent at all levels of total hemoglobin among sickle cell anemia patients and those with associated  $\alpha$ -thalassemia.

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IT HAS BEEN KNOWN for a long time that leg ulceration is a common complication in homozygous sickle cell anemia (SS).<sup>1-4</sup> It is generally believed that between 8% and 10% of SS patients develop leg ulceration between the ages of 10 and 50 years, but higher rates of more than 50% have been described.<sup>2,4,5</sup> Sickle cell leg ulcers appear to occur either spontaneously or as a result of local trauma and often persist for long durations of time. Vessel obstruction by sickled cells, increased venous and capillary pressure, secondary bacterial infection, and decreased oxygen-carrying capacity of blood interfering with proper nutrition and metabolism of blood cells have all been invoked as contributing factors.<sup>6-8</sup> Several kinds of treatment modalities have been reported to aid in the healing of leg ulcers in sickle cell disease, but few comparative or controlled studies have been conducted.<sup>9-14</sup> Data on leg ulcers from the Cooperative Study of the Clinical Course of Sickle Cell Disease will be described in this report.

### MATERIALS AND METHODS

Patients with sickle cell disease entered the Cooperative Study between March 1979 and March 1981, and were followed at 23 participating clinical centers for up to 8 years.<sup>15</sup> Information on leg ulcers in these patients was collected until June 1986. The clinical centers were mostly in urban areas throughout the West, Midwest, Southern, and Eastern parts of the United States with two centers in Southern rural areas. Patients were classified as sickle cell anemia (SS), sickle hemoglobin C disease (SC), sickle  $\beta$  plus thalassemia ( $S\beta^+$  thalassemia) and sickle  $\beta$  zero thalassemia ( $S\beta^0$  thalassemia). Patients with hemoglobin SS were subdivided into those with four or more  $\alpha$  genes (SS) and those with fewer than four  $\alpha$  genes (SS  $\alpha$ -thalassemia). Diagnosis was confirmed at the Centers for Disease Control in Atlanta on the basis of hemoglobin electrophoresis at alkaline and acid pH, hemoglobin solubility, and quantitation of hemoglobins F and A<sub>2</sub>. DNA was extracted from peripheral blood leukocytes and  $\alpha$ -globin gene mapping was performed at the University of California at San Francisco, to detect the presence of  $\alpha$ -thalassemia.<sup>16,17</sup>

A leg ulcer form (data sheet) was initiated whenever a study patient entered the clinic, emergency room, or hospital with ulceration of the skin of the lower leg, with or without a history of trauma, that failed to heal within 2 weeks. A history, physical examination, and laboratory data were obtained to complete the clinical evaluation. A separate form was completed for each ulcer that occurred. Once an ulcer had formed, it was followed until healed with follow-up visits scheduled every month for the first 6 months and thereafter every 3 months. The leg ulcer form collected information on date of occurrence, site, past history, and sites of ulcers that

healed. Description of the ulcer and measurement were detailed in centimeters on an ulcer location chart. Steady-state blood samples for biochemical and hematologic parameters were obtained during scheduled clinic visits. Steady state was defined as the absence of acute vasoocclusive episodes, or any other acute events at the time of entry into the study.

Leg ulcer forms from the clinical centers were forwarded to the Statistical Coordinating Center for processing and analysis. Subjects with missing or incomplete information were excluded from analysis involving the particular variable that was not available. Because occurrence of ulcers in sickle cell disease was rare (< 1%) in patients below 10 years of age, analysis was confined to patients 10 years of age and older. Patients awaiting documentation of genotypes were excluded from the study. For evaluation of risk factors for leg ulcers, we examined the following variables: age, sex, type of sickle cell disease, hemoglobin level, fetal hemoglobin level, and body mass (weight [kg])/(height [m])<sup>2</sup>. The data were also explored for possible associations with other acute or chronic events.

**Statistical methods.** Prevalence rates (per 100 persons) at entry and incidence rates (per 100 person years) were computed for each genotype and for major demographic subgroups (eg, sex, age group, a history of prior leg ulceration, region of residence) and for groups categorized by various hematologic indices. The significance of trends in incidence rates was determined by use of the Cochran-Armitage Test.<sup>18</sup> Pair-wise comparisons of incidence rates between groups were performed by use of tests based on the normal distribution.<sup>19</sup>

Two sample *t* tests were used to compare the mean levels of hematologic indices, fetal hemoglobin, and body mass between sickle cell patients with leg ulcers and those without. Analysis of variance

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(ANOVA) was performed using the total number of ulcers per patient as response variable and various parameters such as month, region of residence, and clinic as independent variables. Scheffe's multiple comparisons were used to compare means between groups.

Chi-square tests from two-way contingency tables were used to compare the rates of associated events, ie, painful episodes, acute chest syndrome, right upper quadrant syndrome, seizure, meningitis, stroke, acute febrile event, aseptic necrosis, renal events, and retinopathy among patients with ulceration and those without. Cox regression was used to compare rates of healing among the different treatment regimens for both hemoglobin SS and hemoglobin SS with  $\alpha$ -thalassemia patients.

## RESULTS

**Prevalence.** The prevalence of leg ulcers per 100 persons 10 years of age and older at entry was 2.5 overall, and was considerably higher among SS and SS  $\alpha$ -thalassemia patients than among those having SC,  $S\beta^+$ , or  $S\beta^0$  genotypes (Table 1). Among 1,700 patients entering the study under 10 years of age, there were no leg ulcers found at the initial examination.

**Incidence.** Because there were no patients with leg ulcers at entry with  $S\beta^+$  thalassemia and the rates were extremely low in genotypes other than SS and SS  $\alpha$ -thalassemia, the incidence rates of leg ulcers are shown only for patients 10 years of age and older having genotypes SS and SS  $\alpha$ -thalassemia (Table 2). Within each age group, incidence rates were higher in patients having SS genotype than in those with SS  $\alpha$ -thalassemia ( $P < .0001$ ) with overall rates being 9.97/100 persons in the group having the SS genotype and 5.7/100 persons in the group having SS  $\alpha$ -thalassemia. Among SS patients with two  $\alpha$  genes, the estimated incidence of leg ulcers was 2.38/100 person years as opposed to an estimated incidence of 6.12/100 person years among patients with three  $\alpha$ -genes ( $P < .05$ ). The incidence of leg ulcers among patients with three  $\alpha$  genes does not differ significantly from SS patients not having  $\alpha$ -thalassemia.

**Sex distribution.** The incidence rates of leg ulceration among males was significantly higher than among females in both genotypes, the rates were approximately 15 and 5/100 person years ( $P < .001$ ) in males and females respectively (Fig 1).

**Age distribution.** Among patients with SS and SS  $\alpha$ -thalassemia genotypes, the incidence of leg ulcers was low among patients between 10 and 19 years of age (3.10/100

person years among hemoglobin SS and 0.671/100 person years among hemoglobin SS  $\alpha$ -thalassemia). There was a sharp increase in incidence rates of leg ulcer after the second decade. Among patients 20 years of age and above, the incidence rates ranged from 14.59 to 19.17 in hemoglobin SS patients and from 7.57 to 11.13 among hemoglobin SS  $\alpha$ -thalassemia patients (Table 2).

**Regional and seasonal variation.** Incidence rates of leg ulcers by month of occurrence and region were computed for hemoglobin SS and hemoglobin SS  $\alpha$ -thalassemia patients (see the Statistical Methods Section). There were no significant differences among regions with respect to incidence rates. In general, there was considerable monthly variation in incidence rates but no clear seasonal trends.

**Past history of leg ulcers.** Information on past history of leg ulcers obtained from medical charts revealed that 10% of SS patients had a past history of leg ulcers that healed and did not recur during the study period. Another 10% who had leg ulcers in the past entered the study without ulcers but developed new ulcers during the study. Further analysis using incidence computation gave the following rates per 100 person years. The SS patients who were ulcer free at entry with no prior ulcer had a rate 0.52, those with a history of prior ulcers but who were ulcer free at entry showed a rate of 11.9, and those with a prior history of ulcers who had an ulcer at entry and continued to recur had a rate of 75.8/100 person years. Similar trends were seen in SS  $\alpha$ -thalassemia patients (Fig 2). Seventy-five percent of patients who never had leg ulcers in the past did not develop them during the study period. Only 5% of the patients developed leg ulcers for the first time during the study period.

**Hemoglobin level and fetal hemoglobin.** Both steady-state hemoglobin level and fetal hemoglobin level were inversely correlated with the incidence of leg ulcers in SS patients and with only fetal hemoglobin in SS  $\alpha$ -thalassemia patients. Among hemoglobin SS patients, incidence of ulcer events decreased steadily from 43.2 events per 100 person years in patients having hemoglobin levels below 6 g to 2.4 events in patients having hemoglobin levels above 12 g ( $P < .0001$ ). This trend did not occur with SS  $\alpha$ -thalassemia patients (Fig 3A). In both genotypes, the incidence of leg ulcer events decreased consistently with an increase in fetal hemoglobin ( $P < .0001$ ) (Fig 4A). For example, hemoglobin SS patients with hemoglobin F levels above 10% had an incidence of leg ulcer events of 0.7/100 person years as

**Table 1. Prevalence of Ulcers at Entry Into Study Among CSSCD Patients According to Genotype (Patients 10 Years of Age and Older)**

Hemoglobin Type	No. of Patients	Prevalence (per 100 Persons) of Ulcers
SS 4.5 $\alpha$ genes	623	4.97
SS 2.3 $\alpha$ genes	280	3.92
SS (unmapped)*	465	1.51
SC	415	0.00
$S\beta^+$ Thalassemia	118	0.00
$S\beta^0$ Thalassemia	116	0.86
Transfused/Unknown Genotypes	58	3.45
Total	2,075	2.51

\*Of 3,775 patients with sickle cell disease entered into the CSSCD study, 1,700 were children under the age of 10 years and were excluded from this report. Similarly, 465 SS patients whose gene statuses were incomplete were also excluded. The majority of the unmapped SS patients were children under 10 years of age.

**Table 2. Incidence of Leg Ulcer Events by Age at Event for Hemoglobin SS and SS  $\alpha$ -Thalassemia Genotypes**

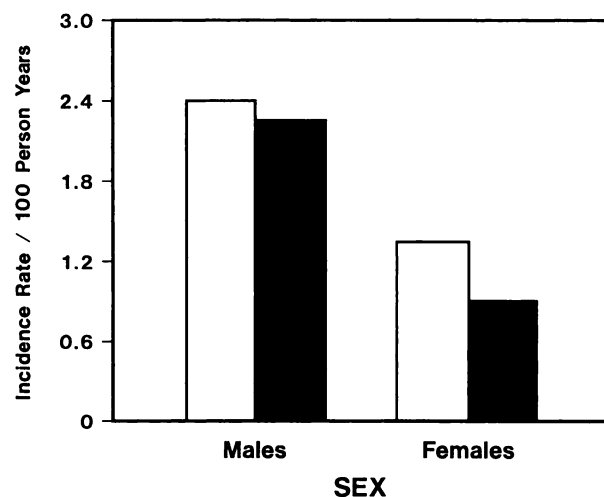
Age Groups (yr)	Hemoglobin SS				SS $\alpha$			
	No. of Patients With Leg Ulcers	No. of Leg Ulcers	Patients at Risk	Incidence Rate (per 100 Person Years)	No. of Patients With Leg Ulcers	No. of Leg Ulcers	Patients at Risk	Incidence Rate (per 100 Person Years)
10 and 20	24	52	431	3.10	3	4	151	0.67
20 and 30	42	171	319	14.59	15	40	123	8.57
30 and 40	22	103	158	16.62	6	28	70	11.13
40 and 50	13	37	50	18.38	3	6	15	8.27
50	4	6	11	19.17	3	5	12	7.57
Total (10 yr and above)	105	369	969	9.97	30	83	371	5.73

Incidence of leg ulcer events for SS and SS  $\alpha$ -thalassemia genotypes were calculated per 100 person years. The incidence rates are higher in SS genotypes than SS  $\alpha$ -thalassemia (9.97 v 5.73).

opposed to 13.0 in patients with hemoglobin F levels below 5%. The data on hemoglobin F levels and hemoglobin concentration and their relationship to the incidence of leg ulcers as independent variables are shown in Figs 3B and 4B for SS and SS  $\alpha$ -thalassemia patients, respectively. The protective effect of hemoglobin F is apparent at all levels of total hemoglobin among SS and SS  $\alpha$ -thalassemia patients.

**Association of leg ulcers with other clinical events.** We compared the occurrence of other acute and chronic clinical events in SS and SS  $\alpha$ -thalassemia patients with leg ulcers. Acute events considered were painful episodes, chest syndrome, right upper quadrant syndrome, anemia, febrile events, and new neurologic events. The chronic events examined were avascular necrosis, chronic renal failure, old cerebrovascular accidents, seizure disorder, and sickle retinopathy. There was no appreciable difference in the occurrence of any acute or chronic event among ulcer formers and those who never developed leg ulcers.

One of the 203 patients with leg ulcers in this study developed chronic osteomyelitis requiring below the knee amputation after 18 years of nonhealing and unsuccessful attempts of treatment that included blood transfusion and multiple skin grafts. The patient had experienced a cerebrovascular accident at the age of 6 years and had been confined to a wheelchair for >30 years.

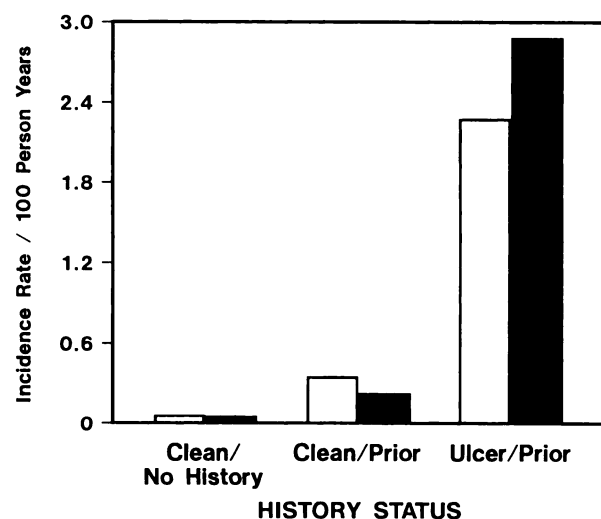


**Fig 1. Sex distribution of incidence of leg ulcer among SS and SS  $\alpha$ -thalassemia genotypes (M > F) ( $P < .001$ ). (□), HB SS; (■), SS  $\alpha$ .**

**Employment status.** Entry demographic information on employment status (defined as employed, unemployed, or disabled) and total income were analyzed for comparison among those patients who had ulcers and those who did not develop ulcers during the study period. Data were analyzed by comparing males, females, type of sickle cell disease, and employment status. There was no statistically significant difference in the total income or the work status of the two groups.

**Description of ulcer.** Patients were grouped into different categories by ulcer sizes, 0 to 5 cm, 5 to 10 cm, 10 to 15 cm, and over 15 cm. Patients were distributed equally in the ulcer size groups during the study period. Ulcers occurred with equal frequency over both medial and lateral aspects of the left and right lower extremities. Patients with new leg ulcers experienced pain and inflammation and these findings were more severe with increasing size and chronicity of the ulcer. Descriptions of presence of old scar, purulence, poor granulation tissue, and nonhealing were common among those ulcers >10 cm in diameter.

**Results of treatment.** Several methods of treatment



**Fig 2. Correlation of past history of leg ulcers and recurrence rate. In SS patients with no previous ulcer who were ulcer free at entry, ulcer developed at a rate of 0.52, those with previous ulcers but ulcer free at entry recurred at a rate of 11.9 and those with past history of ulcer and entered the study with ulcer continued to recur at a rate of 75.9 per 100 person years. (□), HB SS; (■), SS  $\alpha$ .**

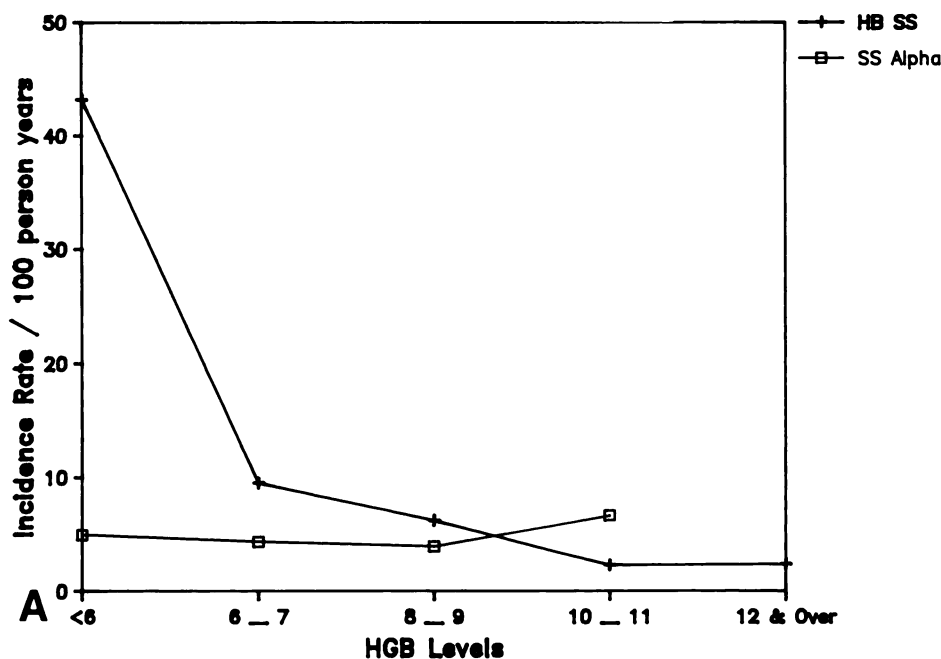
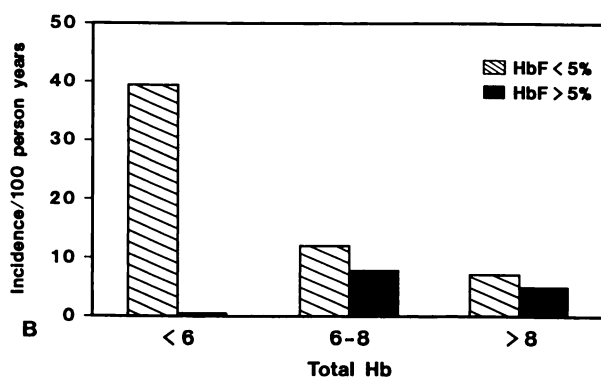


Fig 3. (A) Steady-state hemoglobin level correlated inversely with incidence of leg ulcers in SS patients. This was not seen in SS patients with  $\alpha$ -thalassemia. (B) Incidence of leg ulcers per 100 person years in SS patients with 4, 5  $\alpha$  genes by total hemoglobin and fetal hemoglobin levels. Low hemoglobin and hemoglobin F levels were associated with increase incidence of leg ulcers.



study period, but those ulcers that remained unresolved at time of analysis and exit from the study were active ulcers of duration ranging from 2 to 4 years. Ulcers that recurred after initial healing using any form of therapy did so by approximately 6 to 8 months.

#### DISCUSSION

This prospective study determined the incidence and prevalence of leg ulcers in sickle cell diseases and followed the clinical course of this disorder. SS and SS  $\alpha$ -thalassemia patients had the highest prevalence rate of all genotypes. The point prevalence or the number of existing cases of leg ulcers at entry to the study in patients over 10 years of age was approximately 5% in SS patients and 4% in SS  $\alpha$ -thalassemia. The incidence of leg ulceration was similar in SS patients and SS patients with three  $\alpha$  genes, but was significantly lower in SS patients with two  $\alpha$  gene deletions. Thus,  $\alpha$ -thalassemia seems to be protective against developing leg ulcers only for patients having two  $\alpha$  gene deletions. The percentage of patients who had ulcers in the past that healed, or who entered the study with ulcers or developed new ulcers during the study period was approximately 25%. This is much lower than data from Jamaica, Africa, and earlier reports from the United States.<sup>2,7,9</sup> To evaluate if the reports were higher in patients with sickle cell disease in tropical countries, we analyzed the incidence of leg ulcers from the various geographic regions among the study patients. Analysis of variance was performed using the number of ulcers per patient per month for 4 years as response variables and month as independent variable. There was considerable month-to-month fluctuation but no clear seasonal trends in the incidence of leg ulcers.

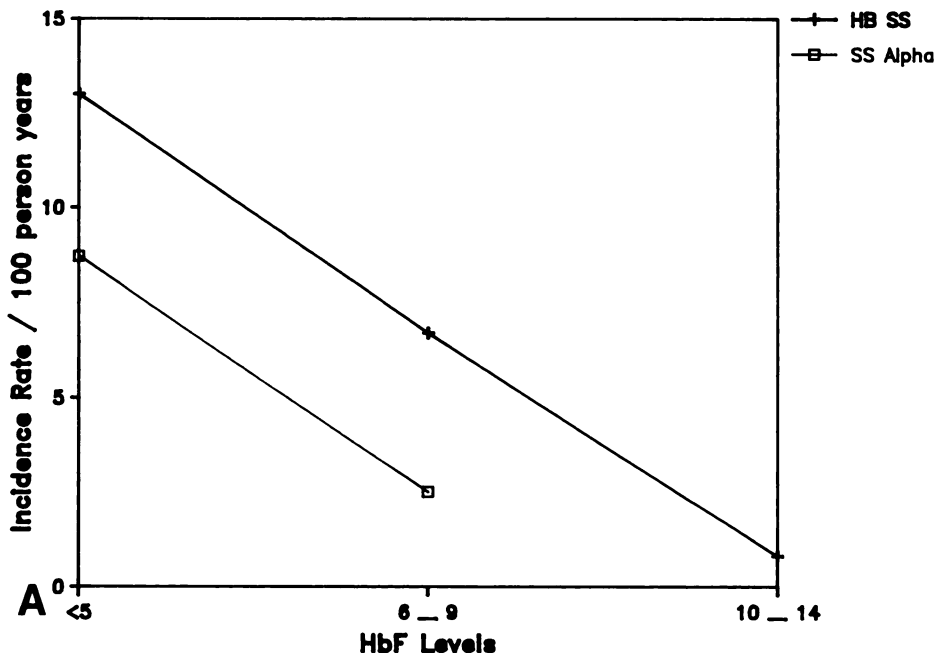
Ulcers were not seen in the 175 patients with  $S\beta^+$  thalassemia and rates were low among patients with SC and  $S\beta^0$  thalassemia, and children under the age of 10 years. Similar

were analyzed. No specific treatment protocol was recommended for the participating clinics. Treatment consisted of use of salves, soaks, whirlpool, gel boots, and local antibiotics solely or in combination. Response to transfusion therapy and skin grafting were also evaluated. Local ulcer care was part of all treatment regimens.

Analysis of response to treatment demonstrated a recurrence rate of 37% with transfusion therapy or gel boot; 25% with local therapy, ie, soaks, salves, whirlpool, zinc, topical antibiotics; 32% with combinations of zinc, antibiotics, and analgesics; and 52% after skin graft surgery. The mean size of healed ulcers, response to therapy, and ulcers that recurred are shown in Table 3. Patients with nonhealing ulcers and patients with less than three separate ulcer measurements were excluded from analysis. There was no statistical difference in the mean size of ulcers that healed and those that recurred. Patients who reported healing of leg ulcers with local therapy had small mean ulcer size.

The log rank test performed on the various treatment modalities did not detect any difference in the rate of healing of ulcer. Ulcers that healed within a year (using any of the methods of treatment) did not generally recur during the

**Fig 4.** Leg ulcer events decreased consistently with increase in fetal hemoglobin ( $P < .001$ ). (B) Incidence of leg ulcers per 100 person years in SS patients with 2, 3,  $\alpha$  genes by total hemoglobin and fetal hemoglobin levels. Low fetal hemoglobin level correlated with increased incidence of leg ulcers. Correlation with hemoglobin level was not present as in Fig 3. The protective effect of hemoglobin F is apparent at all levels of total hemoglobin among SS and SS  $\alpha$ -thalassemia patients (both in Figs 3 and 4).

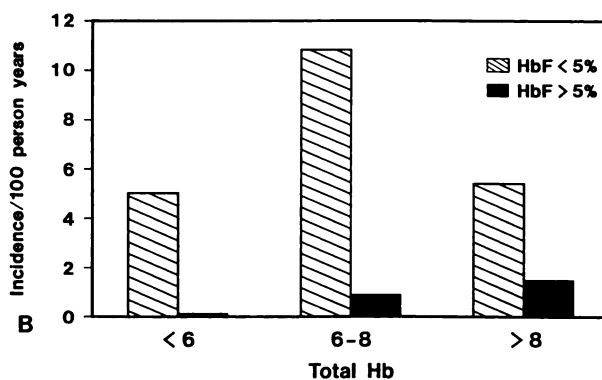


findings were obtained on review of these patients' past medical histories. The higher level of hemoglobin (range, 11 to 14 g), and other factors, ie, lower rates of medical complications and general well-being in SC and  $S\beta^+$  thalassemia patients, may be possible explanations for the extremely low rates of leg ulcers in these genotypes. This is reinforced by our findings that in SS patients, leg ulceration occurred more often in patients with lower hemoglobin and lower fetal hemoglobin levels.

Patients with genotypes SS and SS  $\alpha$ -thalassemia developed ulcers after the age of 10 years with incidence increasing significantly with advancing age and ulceration was more frequent in males than in females. There were no differences in any of the laboratory or demographic variables between the males and females and we were unable to explain why males suffer from more leg ulcers than do females. Analysis of demographic information and laboratory data revealed no differences between ulcer formers and nonulcer formers. Similarly, acute and chronic events were present with equal frequency in both groups.

All methods of treatment were associated with similar recurrence rates. Local treatment was the choice in all clinical centers for ulcers with small mean size diameter (< 4 cm) and there was a recurrence rate of 25%. From analysis of the data, it appears that aggressive forms of treatment with blood transfusion therapy and skin graft were reserved for nonhealing or for ulcers >8 cm in mean diameter. The recurrence rates were 37% and 52% for transfusion therapy and skin graft, respectively (not significant). The high failure rate of 52% after skin graft may be due to the larger diameter of the ulcer, chronicity, and longer duration of the ulcer at time of skin graft surgery. Different protocols were followed for skin grafting. Most clinics followed the basic principles of a clean ulcer base, with good granulation tissue, preparative blood transfusion therapy, and full thickness skin graft.

Blood transfusion therapy was used intermittently and



therapy was discontinued when the ulcer healed. Therefore, we are unable to evaluate if chronic transfusion therapy would prevent the recurrence of leg ulcers.

Ulcers that persisted over 1-year duration became chronic nonhealing ulcers with increasing ulcer size, scar tissue, and chronic local skin changes. Healing was short term and recurrence of ulcers was seen with all methods of treatment.

**Table 3. Mean Size of Healed Ulcers in Different Treatment Groups**

Treatment Type	Does Not Recur			Does Recur		
	N	Mean	SE	N	Mean	SE ( $\pm$ )
I Zinc/Analgesics/Antibiotics	14	$\pm 3.7$	0.64	18	$\pm 4.1$	0.74
II Salves/Soaks/Whirlpool	88	$\pm 3.1$	0.35	30	$\pm 4.1$	0.65
III Gel Boot/Plus I, II	33	$\pm 4.1$	0.75	22	$\pm 5.2$	1.21
IV Transfusion/Plus I, II	29	$\pm 4.6$	0.93	20	$\pm 5.6$	1.28
V Surgery	8	$\pm 12.3$	2.49	10	$\pm 10.0$	2.31

All nonhealed ulcers and patients with <3 ulcer measurements are also excluded. Mean ulcer size was calculated from measurements over the entire ulcer period. Some ulcers recurred after complete healing. There was no statistical difference in the size of ulcers that healed and those that recurred.

Failure of multiple methods of treatment protocol has led to inadequate patient participation in ulcer treatment. The more aggressive forms of treatment, ie, blood transfusions and skin grafts, were reserved for the larger chronic nonhealing ulcers. Because the various treatments resulted in dismal failure rates, it may be necessary to initiate a randomized trial for early aggressive treatment before chronic changes appear.

Because leg ulcerations were less frequent in genotypes with milder forms of disease, we speculate that methods to improve and maintain higher levels of hemoglobin may also prevent the formation of leg ulcers. Methods to improve hemoglobin levels by raising F hemoglobin levels may also have a role in the treatment of this difficult clinical complication. While transfusion therapy did heal ulcers, the routine use of blood transfusion therapy to maintain higher hemoglobin levels is not justified given the well-known potential complications of transfusion therapy. Physicians, patients, and families should be aware that leg ulcers occur most frequently in older (> 10 years) SS and SS  $\alpha$ -thalassemia patients and that male patients are at a higher risk for this complication. Frequent examination of the lower extremities to identify early skin changes, new onset leg ulcers, and institution of aggressive treatment should be encouraged.

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