To the Editor:

Chronic leg ulcers may complicate the course of patients with sickle cell disease; the incidence of ulcers is reported to be influenced by patient age, genotype, and geographical location. Elevated levels of fetal hemoglobin (HbF) and α-thalassemia are thought to protect patients with sickle cell disease from leg ulceration, which is reported as rarely observed in Indian and Saudi Arabian sickle cell disease patients who have both high HbF and with a high frequency of α-thalassemia. Less frequently, ulcers are observed in homozygous β-thalassemia, usually in patients who are not receiving regular transfusions in whom abnormal rheologic properties of red blood cells (RBCs) and high oxygen affinity of blood with elevated levels of HbF have been suggested as possible mechanisms for slow healing of leg ulcers. Numerous treatment modalities have been used to promote healing of these chronic leg ulcers; all are associated with a slow progression to skin closure and high recurrence rates.

Pharmacologic stimulation of HbF synthesis is reported to ameliorate both sickle cell disease and homozygous β-thalassemia and has been achieved in clinical trials by the use of chemotherapeutic agents such as 5-azacytidine, cytarabine, vinblastine, and hydroxyurea, as well as with arginine butyrate.

We have treated eleven patients with sickle cell disease or homozygous β-thalassemia with intravenous arginine butyrate. Two patients, one with HbSS and one homozygous Hb Lepore, had chronic nonhealing leg ulcers at the start of therapy. The course of the first...
Fig 1. A nonhealing leg ulcer adjacent to the right medial malleolus, in a 23-year-old untransfused homozygous Hb Lepore patient before (A) and 6 weeks after (B) starting arginine butyrate therapy.

Patient, a 23-year-old female homozygote Hb Lepore with alloantibodies necessitating termination of transfusions 11 years before therapy with arginine butyrate, has previously been reported. At the start of butyrate therapy, she had marked ineffective erythropoiesis (Hb 4.7 g/dL, nucleated RBC count 800 per 100 white blood cells), extramedullary hematopoiesis, growth impairment, and bony deformities. A 5-cm × 3-cm ulcer on the medial malleolar aspect of her right leg (Fig 1A) had been present for 24 months. Skin care had included daily astringent therapy with aluminum acetate and dressing with chlorhexidine acetate. Arginine butyrate, at a dose of 1,500 to 2,000 mg/kg/d, resulted in an increase in total peripheral Hb from 4.7 to 10.2 g/dL, over 7 weeks of therapy. Ulcer healing to complete skin closure occurred within 6 weeks of initiation of arginine butyrate therapy (Fig 1B).

The second patient, a 21-year-old female with HbSS, had a clinical course notable for 4 to 5 vaso-occlusive crises per year, necessitating repeated hospital admissions and requiring occasional blood transfusions, and a 6-cm leg ulcer on the medial aspect of her right leg, unhealed during at least 12 months before starting arginine butyrate, despite good compliance with topical zinc and antimicrobial (chlorhexidine acetate) therapy. This patient received 10 weeks intravenous arginine butyrate, 2,000 mg/kg/d, 5 days per week, during which time her γ-globin mRNA rose 2.3-fold over baseline, and HbF rose from 7% to 17%, without any change in total Hb concentration. The leg ulcer granulated completely within 6 weeks of starting arginine butyrate therapy, and has remained so for more than 6 months since discontinuing butyrate. While in hospital, the ulcer was also treated with daily hypertonic sodium chloride-impregnated dressings.

Healing of a chronic leg ulcer has been observed previously in one patient with sickle cell disease, receiving therapy aimed at stimulating HbF synthesis. This patient had received 6 months of hydroxyurea (20 mg/kg/d), during which time HbF rose from 3.7% to 18.6%, without improvement in the leg ulceration. High-dose recombinant human erythropoietin (600 to 800 U/kg) was then added to the hydroxyurea, with a further rise in HbF to 24%; within 6 weeks, complete healing of the leg ulcer was observed.

Butyrate, a naturally occurring fatty acid, appears to enhance γ-globin mRNA expression and to increase HbF synthesis in selected patients with β-hemoglobinopathies. The patients reported here represent the first description of rapid and complete healing of chronic leg ulcers, previously resistant to multiple medical therapies including prolonged bed rest, induced by arginine butyrate. In neither patient was ulcer healing believed to be related to prolonged bed rest, as both patients remained ambulatory five days per week while in hospital, and both returned home for 48 hours per week to normal activity, during the course of butyrate therapy. Butyrate-induced leg ulcer healing may be related to an increase in HbF and total Hb concentration in the patient with Hb Lepore, and to elevation in HbF in the patient with sickle cell disease. Other mechanisms may also be operative, such as the ability of butyrate to alter cell maturation, or the induction of other proteins that may act as growth factors to promote ulcer healing. The role of butyrate therapy in the healing of chronic leg ulceration associated with β-hemoglobinopathies requires further study.

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REFERENCES
Rapid healing of chronic leg ulcers during arginine butyrate therapy in patients with sickle cell disease and thalassemia [letter]

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