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CURRENT CONCEPTS

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REACTIONS TO THE STINGS OF THE IMPORTED FIRE ANT

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COEXISTENCE with the pugnacious imported fire ant has become a necessary evil for residents of both the rural and the urban Gulf South.[1] The spread of these insects has produced agricultural problems,[2] and their stings have resulted in increasing numbers of persons with hypersensitivity reactions, secondary infections, and neurologic sequelae.[1,3,4] Two recent evolutionary changes in the ants may make the expansion of their geographical range more likely.[5,6]

IMPORTED FIRE ANTS IN THE UNITED STATES

Both the black imported fire ant, *Solenopsis richteri* (native to Argentina and Uruguay), and the red imported fire ant, *Solenopsis invicta* (native to northern Argentina, Paraguay, and western Brazil), appear to have entered the United States by ship early in this century through the port city of Mobile, Alabama.[7] As a result of their spread by the shipment of nursery stock and sod, fire-ant colonies were present in nine Southern states by the 1950s, when the U.S. Department of Agriculture first issued regulations to monitor and limit their further spread.[8] By 1985 the ants had infested about 250 million acres in much of Florida, South Carolina, Georgia, Alabama, Louisiana, and Mississippi, and they were also present in North Carolina, Tennessee, Arkansas, Oklahoma, Texas (Fig. 1), and Puerto Rico.[10]

Previous estimates suggested that imported fire ants would occupy most areas of the United States where the average minimum yearly temperature is higher than −12.2°C (10°F).[10] However, hybrids of *S. invicta* and *S. richteri* have been found in northern Mississippi and Alabama, the area that is the primary habitat of *S. richteri* and the northernmost extent of the ranges of both fire-ant species. The hybrid is apparently more tolerant of cold than the original types.[11] Moreover, examination of fire-ant mounds, which are now ubiquitous features of the landscape of the Gulf South, has revealed that several reproductive queens may be present in a single mound.[6] The presence of more than one queen increases the probability that a given colony will survive, makes it more resistant to both natural threats and pesticides, and is associated with more aggressive hunting for food by the female worker ants.[12] In view of these changes and the fact that imported fire ants have no natural enemies, it is possible that the insects will ultimately infest one quarter of the land area of the United States.

HUMANS AND ANTS

Problems develop when humans and imported fire ants interact.[13] In rural areas, the collision of machinery with fire-ant mounds injures farmers and damages farm equipment.[2] The omnivorous ants attack farm animals, crops, and the electrical insulation of air conditioners and other appliances. In urban areas, ants build mounds in yards, playgrounds, and open fields in concentrations as high as 200 per acre.[2] In open, sandy areas, the ants form large colonies at ground level. If rain and flooding occur, they become waterborne and sting on contact. Houses have been invaded, especially during heavy rains, and attacks on children and elderly adults have occurred.

Between 30 and 60 percent of the population in urban areas infested by imported fire ants are stung every year.[1,14,15] Our own study found that 58 percent of the residents of a densely populated suburb of New Orleans were stung per year.[1] Stings are more common among children and on the legs, and they occur most frequently during the summer. In stinging, the ant attaches itself to the skin with powerful mandibles, arches its body, and injects 0.04 to 0.11 μl of venom through a stinger located in the distal abdomen (Fig. 2). If undisturbed, the ant will rotate its body about its mandibles to sting repeatedly. The venom induces an immediate, severe burning sensation at the site of the sting, followed by intense itching that may last for hours or days.

LOCAL REACTIONS TO STINGS

Reactions to the stings may be classified as local, systemic–allergic, or "other."[16] At least three types of local reactions occur: a wheal-and-flare reaction, a sterile pustule, and a large local reaction. Almost all persons stung by imported fire ants have a wheal-and-flare reaction at the site of the sting.[1,16] The wheal-and-flare reaction usually resolves in 30 minutes to an hour and evolves into a fully developed sterile pustule at the site of the sting within 24 hours (Fig. 3). The epidermis covering the pustule sloughs off over a period of 48 to 72 hours. Healing takes place as the base of the lesion is covered with new epidermis. No treatment has been shown to prevent or resolve pustules. If

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there are several pustules and if they become excoriated and superinfected, pyoderma and even sepsis can result. This complication is of special concern in diabetic patients.

Between 17 and 56 percent of patients have large local reactions at the site of the insect sting (Fig. 4).[1,15,17] These lesions are erythematous, edematous, and indurated, are extremely pruritic, and last 24 to 72 hours. On histologic examination, large local reactions to fire-ant stings resemble mast cell–dependent, late-phase reactions like those reported after the intradermal injection of ragweed or insulin in subjects with allergies.[18] Such lesions consist of a cellular infiltrate of eosinophils and neutrophils with fibrin deposition

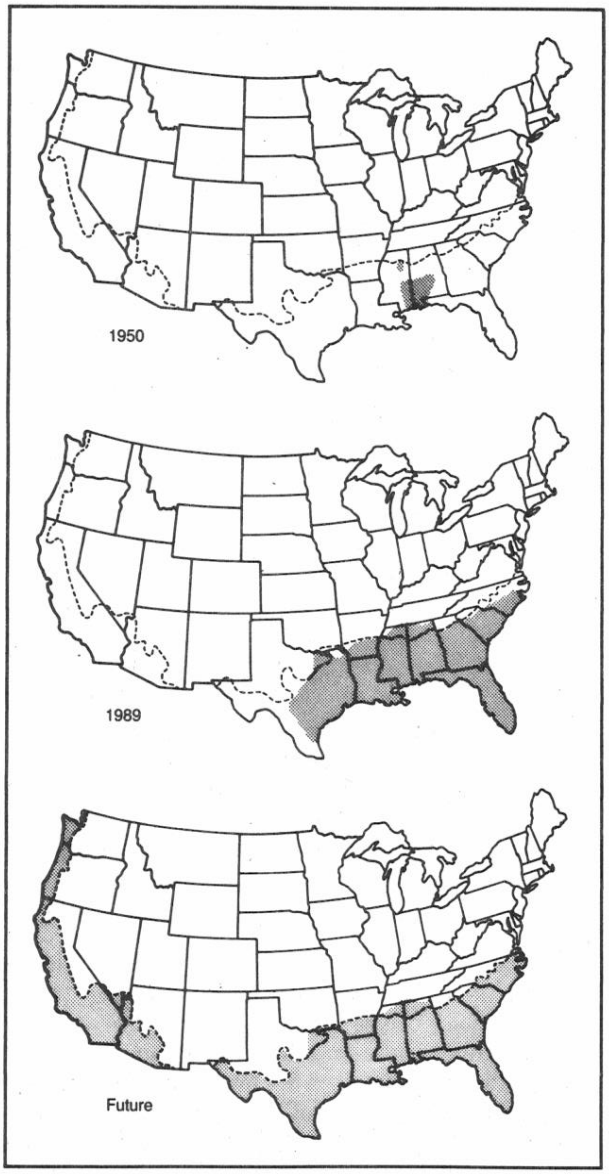

Figure 1. Areas Infested by Imported Fire Ants in 1950 and 1989 and Areas of Possible Future Infestation.

The dotted line indicates the boundary of the area with an average minimum temperature of −12.2°C (10°F). (Adapted from Vinson and Sorensen[9]; used with the permission of the publisher.)

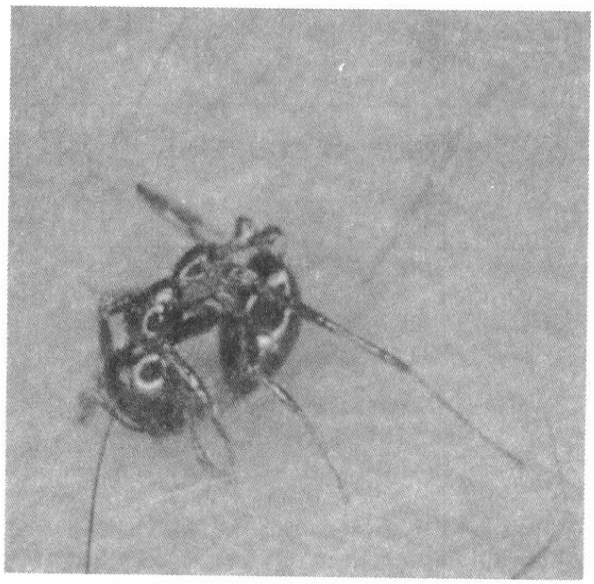

Figure 2. Imported Fire Ant in the Process of Stinging (×50).

in a gel structure. This gel structure facilitates the trapping of tissue fluids and explains the edematous nature of the lesion. In extreme cases the edema may cause compression of nerves or blood vessels. Elevation of the extremity plus treatment with glucocorticoids and antihistamines may prevent the need for decompressive surgery or amputation in such cases.[17] In some cases, the degree of induration present with late reactions suggests cellulitis. Topical corticosteroid ointments, local anesthetic creams, and oral antihistamines appear to be useful for the itching associated with these reactions.

Anaphylaxis and Other Reactions

How commonly fire-ant stings result in anaphylaxis is unclear, although it has been estimated to occur after as many as 0.6 to 1 percent of stings.[17,19] Emergency room physicians in areas infested with imported fire ants know to check between the toes and elsewhere on the lower extremities for evidence of fire-ant stings when patients present with anaphylaxis, since patients do not always realize that they have been stung or associate the sting with the reaction. A recent careful survey of 29,300 physicians identified 32 deaths attributed to anaphylaxis caused by fire-ant stings.[4] The patients who died ranged from 16 months to 65 years of age and had usually been stung fewer than five times. Anaphylaxis may occur hours after a sting.[20] Seizures and mononeuritis have also been reported after fire-ant stings.[21]

The Venom of the Imported Fire Ant

The venom of the imported fire ant differs from the venoms of wasps, bees, and hornets, which are primarily aqueous solutions containing proteins. Fire-ant venom is 95 percent alkaloid with a small aqueous fraction that contains soluble proteins.[22,23] Ninety-

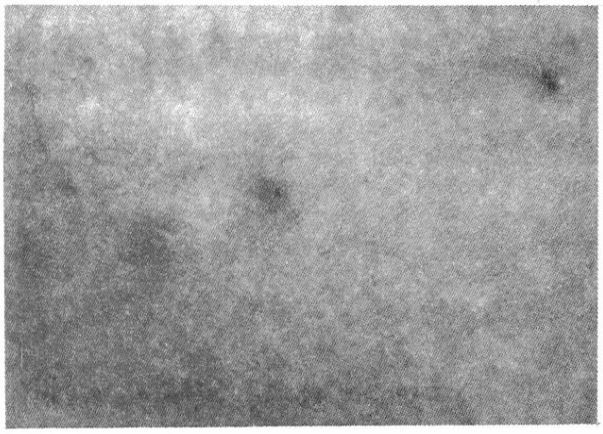

Figure 3. Sterile Pustules Caused by Imported-Fire-Ant Stings, with and without Excoriation.

nine percent of the alkaloid component of fire-ant venom is made up of 2,6,di-substituted piperidines that have hemolytic, antibacterial, insecticidal, and cytotoxic properties.[22-24] Venom alkaloids do not generate IgE antibody responses and thus do not appear to be responsible for allergic reactions to imported-fire-ant stings. The proteins in fire-ant venom, which make up only about 0.1 percent of the venom by weight, induce IgE responses in persons allergic to imported-fire-ant stings.[25-28] The proteins identified in the venom include a phospholipase, a hyaluronidase, and a third protein that has not been fully characterized but appears to be the enzyme *N*-acetyl-β-glucosaminidase.[26,29] The venom of *S. invicta* contains at least four distinct protein antigens (molecular weights, 37, 28, 26, and 15) that induce IgE responses in allergic persons.[29-31] The concentrations of protein antigens are higher in fire-ant venom in the summer than in the cool seasons of the year.[32] There is limited information on cross-reactivity between the venoms of the imported fire ant and other stinging insects. Although preliminary data, obtained with radioallergosorbent inhibition techniques, suggest that there may be such cross-reactivity,[33] crossed-immunoelectrophoretic studies have not demonstrated shared epitopes between fire-ant venom and other hymenoptera venoms.[34]

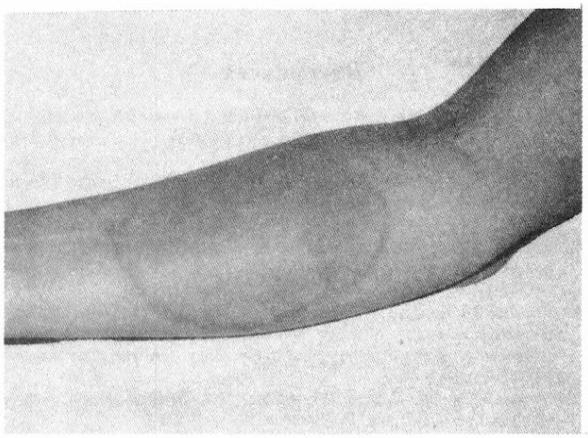

Figure 4. A Large Local Reaction Present 12 Hours after Three Imported-Fire-Ant Stings.

The sites of stings are identifiable by three sterile pustules in the upper portion of the lesion. (Adapted from deShazo et al.[1]; used with the permission of the publisher.)

Whole-Body Extracts

Whole-body extracts of imported fire ants contain various amounts of venom proteins. Crossed-immunoelectrophoretic techniques identify at least 30 antigens in whole-body extracts,[30] five of which bind IgE. Commercial preparations of imported-fire-ant whole-body extracts do not always contain these protein allergens. A study comparing whole-body-extract preparations from three major commercial suppliers with a freshly prepared reference extract showed important differences in allergen content.[35] Only one supplier produced a whole-body extract that inhibited the reference extract by 50 percent on radioallergosorbent testing; none of the whole-body extracts inhibited the imported-fire-ant venom itself by 50 percent. Thus, there is concern about the usefulness of these extracts for diagnostic skin testing, in vitro diagnostic assays, and immunotherapy.

Venom versus Whole-Body Extracts

Venom proteins must be present in reagents used to diagnose and treat hypersensitivity to imported-fire-ant stings.[25,28,36] Since the amount of venom in whole-body extracts varies, it is not surprising that studies of their use in diagnostic skin testing have produced disparate results. In one study, 91 percent of patients who had anaphylactic reactions to fire-ant stings had a positive immediate-hypersensitivity reaction to dilute imported-fire-ant venom on skin testing, whereas only 53 percent reacted to more concentrated solutions of whole-body extract.[25] Another study found that about 90 percent of patients who were allergic to fire-ant stings had positive skin-test reactions to whole-body extract when serial dilutions of up to 1:500 (wt/vol) were used. Specific issues concerning diagnostic skin testing for allergy to fire-ant stings have been reviewed by Stafford et al.[11] Venom is clearly superior to whole-body extract for in vitro diagnostic testing.[26] In one study, 79 percent of serum samples from patients who were hypersensitive to fire-ant stings were positive on radioallergosorbent testing, whereas only 48 percent were positive when a freshly prepared whole-body extract was used.[28]

Immunotherapy for the Prevention of Anaphylaxis

Since the natural history of sensitivity to imported-fire-ant stings is unknown, the indications for immunotherapy to prevent the recurrence of sting-related anaphylaxis are unclear. Studies of anaphylaxis in response to the stings of other insects, such as honeybees

and yellow jackets, have established that the production of IgE after stings is common and often transient.[37] Moreover, there are differences between adults and children in the clinical manifestations of anaphylaxis, the probability of serious reactions after subsequent stings, and the duration of sensitization.[38] This information is useful in selecting patients who would benefit from immunotherapy with honeybee and yellow-jacket venom; unfortunately, similar information is not available for imported-fire-ant venom.

The appropriateness of immunotherapy is also of concern because of the lack of availability of imported-fire-ant venom for treatment. Previous studies of immunotherapy with whole-body extracts of honeybees, yellow jackets, and wasps showed treatment with whole-body extracts to be of no value, since they contained little or no venom.[39] In whole-body extracts of imported fire ants, however, unlike those of other hymenoptera, venom is present in substantial but variable quantities.[27,28] Because it is impossible for sensitized persons who live in infested areas to avoid fire ants, thousands of patients now receive immunotherapy with whole-body extracts.[40] Treatment consists of weekly subcutaneous injections of the extract, with the dose increasing until an empirically determined maintenance dose, usually 0.5 ml of a 1:10 dilution of commercially available whole-body extract, is reached. This maintenance dose is then given approximately once a month. Uncontrolled observations suggest that this technique has a high level of efficacy,[40-42] but some failures of treatment have been reported.[43]

The strongest evidence for the efficacy of immunotherapy with whole-body extract comes from a recent report by Hylander and colleagues, who treated 65 patients with a history of anaphylaxis after imported-fire-ant stings and evidence on skin testing of IgE responses to fire ants.[44] The patients were given whole-body extract according to the regimen described above. Forty-seven (72 percent) were unexpectedly stung by fire ants after treatment; only one had anaphylaxis. Thirty-one patients who were receiving maintenance immunotherapy were stung by a single ant under direct observation, and none had anaphylactic reactions. In a control group of 11 patients who were allergic to fire-ant stings but elected not to undergo immunotherapy, 6 had unexpected stings; all 6 had anaphylaxis.[44]

Chemical Control of Imported Fire Ants

The fire ant's life cycle begins with the swarming of males in the spring. The queens fly through the ant cloud until clasped by a male, at which time impregnation takes place.[45] Sufficient sperm is deposited for the queen to produce 5 to 6 million eggs during a six-year life span. After impregnation, the new queen disengages, lands, sheds her wings, burrows, and begins laying eggs. Within three years, the fire-ant mound contains up to 250,000 ants with the queen deep inside. The average fire-ant mound is 0.25 to 0.38 m (10 by 15 in) high, although it can stand as high as 0.9 m (3 ft) above the ground and extend 0.9 to 1.5 m (3 to 5 ft) below ground level to the water table. Mounds have tunnels that may radiate up to 39 m (130 ft). The ant colony moves up and down within the mound through these tunnels in response to temperature. Food is brought into the mound by worker ants. Since the queen is unable to digest solid food, she is fed liquids from other ants.

Early attempts to control fire ants led to the widespread use of the pesticides heptachlor (in the 1950s and 1960s) and mirex (in the 1960s and 1970s). Heptachlor was found to be toxic to wildlife, and residues of mirex were found in a variety of organisms. Concern for the environment and for public health led to a ban on both chemicals.[45] Two approaches to the control of the ants are currently in use: the treatment of individual mounds and "broadcast treatment."[45] Although drenching individual mounds with such pesticides as diazinon or injecting mounds with chlorpyrifos under pressure may temporarily clear small areas of fire-ant mounds, these areas are soon reinfested from the perimeter. Modern broadcast treatments use attractant baits consisting of soybean oil, corn grits, and a chemical agent. The bait is picked up by worker ants and taken deep into the mound and eventually to the queen. The bait includes such chemical agents as toxicants and synthetic versions of natural insect growth hormones, which cause the death of insects in the pre-adult stages and shifts in ant caste differentiation or prevent egg production by the queen. When used appropriately, these agents appear to be capable of clearing large areas of ants for months at a time.

With the continued spread of these pests, more people will be subjected to the medical sequelae of fire-ant stings.[45] Further research is needed both to control imported-fire-ant populations and to determine the natural history of sensitivity to their stings.

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