Leishmaniasis is a vectorborne disease caused by parasitic protozoa of the genus *Leishmania*. Transmitted to humans by sand flies, the disease is endemic in 88 countries on 4 continents. In the United States, the disease is something of a medical curiosity, although some clinicians may be surprised to read that autochthonous cases of cutaneous leishmaniasis occur in Texas [1], that visceral disease has been described in American dogs [2], and, most recently, several hundred cases of cutaneous disease and a handful of visceral infections have occurred among US servicemen and servicewomen deployed to Iraq and Afghanistan in support of Operation Iraqi Freedom and Operation Enduring Freedom [3, 4]. Outside the United States, leishmaniasis takes a devastating toll, and it is estimated that 1.5–2 million cases of leishmaniasis occur each year, with many of these cases occurring among the world’s most economically disadvantaged patients.

Treatment for leishmaniasis depends on several factors, including the clinical presentation of disease (in broad terms, visceral versus cutaneous), the infecting species of *Leishmania*, and the host’s immune status. For visceral disease, therapy is always indicated, as untreated infection can progress to death. Fortunately, there are several effective options for the treatment of visceral disease. The 2 pentavalent antimonials sodium stibogluconate (Pentostam, Glaxo-Smith-Kline; in the United States, available under investigational new drug protocols via the Centers for Disease Control and Prevention, for civilian use, and via the Walter Reed Army Medical Center, Washington, D.C. and the Brooke Army Medical Center, San Antonio, TX, for the military) and meglumine antimoniate (Glucantime, Specia Rhone Poulenc) have a long track record of success, although rising reports of drug resistance in some part of the world have indicated their effectiveness is limited [5]. Lipid-associated amphotericins have proven very efficacious for visceral leishmaniasis, and liposomal amphotericin B (Ambisome; Fujisawa Healthcare) was approved by the US Food and Drug Administration (FDA) in 1997 for this indication [6]. Unfortunately, the high cost of these drugs and their potential toxicities preclude their use in many areas of the world. Intravenously administered paromomycin offers a lower-cost option, and preliminary results from a recently concluded study suggest good efficacy [7]. Finally, the development of an orally administered drug, miltefosine, offers a real breakthrough in the ability to provide convenient and effective therapy for visceral disease [8].

Cutaneous leishmaniasis, which has numerous colorful eponyms, including “the Delhi boil” and “Baghdad boil,” typically results in chronic, ulcerative lesions. Without treatment, most skin lesions caused by cutaneous leishmaniasis eventually resolve, and thus decisions about whom to treat, and with what, are complex. The time course for healing is variable; there are with reports of self-healing at 3 months in 34% of patients infected with *Leishmania major* in Saudi Arabia [9], in 68% of Guatemalan patients infected with *Leishmania mexicana*, and in 6% of patients infected with *Leishmania braziliensis* [10]. Because it is the unusual patient who develops a life-threatening complication from cutaneous leishmaniasis, treatment is directed at the morbidity, rather than the mortality, associated with the infection, and the ratio of risk to cost is calculated accordingly.

As would be expected for a disease whose first clinical description dates back to the first century A.D., a wide variety of treatment options have been employed throughout history, with variable success. Current choices for therapy include the antimonials (given either parenterally or intralesionally), parenteral pentamidine, amphotericin B, an azole (ketoconazole, itraconazole, or fluconazole), miltefosine, and topical paromomycin compounds. Each of these agents has varying reported
One of the latest advances in direct local therapy as a treatment for cutaneous leishmaniasis is the localized current field-radio frequency (LCF-RF) device. Portable and battery-operated, the device was cleared by the FDA in 2003 for the treatment of cutaneous leishmaniasis. To use the device, the lesion and surrounding skin are anesthetized with lidocaine, and the probes of the device are applied to the lesion. The device delivers precisely controlled localized current-field heat generated by radio-frequency energy. The probes generate heat within the tissue to ~50°C, and a typical application lasts 30 s. For lesions larger than the area encompassed by the probes, multiple adjacent applications are required. On the basis of personal experience with the device, most patients report minimal discomfort at the time of application. However, the blistering and tissue inflammation that occur over the next several days can be disconcerting.

Until the report in this issue of Clinical Infectious Diseases by Reithinger et al. [11], published experience with a LCF-RF device has been limited to New World cutaneous leishmaniasis. Navin et al. [12], compared treatment with an earlier prototype of the device (3 treatments at 1-week intervals) with treatment with meglumine antimonite (850 mg/day intramuscularly for 15 days). Although the cure rates for the 2 patient groups was similar at 13 weeks (73% of patients in the meglumine group were cured, compared with 73% in the heat therapy group), the dosage of meglumine used was lower than what is now recommended (20 mg/kg per day, with no upper limit on the maximum total daily dose), and the study excluded patients with lesions >25 cm² in size, unilaterally lymphadenopathy, subcutaneous nodules in an area of lymph drainage from the lesion, or ear and finger lesions. Despite prophylaxis with dicloxacillin before and for 3 days after treatment with the device, 18% of patients developed moderately severe cellulitis. In addition, the investigators reported that scars were usually larger in the heat therapy group.

Velasco-Castrejon et al. [13] reported results for a single application of a radio-frequency device for 201 patients infected with L. mexicana. Of 122 patients available for follow-up, 95% were cured, including several with ear involvement.

Recently, Aronson et al. [14] reported (in abstract form) results of a trial comparing treatment with a radio frequency device with treatment with sodium stibogluconate (20 mg/kg per day intravenously for 10 days) in patients infected with Old World cutaneous leishmaniasis. Although systemic toxicities were more common in the group receiving antimony, blistering (in 86% of patients), secondary infection (in 27%), and hypopigmentation (in 7%) were noted in the heat therapy group.

Reithinger et al. [11] report on the use of a radio frequency device (Thermomed 1.8; Thermosurgery Technologies) to treat cutaneous leishmaniasis in Kabul, Afghanistan. The investigators compared a one-time application of the device with treatment either intraleisonal or intramuscular sodium stibogluconate (SSG) (20 mg/kg per day for 21 days, up to a maximum total daily dose of 850 mg), and they report that cure rates at day 100 after treatment initiation were 69% of patients in the thermotherapy group, 75% in the intralesional SSG group, and 45% in the intramuscular SSG group. Leishmania tropica was the only parasite identified, and the mean lesion size in all groups was relatively small (median, 10.25 mm in the thermotherapy group). Of note, although 6 patients in the thermotherapy group developed secondary infections, this was not statistically different from the rate in the other treatment groups (perhaps because of the application of chlorine dioxide gel to all lesions to prevent secondary infections). In the Discussion section, the investigators conclude that the thermotherapy device is as effective as intralesional SSG and is more effective than intramuscular sodium SSG.

There are, I believe, a few limitations of this study to be considered. First, the total dose of intramuscular SSG was limited to 850 mg, and although the mean weight of the patients in the intramuscular group was 38.5 kg (which corresponds to a total daily dose of 770 mg), the interquartile range of weight ranges up to 51 kg (a total daily dose of 1020 mg), so at least 25% of the patients in the intramuscular SSG group were underdosed, according to current guidelines. Comparison of the results of treatment with subtherapeutic dosages of SSG with the other treatment modalities may not be reflective of the expected results had full-dose SSG been used, and it would be interesting to know whether more treatment failures in the intramuscular SSG group occurred among heavier patients. Second, the patients participating in this study were fairly select, as they had a single lesion which was approximately one-half the size of a US dime. Whether intraleisonal SSG and the Thermomed device would perform as well in treatment of larger lesions is not known. Third, the lack of a placebo group in a study evaluating a disease that can resolve spontaneously is a weakness, although the investigators explain why that option was not pursued in this study. Finally, the study ended at 100 days after the start of therapy, and a final evaluation (at, perhaps, 6 months) would have been ideal to capture data on late relapses.

In summary, thermotherapy with a LCF-RF device is an important and useful addition to existing treatment modalities, and Reithinger et al. [11] should be commended for conducting a study under dif-
difficult circumstances. The device will be especially useful in situations involving large numbers of patients (in which injections with antimony are impractical); for children (because intralesional injections with antimony are painful); for patients with small, localized lesions; and, potentially, in cases refractory to antimony therapy. There are, however, few data on the efficacy of the device for treatment of large lesions, lesions associated with regional adenopathy, and lesions caused by species (such as L. braziliensis) known to spread outside of the apparent skin lesion and cause late-onset mucosal disease. Significant rates of soft-tissue infection after use have been reported in some studies, and there are scant data on the long-term risk of scarring and keloid formation after treatment.

The LCF-RF device is a technically sophisticated piece of machinery, and its portability and ease of use offer effective therapy to many patients who might otherwise, because of the cost or the unavailability of other therapies, go untreated. Still, the underlying principle (the physical destruction of the parasite, along with some of the host tissue) is not that much different from other direct local therapies, and it is sobering to realize just how far the treatment of cutaneous leishmaniasis has not advanced over the centuries. Stir the cauldron and sprinkle antimony, or reach for the smoldering brand and cauterize? Between the toxicities of antimony, the medical incongruity of burning a lesion to save the skin, and the modest effectiveness of other, alternative therapies, it is clear that the treatment of cutaneous leishmaniasis is far from its apogee. We still lack a safe, affordable, and effective treatment, and although LCF-RF device is one more stone laid on the path, we still have a long road to travel.

Acknowledgments

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References