

Review article

Fire ant venom allergy

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D. R. Hoffman, PhD

Department of Pathology and Laboratory
Medicine, East Carolina University School of
Medicine, Greenville, NC 27858, USA

Dr Donald R. Hoffman
Department of Pathology and Laboratory
Medicine
East Carolina University School of Medicine
Greenville, NC 27858
USA

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Fire ants are the larger free-living species of the genus *Solenopsis* native to the Americas (74). Most of the numerous species of the genus *Solenopsis* are small ants which are leptoecious; they live in or near nests of larger ants from which they steal food and brood. Other species are social parasites. *Solenopsis* species are found over most of the tropical and temperate parts of the world including mid-Europe, central Asia, Pacific Asia, Africa, Australia, and the Pacific islands (25). The tropical fire ant, *S. geminata*, is a tramp species and has been carried by seaborne commerce from tropical America to Southeast Asia and the Pacific islands (25, 74). A South American species, *S. richteri*, was introduced accidentally into the USA near Mobile, Alabama, in about 1918 from Uruguay or Argentina. This species spread across Alabama and Mississippi, but has since been displaced by the Brazilian species, *S. invicta*, introduced into southern Alabama between 1933 and 1941 (66). *S. richteri* is now limited to an area of northeastern Mississippi and northwestern Alabama. *S. invicta* has since spread across the southern USA and is now found as far north as Richmond, Virginia, and westward throughout much of Texas (76, 77). Imported fire ant colonies have been found in the southwestern USA, but, reportedly, have been exterminated (27). Stings from imported fire ants have become a major medical problem in much of the southeastern USA (20, 68, 77, 83). In addition to the risk to people, imported fire ants threaten the natural

fauna and domestic livestock, and their mounds pose problems to farming and roads (6, 32, 52). Fire ants contain magnetite, which functions as a compass to orient them to a north–south axis; in addition, the magnetite senses other magnetic and electric fields, attracting the ants to underground power lines (3). Although fire ants seem to be well controlled in their natural ecosystems, there have been recent reports of *S. saevissima* spreading out of control because of development and habitat destruction in the Brazilian Amazon (3).

Biology

There are about 18 species of fire ants, the workers ranging from about 1.8 to 6 mm in length. A specimen of an *S. invicta* worker is illustrated in Fig. 1. *Solenopsis* belongs to the subfamily Myrmicinae and the tribe Solenopsidini (74). Among the identifying characteristics are the two humps on the petiole, which connects the alitrunk (thorax) to the gaster (abdomen); and the clubbing of the last two segments of the antennae (25). The sexual forms are usually larger than the workers and are winged. Only the workers sting. The classification of the South American fire ants of the *S. saevissima* species group, which includes *S. invicta* and *S. richteri*, is still controversial (10, 52). Mating occurs in the spring under very restricted conditions of temperature, humidity, and other variables. The sexual forms fly into the air



Fig. 1. Photomicrograph of imported fire ant, *Solenopsis invicta*, worker. Specimens are typically 3–4 mm in length and weigh, on average, 1 mg. Note two-humped petiole, which connects thorax and abdomen, and clubbed appearance of last two antenna segments. Relatively large, toothed mandibles are visible. Sting is located at tip of gaster (abdomen).

and mate; a small fraction of the fertile queens successfully establish colonies (52).

Three species of fire ants are native to the USA, *S. geminata*, *S. xyloni*, and *S. aurea*; all of these form relatively small colonies and do not pose significant

medical or economic problems. The imported fire ants *S. invicta* and *S. richteri* form much larger colonies with mounds above the ground, like the *S. invicta* mound illustrated in Fig. 2. These mounds can become significantly larger in areas with warmer



Fig. 2. *Solenopsis invicta* mound in eastern North Carolina. It is located in partially cleared area between road and forest. Trowel is approximately 25 cm long. Mounds are commonly found in lawns, beside walks and roads, and in fields. Inside structure consists of numerous tunnels extending below ground level. This is single-queen colony containing thousands of workers (courtesy of Robert Jacobson).

climates. A mound of *S. saevissima* over 3 m long, containing over a million ants, was found in Envira, Brazil (3). The largest colonies are different from those of almost all other known social Hymenoptera in that they contain numerous functioning fertile queens (29, 54, 71, 87). Many of these multiqueen nests appear to be perennial. Although *S. invicta* initially displaced *S. richteri* from most of Alabama and Mississippi, the two species have recently been found to form true hybrids (23, 70, 84, 85, 86). Limited studies suggest that the hybrids can live at higher altitudes and can tolerate lower temperature conditions than either pure species.

Imported fire ants spread primarily by passive mechanisms. They generally do not fly very far during mating. The most important method of spread in the USA is carriage of fertile queens in soil or on plant matter. The ants can also move during flood seasons. When a colony is flooded, the ants form a rotating ball with the queen at the center, which can be carried downstream until it lands. This is why many mounds are found in dry riverbeds in South America (3, 52). *S. geminata* has been carried across the Pacific by ships carrying cargo from Central America or the Caribbean. A number of estimates of the northern limit of the spread of *S. invicta* have been made, and the ants have exceeded even the most pessimistic forecasts. The major determining factors appear to be length and intensity of hard freezes, temperature and humidity during the mating season, and minimum humidity levels (17, 52). However, the fire ants may be more adaptable than many entomologists assume, since some thief ant species of *Solenopsis* are native to the Sahara desert (25) and

imported fire ants have become established in the North American desert (27). The increased cold tolerance of the *invicta-richteri* hybrids suggests that the imported fire ants may be highly adaptable when outside their native habitat.

Fire ant stings

Fire ant workers sting by grasping the skin with their mandibles, inserting the stinger into the skin, and slowly injecting venom. The stings are much slower than those from bees and wasps, and are not immediately painful. Fire ants sting repeatedly, many times rotating in a circular pattern, while maintaining a grip with their mandibles. Each sting consists of only a very small volume, usually nanoliters containing 10–100 ng of protein (40). The name “fire ant” comes from the pain that appears soon after the stinging, but this pain is usually less intense than that from bee or wasp stings. Each site then becomes pruritic and a wheal-and-flare reaction develops. This initial reaction subsides, usually within 2 h. A sterile pustule develops at most of the sting sites from imported fire ants, and occasionally at sites of *S. geminata*, *S. xyloni*, or *S. aurea* stings over the next 12–24 h (16). These pustules, which are pathognomonic for fire ant stings, are illustrated in Fig. 3. Similar pustules are produced by all species of South American fire ants. The pustules usually resolve spontaneously over time, but can become secondarily infected or lead to scarring (50, 83). The pustules result from the alkaloid components of the venom (48). There is no known effective treatment for the pustules. The fire ant sting reactions have been studied histologically

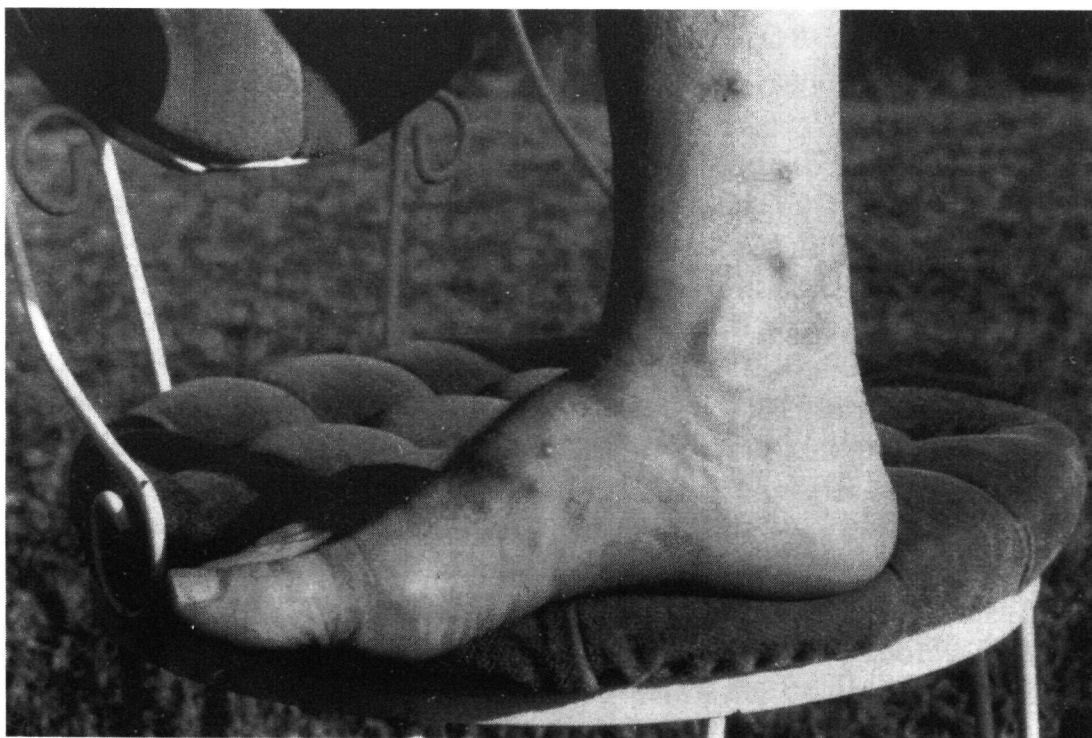


Fig. 3. Multiple sterile pustules on foot of *Solenopsis invicta* sting victim, about 24 h after incident. This outcome is common after stepping in or kicking mound (courtesy Miles Guralnick, Vespa Laboratories, Inc).

(16, 21). As the pustule develops, the first fluid is clear, at 24 h necrotic polymorphonuclear cells and lymphocytes predominate, and at 72 h necrotic plasma cells are most common. As the lesion begins to heal, the pustule floor becomes obliterated, and the infiltrate spreads into connective tissue. Non-allergic victims have suffered hundreds and thousands of stings with no adverse consequences other than the pustules (22).

Large local reactions to fire ant stings appear to be similar to large local reactions to other insect venoms. The reactions begin with a wheal-and-flare like a normal reaction, and then evolve into a second phase of pruritic edema and induration over a period of hours. This phase may continue to increase up to and beyond 24 h, and usually does not begin to subside for 48 h. The reactions are usually painful and may involve an entire extremity. Biopsy studies of the pustular parts of the lesions show the presence of many eosinophils and evidence of extensive fibrin deposition in the indurated area (21).

Serious systemic allergic reactions occur in about 2% of fire ant sting patients who seek medical care (77). These reactions are similar to systemic reactions from other stinging insect venoms (30, 47, 51, 67), except that the culprit insect can almost always be identified by the development of sterile pustules by the next day. The treatment of anaphylactic reactions to fire ant venom is the same as the treatment of any other anaphylactic reaction. Fatal allergic reactions are becoming more common, especially in Florida and Texas (8, 19, 34, 68, 75, 83). Fatal reactions in allergic individuals have been caused by attacks ranging from only a single sting to as many as hundreds of stings. There are no recorded deaths of people from toxic doses of fire ant venom, but small animals including dogs have been stung to death.

Unusual reactions to fire ant venom occasionally occur. Most of the reported reactions are neurologic, with six cases of seizures and one of mononeuropathy having been reported (15, 26). Some of these victims may have suffered anaphylactic reactions before the seizures. Reactions investigated in our laboratory have included cases of Guillain-Barré syndrome and progressive motor dysfunction, but these could be related to fire ant stings only by the observation of symptoms following sting incidents in time and by the patients having IgE antibodies reacting against fire ant venom.

The density of imported fire ant colonies is very high in many of the infested areas of the southern USA; it can exceed 100 colonies per acre. Several studies have estimated the annual attack rates in these regions from 6% to 58% of the population annually (1, 2, 21, 55, 89). If we take into account the variations in methodologies and the populations

studied, an average estimate of a 20% to 30% annual attack rate in these areas is reasonable. This has been confirmed by a laboratory study of a group of employees of the Medical College of Georgia in Augusta; none of the participants had a history of allergic reactions to fire ant stings or other stinging insects, but 24% had IgE antibodies reacting to imported fire ant venom (41).

Individuals at risk for allergic reactions to imported fire ant venom do not include only those who have been previously sensitized by fire ant stings (41, 51, 59). Patients with no previous exposure to fire ants from either the northern or western USA (41, 51) or even from northern Europe (59) have suffered anaphylactic reactions to their first fire ant sting. Most of these patients appear to have been sensitized to *Vespula* (yellow jacket) venom. This conclusion is supported by both clinical and laboratory studies (41, 59).

Fire ant venom

Studies on the composition of fire ant venom were limited for many years by the inability to obtain significant amounts of pure venom. The original method used for obtaining venom for studies of the organic phase (9) and preliminary studies of the aqueous phase (4) was to have the ants sting into microcapillary tubes. One end of the tube was sealed, and the tube was then centrifuged to separate the phases. This method was improved for the collection of reference specimens of venom by Hannan et al. (33) and Hoffman et al. (40) by the use of vacuum and a larger collecting tube, as illustrated in Fig. 4. However, since fire ants are slow stingers and since only a single ant can be processed at one time, this method is extremely laborious, and only relatively small amounts can be collected. The separation of reference venom collected by this method has been illustrated (40). A proprietary electric stimulation method has been developed for the collection of commercial-grade venom (40). This method is capable of producing gram quantities of venom proteins of a purity comparable to that found in hand-collected venom (40).

Approximately 90–95% of fire ant venom consists of water-insoluble 2,6-disubstituted piperidine alkaloids (4, 9). The alkaloids from imported fire ants have an alkenyl substituent in the 6 position and a *trans* configuration about the ring, while those from the native North American fire ants have alkyl substituents and are both *cis* and *trans* about the ring (9). Other South American species have venom alkaloids similar to *S. invicta* and *S. richteri* with alkenyl groups and *trans* configuration (53). In addition, the 2-substituents on the alkaloids are 13 and 15 carbons long in the South American species and pri-

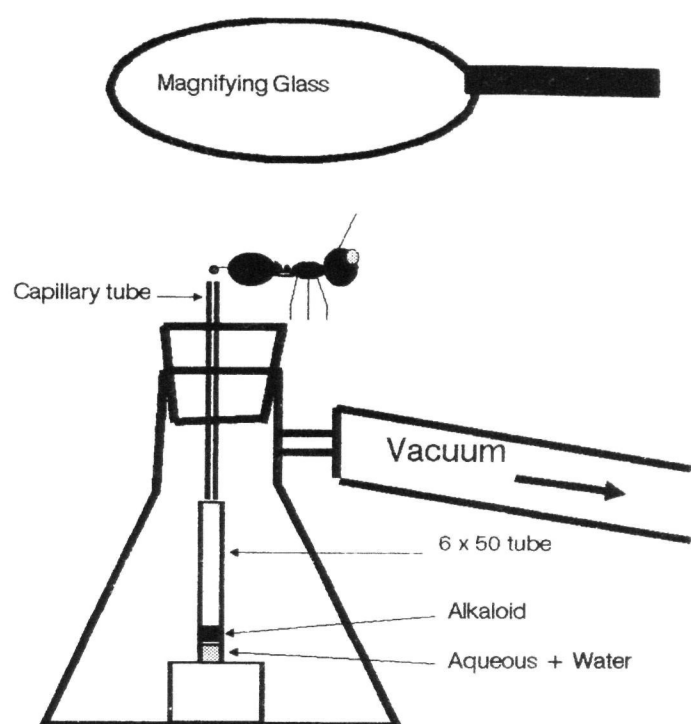


Fig. 4. Method used in our laboratory for hand-milking fire ants. Magnifying glass has been replaced by dissecting microscope. Extra water is placed in 6 x 50 mm test tube to prevent complete evaporation of water from aqueous phase of venom. Venom from about 1000 or more ants is collected into single tube. Alkaloid phase is removed by extraction with hexane.

marily 11 carbons in the North American species. The alkaloids with the longer-chain unsaturated substituents are more potent at inducing the typical fire ant sting pustule, which is almost always found at the sites of *S. invicta*, *S. richteri*, and *S. saevissima* stings, but rarely at the sites of *S. geminata*, *S. xyloni*, and *S. aurea* stings (24, 51, 88).

It was very difficult to study the proteins in fire ant venom (4, 35) until commercial-grade venom became available. The aqueous phase of *S. invicta* venom contains four major allergenic protein components (40). Sol i 2 comprises about half to two-thirds of the venom protein. It is a disulfide-linked homodimer of 119 amino acid chains of mol. wt. 13 217, each containing seven cysteine residues (36). It is very basic with an isoelectric point of 9.63. Its structure is not related to any other proteins in the Protein Identification Resource or Swiss-Prot databases. The molecule is easily susceptible to proteolysis and has an acid labile aspartyl-prolyl bond at position 70. Sol i 2 has a relatively low absorbance at 280 nm since each subunit contains only one tyrosine and one tryptophan. The cDNA for Sol i 2 has been cloned and gives a sequence identical to that obtained by protein sequencing (72). Immunoreactive Sol i 2 has been expressed in a baculovirus system. Sol i 4 is a 117-amino-acid single-chain protein of mol. w. 13 340 with 35% identity to Sol i 2, including its six cysteine residues (36). It comprises about 8–10% of the venom protein and is the most basic protein component with a pI of 10.08. Sol i 4 has no trypto-

phan residues and has two variant forms differing by two amino acids. Sol i 4 is not immunologically cross-reactive with Sol i 2.

Sol i 3 makes up about 15–25% of the venom protein (40). It is a single-chain molecule of 212 amino acids having a mol. wt. of 24 040 and an isoelectric point of 8.24 (36). It has about 44–50% identity with antigen 5 molecules from *Vespula* (yellow jackets), *Dolichovespula*, and *Vespa* (hornets). The cDNA has been cloned; and the revised sequence, verified by protein sequencing, is compared to the sequence of a yellow jacket antigen 5 from *Vespula vulgaris* (37) in Fig. 5. Although there is a significant amount of amino acid sequence homology, we have not been able to demonstrate consistent immunologic cross-reactivity between Sol i 3 and vespid antigen 5 (41).

Although Sol i 1 comprises only 2–4% of the venom protein (40), it is a particularly interesting molecule. The native mol. wt. appears to be about 37 000, but smaller pieces are found on reduction. The IgE antibodies from many vespid-venom-sensitive sera bind to Sol i 1 in both RAST and immunoblot studies (41). This fraction has phospholipase A and B activities (36). It has proven to be extremely difficult to purify critically and obtain structural information on Sol i 1. Recently, we have been able to obtain an N-terminal sequence and the sequences of a number of proteolytic fragment peptides from Sol i 1 (39). These are shown aligned with the sequence of *Vespula maculifrons* phospholipase (38) in Fig. 6. Note that there are several regions of complete or almost complete identity; this may be the origin of the observed cross-reactivity with vespid venom phospholipases. Attempts to clone the complete cDNA for Sol i 1 are currently in progress. The native molecule appears to be susceptible to a number of natural proteolytic cleavages. No peptides homologous with the C-terminal 115 amino acids of vespid phospholipases have yet been isolated from Sol i 1; the cloning studies should elucidate whether the full-length enzyme is produced. The finding that both Sol i 1 and Sol i 3 are homologous to proteins found in vespid venoms supports the modern taxonomy which places the ants in the same superfamily, Vespoidea, along with the vespid wasps.

The venom proteins from *S. richteri* have been studied (43). Three proteins have been isolated, Sol r 1, Sol r 2, and Sol r 3, all homologous to the *S. invicta* proteins. There is no protein corresponding to Sol i 4 in *S. richteri* venom. Immunologically, *S. richteri* venom is highly cross-reactive with *S. invicta* venom (43). Our laboratory has completely sequenced Sol r 2 and Sol r 3, and has obtained N-terminal sequence data on Sol r 1. The amino acid sequences of Sol i 3 and Sol r 3 are 95.8% identical, with 7/9 substitutions being conservative

	10	20	30	40	50	60
SOL I 3	TNYCNLQSCKRNNAIHTMCQYTSPTPGPMCLEYSNVGFTDAEKDAIVNKHNELRQRVASG					
VES V 5	NNYCKIK-CLK-GGVHTACKYGSCLKPNCGNKVVVSYGLTKQEKQDILKEHNDFRQKIARG					
	10	20	30	40	50	
	70	80	90	100	110	120
SOL I 3	KEMRGNTNGPQPPAVKMPNLTWDPCLATIAQRWANQCTFEHDACRNVERFAVGQNIATSS					
VES V 5	LETRGNPGPQPPAKNMKNLVWDELAYVAQVWANQCQYGHDTCRDVAKYQVGVQNVALTGS					
	60	70	80	90	100	110
	130	140	150	160	170	180
SOL I 3	SGKNKSTPNEMILLWYNEVKDFDNRWISSFPSDDNIMKVGHYTQIVWAKTTKIGCGRIM					
VES V 5	TAAKYDDPVKLVKMWEDEVKDYNNPK--KKFSGND--FLKTGHYTQMVWANTKEVGCGRIM					
	120	130	140	150	160	170
	190	200	210			
SOL I 3	FKEPDNWTKHLYVCNYGPAGNVLGAPIYEIK					
VES V 5	YIQ-EKWHKHLYVCNYGPSGNFMNEELYQTK					
	180	190	200			

Fig. 5. Revised amino acid sequence of Sol i 3 compared to sequence of *Vespula vulgaris* antigen 5 (37). Dashes indicate spaces added to maximize homology. Double dots between sequences indicate identical residues, and single dots conservative changes involving only single base. Note that seven of eight cysteine residues were aligned by computer and that eighth at residue 30 was displaced by only two positions. Sequences show 44% identity and further 37% conservative changes. Sequence of Sol i 3 is revised from that originally published (36) and is consistent with both protein sequence and cDNA sequence.

changes. The sequences of Sol i 2 and Sol r 2 show only 78.1% identity, which is enough to be highly cross-reactive, but yet still individually recognizable (37). The N-terminal sequence of Sol r 1 is identical to that of Sol i 1. Studies on patients reactive with other species, including *S. geminata*, *S. xyloni*, and *S. aurea*, are very limited (24, 51, 88). Sera from patients sensitized to these insects show strong reactivity with the 1 and 3 allergens, and more limited reactivity with the 2 allergen from *S. invicta*, as has been found with *S. richteri*-sensitized individuals (43). Monoclonal antibodies have been produced in

mice which recognize the species-specific determinants on both Sol i 2 and Sol i 3 (42, 73).

Allergenic extracts

Commercial extracts from fire ants are all whole-body extracts. Venom has not yet been developed for sale as a commercial product. Many studies have been reported which compare various commercial extracts to various "venom" preparations by skin testing (5, 46, 61, 82), *in vitro* IgE testing (5, 11, 13, 14, 33, 59, 82), and immunochemical testing (12, 14,

	10	20	30	40	50	60
Sol i 1	GAASSNTYDIGQLMAKYTVDLNKNLGNQQSCQDINASLPVVFITHGFTSSAQVSTFK					
Ves m 1	FNSDTSVSIIEITRENRNRDLTYLTQLQNHPEFKKKTITRPVVFITHGFTSSASEKNFINL					
	10	20	30	40	50	60
	70	80	90	100	110	120
Sol i 1	IVDWSEAACTDGLPGVQ					WK
Ves m 1	AKALVDKDNMVISIDWQTAACNEYPGLKYAAYPTAASNTRLVGQYIATITQKLVDYK					
	70	80	90	100	110	120
	130	140	150	160	170	
Sol i 1	IPLNNIQYVGHSLGSHVSGFAAK			NDNTFEGEYHAF--PDCARNLFKGRQ		
Ves m 1	ISMANIRLIGHSLGAHVSGFAGKRVQELKLGKYEIIGLDPARPSFDSNHCSERLCETDA					
	130	140	150	160	170	180
	180	190	200	210	220	230
Sol i 1	QE			SQPACSW-YDVPCSHSEXVYXTGVPS		
Ves m 1	EYVQIIHTSNYLGTETKILGTVDVFYMNGKNNPGCGRFFSEVCSHTRAVIYMAECIK					
	190	200	210	220	230	240

Fig. 6. Comparison of N-terminal amino acid sequence and number of peptides derived by proteolytic cleavage from Sol i 1 with N-terminal part of sequence of *Vespula maculifrons* phospholipase (36, 38). Symbols are same as in Fig. 5. Note regions of complete and almost complete identity at residues 40–52, 75–88, and 130–143.

59). These studies have generally shown significant allergen activity in whole-body extracts, but in many cases the "venom" preparations being used were clearly superior, especially for *in vitro* testing, since there was less dilution by inactive materials derived from the insect bodies. In some cases, whole-body extracts were reported to give poor results or non-specific positive reactions. After the initial characterization and separation of *S. invicta* venom, it became possible to develop monoclonal-antibody-based immunoassays for the venom allergens (42, 73). Studies of commercial fire ant whole-body extracts showed that all of those studied contained significant amounts of Sol i 3 (42), but that some were deficient in Sol i 2 (73). In some more recent studies (78, 80), characterized preparations of venom and whole-body extracts were compared. Venom was more potent than whole-body extract in skin testing, but sensitivities were similar. Problems with large local reactions were noted in some patients, who required higher doses of whole-body extract, especially control subjects. RAST testing was more sensitive with venom than with whole-body extract, and was less sensitive with both extracts than skin testing. Allergenic extract manufacturers in the USA are beginning a voluntary program to verify Sol i 2 and Sol i 3 contents of *S. invicta* whole-body extracts.

Diagnoses and immunotherapy

Both intradermal skin testing and *in vitro* tests, such as RAST and ELISA, can be used to confirm the clinical history of an allergic reaction to fire ant stings (14, 41, 51, 61, 78, 80, 83). If whole-body extracts with verified venom allergen content are used, the sensitivity, specificity, and predictive value of a positive test are comparable to intradermal skin testing using pure venom (80). Whole-body extracts have been reported to cause nonspecific positive reactions and large local reactions at high doses (61, 80). Pure venom is superior to whole-body extracts for *in vitro* tests, since the active material is not diluted by body-derived, allergenically inactive substances (78). Patients without a clinical history of an allergic reaction to a fire ant sting should not be tested, since there is a large incidence of asymptomatic IgE antibody production in the exposed population (41, 80). This is similar to the findings of Golden (30) and Golden et al. (31) in epidemiologic studies of the prevalence of skin test reactivity to other Hymenoptera venoms. Asymptomatic skin test reactivity is particularly common in the endemic fire ant regions because of exposure from the high annual attack rate (1, 2, 89). In a prospective study, 56 of 112 previously unexposed patients brought into a highly endemic area were stung over a period of 3 weeks during the

summer; 3.6% experienced a large local reaction to a fire ant sting; 22% converted to positive skin tests, and 5% converted to positive RAST tests (63). Many patients sensitized to vespids have IgE antibodies cross-reactive to fire ant venom (41), although they may have never been exposed to fire ants.

Triplett first reported successful immunotherapy with whole-body extracts for fire ant venom allergy in 1973 (83). Since that time, several documented failures have been reported (60, 69). However, immunotherapy with whole-body extract of *S. invicta* is widely used by allergists in the USA (79). No systematic studies of effectiveness of fire ant whole-body extract immunotherapy were reported until the use of sting challenges by Hylander et al. in 1988 (44, 45). They showed that immunotherapy with whole-body extracts of verified potency provided a high degree of protection to almost all patients. Only one of 112 sting events in immunized patients led to a serious reaction, while there were two cutaneous and four serious generalized reactions out of 11 sting events in an untreated population (28). When sting challenge tests and reactions to field stings are used as monitors, a state of protection has been found to persist for at least several years after discontinuation of whole-body extract immunotherapy (56, 57, 62). There are no systematic controlled studies with sting challenges of immunologic parameters during immunotherapy, although preliminary studies show a rise in IgG and IgG4 antibodies (64). These parameters are probably of limited value in assessing the state of protection, as has been found in allergy to other venoms (65). Many physicians experienced in the use of fire ant whole-body extract immunotherapy recommend a maximum dose of 0.5 ml of a 1:100 weight per volume dilution of an extract known to be potent by skin test reactivity on a panel of known positive patients (28). Some patients may tolerate only lower doses; higher doses lead to an excess of large local reactions.

Control of fire ants

In the USA, the multicyclic chlorinated hydrocarbon pesticide Mirex was used for many years in large-scale attempts to control fire ant infestations (32, 52, 66). In the 1970s, Mirex was determined to be environmentally unacceptable, and it is no longer manufactured. Other nonspecific pesticides such as chlordane and DDT are known to be effective against fire ants, but are not approved for these uses because of toxicologic and environmental risks. In the Amazon, the widespread use of DDT to control mosquitoes and blackflies probably led to control of indigenous fire ants in populated areas (3). Many common approved contact insecticides, including diazinon, are effective against single fire ant colonies

(49). Contact insecticides are not effective for large-scale control and are not specific for fire ants, and rapid reinfestation is common after their use. Current practice for large-scale control is to use baits treated with growth regulators, which are carried back to the nest and prevent the development of adult workers (7, 18, 81). These products are fenoxycarb (trade name LOGIC) and hydramethylnon (trade name AMDRO), which are both environmentally acceptable substances. The major drawback to the use of growth regulators is that they act slowly over a period of days to months. Their effectiveness persists over an entire season; but they are not specific for fire ants. Some methods under study for more specific and effective control are the treatment of growth regulator baits with *Solenopsis* pheromones (3, 52) and the use of specific parasites, including the nematode *Tetradonema solenopsis* (58) and the microsporidian *Thelohania solenopsis* (3). The microsporidian infects blood and fat cells and can be used to infect ants by direct feeding.

The future

A prototype commercial *S. invicta* venom preparation has been tested as a diagnostic material (80), but it is improbable that a product will be marketed. Although venom is somewhat superior to whole-body extracts in potency and specificity, the cost of more than US\$1 000 000 to market a new extract cannot be justified commercially by the limited demand. Several extract manufacturers are developing a voluntary consistency monitoring program in which they will test extracts by immunoassays for Sol i 2 and Sol i 3 contents, and release only materials with demonstrated potency for sale.

The spread of *S. invicta* in the USA is expected to continue. Although the ants may be reaching their northernmost limits in Virginia or Maryland, there is no reason that they cannot live in much of the West, especially in urban and suburban areas of New Mexico, Arizona, California, and Oregon. It may not be possible to prevent infestation in the western states by exterminating colonies. The future of the hybrid fire ants is unknown. At present, they have not spread near the outer limits of *S. invicta*-infested areas, except at higher elevations. Their increased cold tolerance may eventually lead to spread farther north.

In South America, continued deforestation and uncontrolled settlement and development, with the associated destruction of natural ecosystems, may lead to more catastrophic fire ant problems like those seen in Envira, Brazil (3). It is particularly important that attention be paid to protecting the river basins, especially the dry river beds that flood only in the rainy season. Until recently, the areas in South

America where fire ants are native have had relatively sparse population. The rapidly increasing population density in some of these areas will lead to a much higher incidence of fire ant venom allergy. Although fire ant colonies can be partially controlled by growth regulator baits and possibly by parasites, experience in the southern USA shows that they cannot be eliminated or well controlled even by the widespread use of highly toxic pesticides.

Since thief ants of the genus *Solenopsis* live in southern and temperate Europe, there is no reason to assume that fire ants could not live in Europe. The Mediterranean climate regions should be especially appropriate. Fire ants are omnivorous and very adaptable to varying environmental conditions. Agricultural and customs inspectors should exercise continued vigilance to prevent introduction of fire ants by passive carriage of fertile queens with living plants and agricultural products.

Many tourists from all over the world visit fire ant endemic areas for short and long vacations. Such tourists who are vespid sensitive are at increased risk of allergic reactions from fire ant stings (41, 59); some will acquire *de novo* sensitization from even short-term exposure (63). If these allergic subjects plan to return to infested areas, they may require diagnostic studies and immunotherapy, when appropriate for life-threatening reactions. Large local reactors and those with purely cutaneous symptoms do not require treatment, especially if they have only limited risk of exposure.

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