IMPORTED FIRE ANTS: 50 YEARS OF DEATH AND DESTRUCTION

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INTRODUCTION

Since their introduction into the United States more than 80 years ago, imported fire ants have risen from a mere nuisance to a significant agricultural pest and public health problem. Fire ants are a significant economic problem with over $2.7 billion/year in estimated total costs to the U.S.[1] Stings from the imported fire ants have become the most common cause of insect hypersensitivity in the southeastern United States including Texas.[2,3] In this grand rounds, I will attempt to review the biology of fire ants, their environmental and economic impact, adverse health effects from their stings, fire ant allergy and its diagnosis and treatment, and current and future control measures for these pugnacious predators.

FIRE ANT SPECIES

Fire ants are classified in the order Hymenoptera and family Formicidae.(Fig 1) Two species of fire ants are responsible for the majority of health and economic consequences of fire ants: *Solenopsis invicta* and *Solenopsis richteri*. Both species are native to specific regions of South America but were then "imported" into the U.S. hence the name, imported fire ants. *Solenopsis richteri*'s homeland is in southernmost Brazil, Uruguay, and Argentina. *Solenopsis invicta* is localized to the state of Mato Grosso in Brazil, specifically the Pantanal, the large flood plain of the head waters of the Paraguay River and its fringes.[4] The first collections of imported fire ants were reported in Mobile, Alabama by W. P. Loding an amateur entomologist in 1929.[5] Loding estimated they were introduced into the Mobile area around 1918. He believed that their early spread was hampered by the Argentine ant, *Iridomyrmex humilis*, another species that occurred in large numbers in the same area. Creighton later identified the ant as *Solenopsis saevissima var*[6], but was subsequently named *Solenopsis richteri*. By 1931 they were found in three other small communities in Mobile County and neighboring Baldwin County and six years later were so abundant in Baldwin County that county, state, and federal agencies combined in an effort to control them and 80% of active mounds were reported to be exterminated.[7] *S. richteri* is presently limited to a small area along the northern border between Mississippi and Alabama.[8] In the late 1940's it was recognized that another form of fire ant that was more reddish in color was becoming more dominant. It was not until 1972 when Buren concluded there were two separate species of fire ants and assigned them their current scientific names: *Solenopsis invicta* Buren (the red imported fire ant) and *Solenopsis richteri* Forel (the black imported fire ant).[9] *S. invicta* was imported to the Mobile area between 1933 and 1945, however the exact mode of entry of the ants has not been

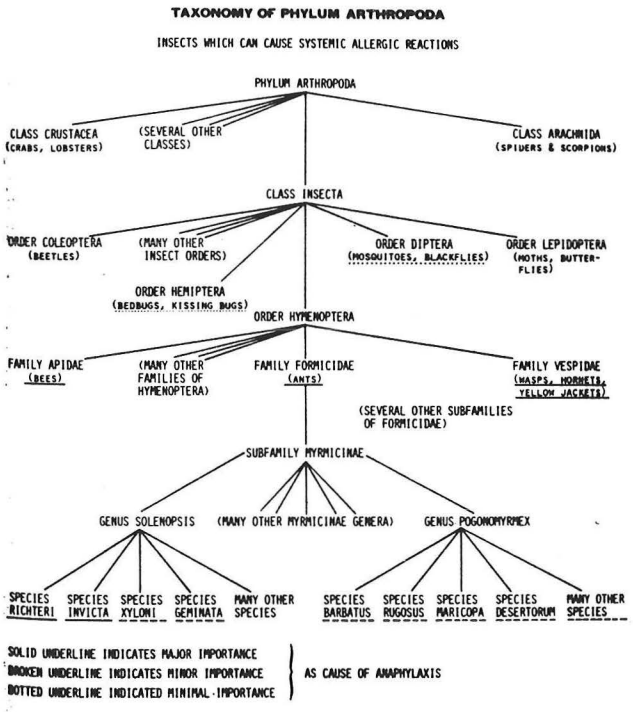

Figure 1. Phylogenetic relationship of imported fire ants with other Hymenoptera and insects that cause anaphylaxis.[108]

determined.[4] By 1949, the first USDA survey revealed light to heavy infestation in 14 counties in Mississippi, 12 in Alabama, and 2 in Florida. In 1953, the USDA performed another survey and found imported fire ants in 102 counties in 10 states. Imported fire ants spread naturally via nuptial flights, colony movement or even by floating to new areas during flooding. However, the major cause of their rapid spread was caused by man. It was during the 1953 USDA survey that the sale of nursery plants and grass sod and their transportation was linked to the spread of fire ants.[7]

Solenopsis invicta is the most aggressive species of fire ant and now infests 13 southern states. It has largely displaced the other imported fire ant, *S. richteri*, as well as the native species *S. xyloni* and *S. geminata*. *S. invicta* has spread as far north as Maryland,[10] and isolated colonies have been found as far west as New Mexico, Arizona[2] and even Southern California.[11] The present area of infestation is shown in Fig 2. The 10°F isotherm (average minimum yearly temperature) has been considered to be the thermal boundary of fire ant infestation due to *S. invicta*'s limited cold tolerance.[4,7] However, it has been discovered that *S. invicta* and *S. richteri* hybridize freely and the hybrids appear to be more tolerant of the cold.[12] Furthermore, they are wintering beneath interstate highways since these highways are kept free of snow and absorb sunlight and heat.[13] Over the next decade *S. invicta* is projected to spread further into California and up the Pacific coast to the Canadian border.[8]

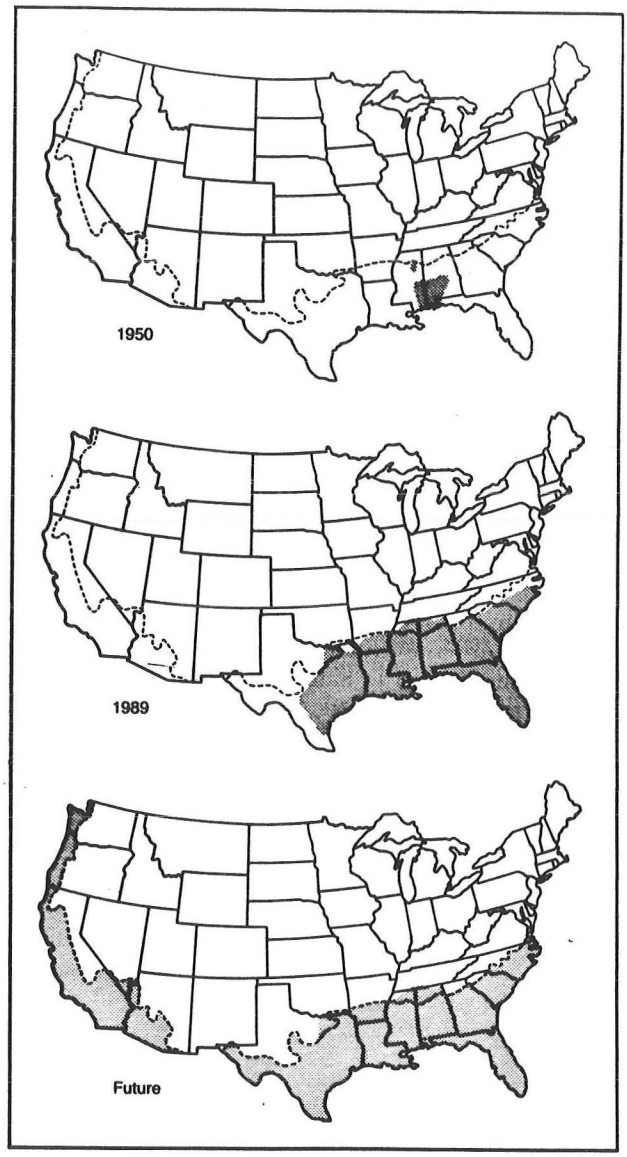

Figure 2. Areas infested by imported fire ants in 1950, 1989, and future predicted spread. Dotted line is 10°F isotherm. (DeShazo et al. NEJM 1990;323:462-6.)

Recent ecological studies of imported fire ants reveal that their colony sizes and densities are much greater than those in their native range.[14] This is presumably due to abundant food sources and their lack of natural enemies in the United States as well as their omnivorousness.[15] High population densities in the United States are likely to reduce the availability of new nesting sites leading to habitat saturation and the formation of multiple-queen (polygyne) colonies. This high population density has also created a biologic shift in the evolution of imported fire ants such that the workers are less related to the queens and a higher female-biased sex ratio exists in imported fire ants than their native counterparts.[16] While monogyne colonies may contain 100,000 ants, polygyne colonies

may contain as many as 500,000 ants.[15] A relatively recent survey of Texas counties indicated that over 50% of fire ant colonies were polygyne forms and these sites averaged more than twice as many mounds per hectare as monogyne sites.[17]

There are 18 species of fire ants with workers ranging in size from 1.8-6 mm.[18] The vast majority of all allergic reactions to ant stings in the United States are due to the red imported fire ant *Solenopsis invicta*. However, a few other fire ants in the United States and other species of ants in other areas of the world are capable of causing anaphylaxis.

Ants of the genus *Myrmecia* are distributed almost exclusively in Australia. Two species of ants are capable of causing allergic reactions after stings. *Myrmecia pilosula*, the jumper ant, is responsible for most of the allergic reactions but *Myrmecia pyriformis*, the bull ant, is also capable of causing anaphylaxis.[19] The prevalence of systemic reactions to jumper or bull-ant stings in southeastern Australia is 2.4% which is about the same as the prevalence to bee stings. Fatalities to the stings of these ants has not been reported.[20] In the United Arab Emirates, stings from *Pachycondyla sennaarensis*, the Sansum ant, have become a public health hazard and fatalities have been reported.[21] In Korea, Ectomomyrmex, an ant of the subfamily Ponerinae has been reported to cause anaphylaxis.[22] Finally, in Europe, a single case of anaphylaxis to the common red harvester ant, *Formica rufa* has been reported.[23]

The tropical fire ant *Solenopsis geminata* Fabricus was once common in Florida, the gulf coast, Mexico, Central America and the Caribbean.[7] *S. geminata* has largely been displaced by *S. invicta* and is now uncommon in the United States and much of the Caribbean with some colonies around Jacksonville and Gainesville, Florida.[24] It has become an important pest in Okinawa and Guam where it was likely imported by ships carrying cargo from Central America or the Caribbean.[18] *S. geminata* has an extremely large head, out of proportion to the rest of its body and mandibles usually without teeth.[25] *S. geminata* stings often do not form the characteristic pustule seen with *S. invicta* and *S. richteri*.[24]

Solenopsis xyloni McCook, the southern fire ant has also been displaced by *S. invicta* but is still found here in Texas, California , and Mexico. In 1974, Lockey reported a four year old boy with a systemic reaction to ant stings which were identified as *S. xyloni*.[26] Most of the recently reported cases of sting reactions to *S. xyloni* have occurred in the arid and semiarid regions of southern and central California.[24]

Solenopsis aurea, the desert fire ant, has a bright golden color. *S. aurea* is a rare species found only in the southwestern desert, especially southern California.[24] Stings from *S. aurea* can produce systemic and large local reactions.[27]

In 1974, Lockey reported a case of a 9 year old girl who was stung by 2 large red ants without development of a pustule and developed severe asthma and lethargy 30 minutes later.[26] The following day ants were collected at the site and identified as *Pogonomyrmex barbatus,* red harvester ants. Subsequent to this report, few if any other cases of harvester ant allergic reactions have been reported in the United States.

Since almost all allergic reactions to ant stings in Texas are due to *S. invicta*, it is usually not necessary to try and identify the species of ant. Entomologists can typically differentiate these ants on visual inspection by their 10-segmented antennae with a 2-segmented club, the presence of a sting, a two-segmented pedicel and an unarmed propodeum however identification at the species level is somewhat more difficult. The cuticular hydrocarbon patterns can be analyzed to differentiate the two imported fire ant species.[28] Furthermore, patients who have had systemic reactions to *Solenopsis richteri, xyloni, geminata,* and *aurea* are reactive to *S. invicta* venom via RAST and *S. invicta* whole body extract via skin testing.[24] This cross-reactivity appears to be both immunologic and clinical and therefore it may be possible to treat patients reactive to these other fire ant species with *S. invicta* extracts. Nevertheless, there are some clues that are helpful in identifying the other less common species of fire ants. The native fire ants *S. xyloni* and *S. aurea* do not produce pustules at sting sites, however *S. geminata* can produce pustules. *S. xyloni* and *S. aurea* also do not build mounds and *S. geminata* build very low mounds.

ECONOMIC IMPACT OF FIRE ANTS

Due to the prolific spread of S. invicta throughout the southeastern U.S., imported fire ants have made a significant economic impact on public health, agriculture, wildlife, and other areas. Between 1957-1981, $172 million dollars were spent by federal, state, and other governmental agencies for control of imported fire ants. Recently it has been estimated that homeowners in Georgia spend an estimated $32 million annually on fire ant control measures.[29] Freeman noted an estimate of $2.77 billion/year for total U.S. costs,[1] however accurate economic data is lacking. Current economic data for fire ant related costs is in the process of being collected for the state of Texas. Based on studies of patients requiring acute medical treatment for stings and the attack rate of fire ants, Lofgren estimated in 1986 that approximately $2.84 million is spent annually on medical office visits.[30] This estimate was based on an office visit cost of $23.10 and so likely is a significant underestimate for today's healthcare environment. From an agricultural standpoint, imported fire ants have been determined to cause damage to 57 species of cultivated plants including: soybeans, citrus trees, corn, hay, eggplant, okra, peanuts, potatoes, sweet potatoes, strawberries, watermelon, cabbage, and pine trees.[30,31] For 1981 an estimated $125 million was lost in soybean sales due to fire ants.[30] This is due to their effects on the soybean crop itself by destroying seeds and seedlings as well as interference in harvesting due to their mounds impeding combines and potentially causing equipment damage. Fire ants have been reported to destroy more than 50% of citrus trees in some groves due to chewing the bark and feeding on sap causing a "bleeding phenomenon". In 1983, Adams reported an estimated crop loss of up to $90,000 from a single field of eggplants destroyed by fire ants.[32] Fire ants have also been reported to affect drip irrigation by building their mounds over emitters and blocking flow of water and in some cases causing physical damage to sprinkler systems.[33] Even the killing of newborn calves and pigs in pastures has been reported from fire ants.[30] Fire ants as predators have achieved a long list of prey including: beetles, ants, spiders, turtles, skinks, snakes, nighthawks, doves, quail, rabbits, ducks, worms, weevils, flies, and earwigs. Population declines of at least two-fold have occurred among some species of snakes and lizards, particularly five-lined skinks, mice , and turtles[10,34] with some species being completely eliminated from an ecosystem[35]. Imported fire ants may have some beneficial effects as predators of other pests such as the sugarcane borer and the boll weevil thereby reducing damage to sugarcane and cotton fields respectively.

Fire ants have also been known to damage electrical systems. Ironically, Lofgren noted while writing his chapter on the economic importance of fire ants, his air-conditioning system was inactivated twice because fire ants invaded the electrical control box in his office building![30] A firm in Marshall, Texas estimated at least $1000-1500 in their business was attributable to fire ant damage of air conditioners. Fire ants have also been known to invade telephone cables and wires, and even were responsible for inactivation of airport runway lights.[4] Road damage has even been reported due to fire ants tunneling underneath the asphalt and removing enough dirt to cause collapse of a small portion of the road.

BIOLOGY OF FIRE ANTS

Imported fire ants vary in color from dark red to brown or black and may vary in color considerably even within the same colony.[26] . They have two humps on the petiole and prominent mandibles used for carrying food, attacking, and grasping (biting) allowing fixation of the ant on the prey and positioning of the stinger. The stinger of the fire ant is a modified ovipositer 0.5-1.0 mm long and the venom, which contains no formic acid, is extruded from the abdomen. Fire ants sting more slowly than other Hymenoptera (bees) and inject their venom over seconds to minutes.[2] Colonies of fire ants consist of eggs, brood (immature ants), polymorphic workers, winged (alate) males, winged females and one or more reproductive queens. The sexual castes include winged males, winged, unmated females, and one or more mated queens. Three types of worker ants exist, all are sterile females. Minims are the first workers produced from a new colony and are small in size due to the limited energy the queen could devote to their development. Two other common workers include major workers which measure up to 1/4 inch long and minor workers that are approximately 1/8 inch in length. Labor is divided amongst the workers by age more than size. Younger workers take care of brood, middle aged workers maintain and protect the colony and the oldest workers forage for food. Queens are larger winged ants measuring 1 cm in length. Alate forms are more abundant in the late spring and summer. Alate males may be distinguished by their smaller size, glossy black color and smaller head.

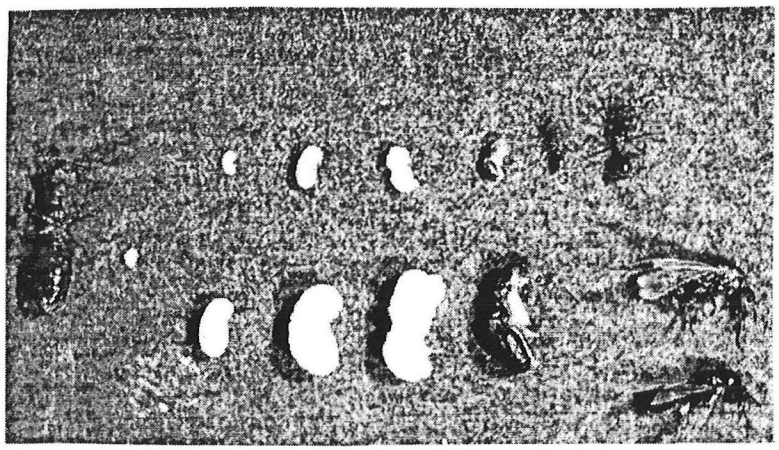

Figure 3. Stages of development of ant castes. Queen is on the far left, workers on top and alate male and female on bottom (female is uppermost alate form)

In monogyne colonies where only one egg-laying queen exists, the queen begins the colony 4 hours after her mating flight by breaking off her wings and burrowing into the ground or under solid objects. In the polygyne form, queens and workers from an existing colony emigrate as a group to form a new colony near the parent colony.[36] In laboratory studies, *S. invicta* queens laid 15-20 eggs within 2-3 days and 20-125 eggs by the time the first larvae emerged, usually about 3 weeks after egg deposition.[4] The queen lives up to seven years and produces an average of 1600 eggs per day.[10] The success of the colony founding process is dependent on numerous factors including soil properties, climate, food availability, and the reproductive success of fire ant queens which is strongly influence by their genotype.[37] Over a period of years colonies grow and mature. At 5 months only 1000 worker ants are present with 11,000 workers at 1 year, and 50-70,000 at 2-3 years. Colonies over 3 years old are considered mature. Some ants have queens that have life spans over 15 years.[38]

Fire ants build characteristic conically-shaped mounds of excavated soil that has a hard, rain resistant crust. Mounds of mature colonies of fire ants are typically 18 inches in diameter and height and occupy a volume of 40 liters but may reach sizes of 3 feet in height.[4,39] Mounds vary depending on the soil types and moisture. In sandy areas they tend to be flat and broad while in clay they are usually much larger. They are usually constructed in cultivated fields, pastures, and lawns. While mounds are important to a colony they are not essential for their existence and fire ants may nest in a variety of locations given a protected site with adequate moisture and food including rotten logs, automobiles, dried cow manure and recently within inhabited dwellings.[40,41] Fire ant mounds serve three purposes. They are a platform for nuptial flights. They raise the colony above the water table in saturated ground. Finally, they act as a solar sink to supply warmth to the colony in cooler months. Typically 5-6 tunnels radiate from the mound at a depth of 1/4 inch with some tunnels being as long as 80 ft to allow foraging workers access to food. Ants may change the location of the colony often, even as many as three times in 24 hours.[39]

The seasonal reproductive cycle of fire ants begins in March and brood production stops with the approach of winter. Winged males and females mate in flight. After an unknown stimulus, thousands of males fly from their mounds simultaneously concentrating at an altitude of 90-150 meters and remain airborne for several hours.[4] About 30-60 minutes later, virgin queen females ascend into the swarm of males and mate with a single male, then descend rapidly to the ground to burrow a nest while the males fall prey to predators after mating. Nuptial flights generally occur 1-2 days after rain and between 1-3 PM for *S. invicta*. After a major nuptial flight, as many as 6 queens per square yard or 45,000 newly fertilized queens per acre are beginning to start colonies![38]

Fire ants are omnivorous and opportunistic and will feed upon whatever plant or animal they encounter. The primary diet of the fire ant is insects, spiders, myriapods, earthworms, and other small invertebrates. Fats and oils are consistently the most acceptable foods.[4] Workers exit the mound and forage for food randomly. Once food is discovered, the forager returns to the mound leaving a trail pheromone. Additional workers than establish a continuous stream of ants between the food source and the mound. Food distribution is fairly complex but efficient. Within 9 hrs of feeding colonies ^{32}P-labeled food high in lipid and protein, labeled food was detected in 93-99% of workers, 80% of larvae and 83% of the queens.[4]

Fire ants have very well developed senses including a sharp sense of compound-motion responsive vision, vibration, touch, and extremely sensitive chemoreceptors in their antennae.[38] These chemoreceptors are critical in communication and organized activities via secreted pheromones. Several pheromones are used by fire ants including alarm pheromones to cause alarm and attention, trailing pheromones leading workers back to food, and brood and queen tending pheromones.[4]

FIRE ANT ATTACK RATE

Fire ants are very aggressive and due to their increasing density in populated areas the attack rate is fairly high. Various surveys have determined the annual sting attack rate to be between 6-58% and Stafford reported that 30% is a conservative estimate.[2] A phone survey of an upper middle class New Orleans suburb in 1973 revealed 29% of the study population were stung between June and August, however the sting rate for children under 10 was 55%.[42] Similar results were obtained from another phone survey in a more rural county of Georgia done in 1976.[43] Thirty-one percent of this rural population was stung by fire ants and 42% of children under 10 were stung. Multiple sting attacks occurred in 12% of subjects. In this year long survey, the highest sting attacks occurred between April-June. Overall 35% of the population was stung at least once during the year. Another survey of a middle-class residential area of New Orleans, this time done by actual home visitation, revealed that 58% of residents were stung by fire ants in the prior year.[44] A more recent prospective study of military medical students undergoing a 3 week educational program in San Antonio revealed an impressive 51% sting attack rate in this brief time period.[45]

REACTIONS TO FIRE ANT STINGS

The fire ant derives its name from the fierce, burning pain associated with its sting. A detailed description of the stinging process has been provided by Caro and colleagues who performed intentional sting challenges on volunteers in New Orleans in the 1950's.[46] The ant first fixates itself with the mandibles by grasping the skin, then arches it back at the peduncle and inserts the stinger. It maintains this position for several seconds, usually 20-25. It may then remove the stinger, and using its head as a pivot, rotate and reinsert the stinger in 2-3 more sites. On careful inspection, one may see the two minute hemorrhagic puncta from the ant "bite", but nothing further develops at these areas. At the site of the sting, there is an almost immediate flare of 25-50 mm, and within a minute a wheal appears and grows to 2-10 mm in diameter. Small prominences are seen at the site of stings 1.5-2 hours later and within 4 hours these become very superficial vesicles containing clear fluid. Eight to ten hours later the fluid becomes cloudy and eventually purulent. After 24 hours the sting sites are slightly umbilicated pustules and in some instances are surrounded by a narrow red halo. The pustule remains 3-10 days and then ruptures with crust formation. Pigmented macules persisting for days to weeks and scar formation may also commonly occur.

Caro and colleagues have also studied the histopathology of sting sites. At six minutes, no changes are observed. At 30 minutes, intracellular edema, a light infiltrate of lymphocytes, plasma cells and histiocytes, and early necrosis in the cornium are observed. At 24 hours the lesion is a superficial pustule with necrotic polymorphonuclear leukocytes and lymphocytes and a base of necrotic connective tissue. By 72 hours, eosinophils and plasma cells were also present in the

pustule. The pustule of the fire ant sting is sterile. The fire ant venom alkaloid which consists of water insoluble cis and trans isomers of 2-methyl, 6-n-alkyl piperidine compounds is responsible for the development of the pustule and associated tissue inflammation.[8]

Reactions to fire ants stings are typically classified as local, systemic, or "other" unusual reactions. Three types of local reactions occur: a wheal and flare response, pustule formation, and large local reactions. The wheal and flare reactions and pustule formation are normal reactions which occur in the vast majority of individuals stung by fire ants. The sterile pustule (Fig. 4) is considered pathognomnic of solenopsis species envenomation.[38] If left alone, these pustules will rupture and heal with little residual. Nevertheless, people frequently scratch and rupture these pustules, infecting them secondarily. Triplett performed a survey of physicians in Mississippi, Georgia, and Alabama and received responses from 901 physicians who reported treating 12,438 patients in a seven month period in 1971.[47] Of these, 6778 (54% total) required treatment for secondary infections, eight required skin grafts, and five required amputation of a limb.

Large local reactions to fire ant stings is another common type of local reaction occurring in 17-56% of individuals.[42,44] DeShazo and colleagues performed intentional sting challenges in 12 "nonreactor" individuals with typical sting-pustule reactions and 9 "reactors" with histories of persistent local reactions.[44] The "reactors" had a biphasic response with an immediate wheal and flare at 20-30 minutes and a late reaction developing after 1-2 hours. This late reaction developed an area of well-defined, intensely pruritic area of erythema and induration that was prominent at 6 hours and peaked at 24 hours. The larger the reaction at 20 minutes, the larger the reaction at 6 hours. Histopathologic studies of the late phase reactions revealed large amounts of fibrin in the reticular dermis and eosinophils in blister fluid at 24 hours, similar to mast cell-dependent late phase reactions. Passive transfer using the P-K technique of a late phase response was accomplished using one of two reactor sera. The fact that some of the reactors were unreactive to fire ant whole body extract skin testing, the failure of passive transfer with one of the reactor sera, and the high incidence of late phase reactions suggests that some of these reactions may occur on a nonimmunologic basis. Other studies have also demonstrated the lack of specific IgE in 57-100% of patients with large local reactions depending on the testing method.[48]

Figure 4. Sterile pustules on arm after multiple fire ant stings.

Systemic reactions including life-threatening and fatal anaphylaxis can also occur after fire ant stings. The incidence of systemic reactions to fire ants has not been clearly determined. Most general population surveys have included relatively small numbers of residents and some did not

distinguish systemic reactions from other adverse reactions. In a survey of an upper middle class suburb of New Orleans, 1.3% of the exposed population sought medical care and 4.4% of those stung sought medical care but how many of these had systemic reactions is unknown.[42] In a more rural population of Georgia, the incidence of "severe" reactions was 1% amongst those stung. Several surveys of physicians along with clinic surveys of patients seeking medical care for fire ant stings have been performed. A survey of 1,020 South Carolina physicians revealed that 6% of cases of fire ant sting patients had anaphylactic shock.[49] In the aforementioned survey by Triplett, 16% were treated for systemic reactions and 0.6% for anaphylactic shock.[47] A prospective survey of patients seeking care for fire ant stings at a U.S. Army training facility at Ft. Stewart, GA, revealed that 51% had urticaria and 5% exhibited symptoms of shock.[50] A survey of 2,022 AMA members in 13 southern states estimated that 2% of 20,755 patients required treatment for anaphylaxis.[51] Dr. Ginsburg at Children's Medical Center in Dallas made an estimate based on anecdotes of systemic reactions in 2-3/100,000 children.[52] Finally, a minimal incidence of systemic reactions in Jacksonville was estimated to be 3.8/100,000/year.[53] In summary, the incidence of anaphylaxis after fire ant stings is approximately 0.6-6%. This is very similar to the incidence of anaphylaxis to other Hymenoptera which is 0.15-3.3%.[54-56]

Fatalities due to fire ant stings have been reported since the 1950's. Parrish reviewed death certificates from the National Office of Vital Statistics from 1950-1959 and reported 4 deaths due to ants, accounting for 0.8% of deaths from Hymenoptera.[57] The first well documented fatality was reported in 1950 and occurred in a boy from North Texas who likely had anaphylaxis after being bitten by 3 ants.[58] Since imported fire ants were not reported in North Texas at this time, another ant species was the likely culprit. Since then several case reports and surveys have reported on almost 100 deaths due to fire ant stings, with the most recently reported death in the literature by Drs. Prahlow and Barnard at UT Southwestern.[53,59-65] A large physician questionnaire disclosed 84 fatal reactions, but after further analysis and excluding duplicate reports, 32 anaphylactic deaths were documented.[63] Most of the documented fatal anaphylaxis cases occurred in Texas.

A few case reports have described more unusual reactions to fire ant stings. Six patients have been reported to have had seizures after fire ant stings.[66,67] Fifty percent of these cases had seizures during or after anaphylaxis from the fire ant stings. Of the remaining three cases, one case occurred after hundreds of stings while the other two developed after 2-20 stings. The mechanisms of these seizures have been postulated to be due to hypoxia, an IgE mediated hypersensitivity or that the venom acts as a toxin via a secondary transmitter or by altering a biological pathway.[67] None of these mechanisms however have been validated. Immunotherapy has been advocated by the authors of both of these separate case reports based on the observation that 2 patients with seizures induced by fire ant stings did not have a recurrence of seizures when re-stung while on immunotherapy.[66] If the seizure occurs in the context of anaphylaxis this would certainly be prudent. Radial mononeuropathy has been described in a single case report of a man stung by 200 fire ants in the right arm.[66] Minimal change nephrotic syndrome was reported in a 3 year old boy stung by an unknown number of fire ants.[68] Recently, corneal injury with severe bilateral keratitis was reported in a developmentally delayed infant stung at least 30 times in the eyes.[69]

Due to the aggressive nature of fire ants, multiple stings are very common. Interestingly, patients who have suffered thousands of stings at one time usually have no serious adverse effects. Smith et al. described an interesting case of multiple fire ant stings as a complication of alcoholism.[70]

The patient was a 49 year old alcoholic who had been drinking all day and night and went to sleep in a ditch in front of his friend's house, and in the dark selected a fire ant mound as his pillow! He was discovered by his friend a few hours later with thousands of ants crawling on him. He was taken to the hospital where approximately 5,000 pustular lesions were scattered over his body but other than a hangover suffered no adverse effects other than the pustules. The authors of this case report stressed that "After a night on the town, one should make an all-out effort to return home for the fire ant is quite reluctant to share his bed with strangers." Other cases of massive sting episodes have been reported with no adverse effects including an 84 year old women with senile dementia who was found in bed with thousands of ants on her and sustained an estimated 10,000 stings![41,71,72] Most cases of massive stings have occurred in individuals who were unable to escape including infants, patients with dementia, or were unaware as in a case of a diabetic man with probable neuropathy who was stung multiple times on his extremities while in a motel bed. It is also interesting to note that many of the recent reports of multiple stings have occurred indoors in inhabited buildings. Due to the increased density of ants and competition for food sources, fire ants are now looking indoors for their next meal, which may be human!

Toxic reactions to other Hymenoptera (bees, yellow jackets, etc.) do occur after approximately 50-100 stings.[73] Toxic reactions to fire ant stings appear to be uncommon. A 5 day old boy was stung 2,000 times in his playpen and had a near fatal event presenting to the local ER with apnea and asystole and at 6 months had mild developmental delay.[74] Death of an abandoned newborn stung multiply by fire ants has also been reported and the stings were felt to be a contributing factor in the death.[46] A 90 year old woman with severe dementia and chronic congestive heart failure suffered multiple stings in her bed in a nursing home. She was found with ants crawling from her mouth and died of "respiratory failure" 6 days later.[41] Fire ant venom has a high concentration of piperidine toxins consisting of 90-95% water insoluble n-alkyl and n-alkenyl piperidine alkaloids. These piperidines possess hemolytic, bactericidal, and insecticidal activities[75,76] and the venom has a high LD_{50} in mice.[71] It is possible that direct toxic effects from fire ant venom can occur in infants due to their small size and possibly in patients with cardiovascular disease.

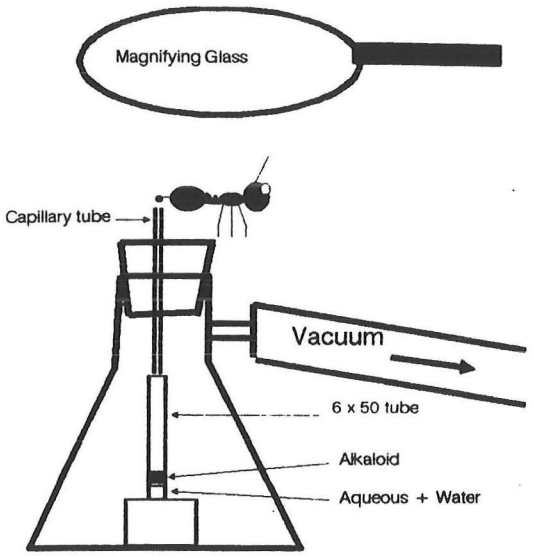

Figure 5. Method used to hand-milk fire ants to collect venom.[18]

FIRE ANT VENOM

Studies on fire ant venom have been limited for many years due to the inability to obtain significant amounts of pure venom.[18] The original methods used for obtaining venoms was to have the ants sting into microcapillary tubes or by directly squeezing venom sacs.[77] In this latter method of "milking", under a dissecting microscope, the abdomen of the ant is dissected free and stroked with a 0.5 µl pipette.[78] Venom is produced at the tip of the stinger in the amount of 0.015 µl per drop with about 4-5 drops produced from a single worker. These methods are extremely laborious even to obtain small amounts of venom since the venom sac of each ant contains only 40 nl of venom.[79] This method was improved by the use of a vacuum and a larger collecting tube (Fig. 5).[77] A proprietary electric stimulation method has been developed for the collection of commercial grade venom and is capable of producing gram quantities which are comparable in purity to hand-milked venom.[77]

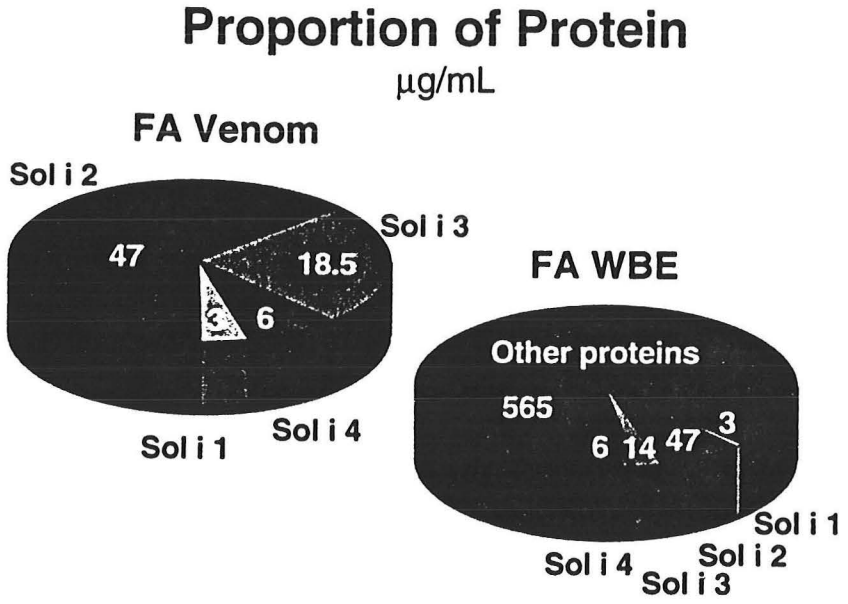

Figure 6. Left: Concentration of Sol i allergens in fire ant venom. Right: Sol i allergen concentration compared to large amount of extraneous body proteins in whole-body extract.[8]

Fire ant venom is different than venom from the venoms of bees and vespids which are primarily aqueous and contain significant amounts of protein. Fire ant venom is 95% alkaloid with a small aqueous fraction that contains a small amount of protein. The water insoluble fraction consists of 2,6-disubstituted piperidine alkaloids. Imported fire ants have an alkenyl substituent in a *trans* configuration while native North American fire ants have alkyl substituents and are both *cis* and *trans* about the ring.[18] Venom alkaloids have hemolytic, antibacterial and insecticidal properties[75,76] and are capable of lytic release of histamine from mast cells [80]and activation of platelets and neutrophils.[81] These piperidine alkaloids are responsible for the characteristic pustular lesion at the sting site but are not responsible for IgE mediated allergic reactions.

Solenopsis Invicta Venom			
Transpiperidine alkaloids	95% venom		Induce sterile pustule
Venom proteins	0.1% venom wt.		Induce hypersensitivity
Sol i I	2-4% venom protein	37kD	Cross-reacts with yellow jacket phospholipase
Sol i II	50-67% venom protein	13 kD	Homodimer
Sol i III	15-25% venom protein	24 kD	Vespid antigen 5 family
Sol i IV	8-10% venom protein	13 kD	Sequence similar to Sol i 2

Four major protein allergens have been isolated and characterized from *S. invicta* venom.[82] Sol i 1 is the largest molecular weight protein but comprises only 2-4% of the venom protein and contains phospholipase A and B activities. It has been very difficult to purify and structurally characterize and thus far has not been sequenced or cloned. This protein is partially responsible for cross-reactivity with bee and vespid proteins. Sera from patients sensitive to honeybee and vespid venoms who had no exposure to fire ants demonstrated binding to Sol i 1 as tested by RAST inhibition and immunoblot studies.[83] Several regions of Sol i 1 have complete or almost complete identity with sequences from *Vespula maculifrons* (yellow jacket) phospholipase and white faced hornet and this is thought to be the origin of the observed cross-reactivity.[18,84] Sol i 2 is the most abundant protein in fire ant venom comprising half to two-thirds of the venom protein. It is a disulfide-linked homodimer of 119 amino acid chains and is very basic with a pI of 9.63.[85] The cDNA for Sol i 2 has recently been cloned and gives a sequence identical to that obtained by protein sequencing.[86] A recombinant form of Sol i 2 has recently been developed in a baculovirus expression system that is in its fully immunoreactive native form.[87] Its structure is unrelated to any other proteins in the Protein Identification Resource or Swiss-Prot databases. Sol i 3 makes up 15-25% of the venom protein. It is a single chain molecule of 212 amino acids which is not quite as basic as Sol i 2 with a pI of 8.24.[85] It has 44-50% identity with antigen 5 molecules from yellow jackets and hornets and its cDNA has been cloned.[88] Despite its sequence homology with vespid antigens, immunologic cross-reactivity has not been clearly established.[83] Sol i 4 is a 117 amino acid single chain protein which has 35% identity to Sol i 2.[85] Although the two are related to each other by sequence, they appear to be unrelated antigenically with both human IgE and monoclonal mouse antibodies.[82] Like Sol i 2, it appears to be totally unrelated to other known venom proteins from insects of other genera.[85]

The venom proteins from *S. richteri* have also been studied. Three proteins have been isolated, Sol r 1, Sol r 2, and Sol r 3, all are homologous to *S. invicta* proteins.[89]. Sol r 1 appears similar on electrophoresis to Sol i 1 and the N-terminal sequence is identical . Sol r 2 has been sequenced and has 78% identity with Sol i 2 which is enough to be cross-reactive yet still individually recognizable.[18] The sequences of Sol r 3 and Sol i 3 are 96% identical. There is no molecule analogous to Sol i 4 in *S.richteri* venom. Venom from hybrid *S. richteri-invicta* ants contain antigens of both species.

WHOLE-BODY EXTRACTS

Fire ant whole-body extracts are the only commercially available extracts for diagnostic testing and treatment with immunotherapy. Crossed immunoelectrophoresis studies of whole-body extracts appear to contain most but not all antigens associated with fire ant venom and also contain a number of immunogenic substances not involved in the allergic reactions.[90,91] Butcher and Reed evaluated 3 commercial extracts from different companies and showed significant variability in their antigenic content and potency.[92] Total protein antigens varied from 5-18 and venom antigens from 0-3, none contained all four. Potency of commercial extracts were also variable and the most potent were still 10 fold less than fire ant venom. Other investigators have also noted significant variability in commercial whole-body extracts.[48] Using a monoclonal antibody ELISA, Sol i 3 content was evaluated in commercial whole-body extracts and was found to be in significant quantities.[93] Sol i 3 also appeared fairly stable since the amount found in the commercial extract was only slightly less than in a freshly prepared extract.

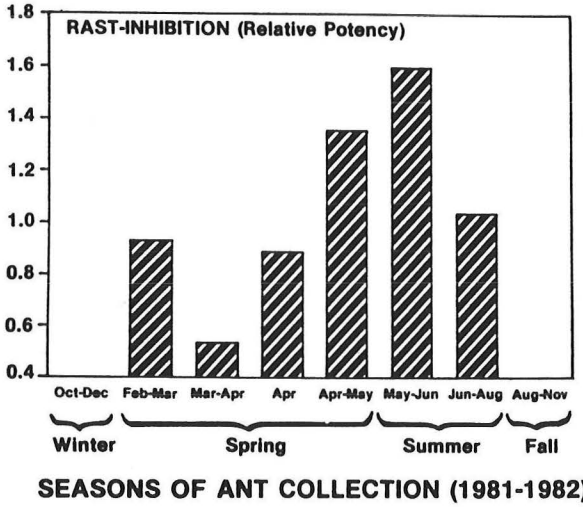

Figure 7. RAST inhibition of 8 different *Solenopsis invicta* extracts obtained at different times of the year.[94]

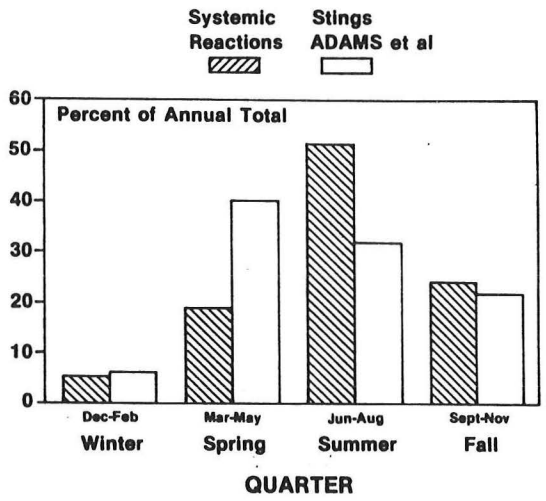

Figure 8. Comparison of quarterly incidence of fire ant stings and systemic reactions in rural Georgia.[94]

Whole-body extracts may also vary in allergenic potency based on the seasons ants were collected. Hannan et al. evaluated 8 lots of whole-body extract from ants collected at different times over an 18 month period.[94] Each lot was analyzed for enzyme activity including phospholipase activity and potency was assessed by venom RAST inhibition. Phospholipase activity and extract potency were highest from ants collected from May-June and lowest in the winter months from October-December (Fig. 7). Phospholipase activity varied by as much as 100-fold between summer and winter months. These authors further noted that in a retrospective chart review of their practices in Georgia over a 3-year period, most systemic reactions were in the summer (51%) with only 19% in the spring(Fig. 8). In looking at sting attack rates for rural Georgia,[50] the peak attack rate occurred in spring, followed by summer. This suggests that perhaps greater venom potency is related to higher systemic reactions, not just the sting attack rate. This seasonal variation in extract potency may further vary the quality of commercial whole-body extracts.

DIAGNOSIS OF FIRE ANT ALLERGY

The diagnosis of fire ant allergy is usually fairly straight forward in endemic areas such as Texas. Since the sting from fire ants is quite painful, most patients are aware of when they are stung and notice the insect stinging them. The development of the characteristic sterile pustule is pathognomonic for fire ant stings and most patients do develop pustules after being stung. The diagnosis of systemic reactions to fire ants can be confirmed by correlating clinical manifestations with the results of specific IgE for imported fire ants by skin testing or RAST. The mere presence of specific IgE to fire ant is not enough to make a diagnosis of fire ant allergy since approximately one in four people in endemic areas with no fire ant allergy history have detectable specific IgE. Hoffman et al. evaluated 21 serum samples from individuals with no history of fire ant allergy and found 24% to have specific IgE by RAST.[83] In contrast, 0/100 patients without a history of fire ant allergy and living in a fire ant free area had positive RAST to fire ant. Similar data have been obtained using skin tests. Lockey noted that 3/7 controls (43%) had positive skin tests, but the skin testing concentrations used were fairly high and may have been irritative.[26] Rhoades et al, reported that 23% of patients referred for evaluation of allergic disorders other than insect allergy had positive intradermal skin tests with fire ant whole-body extract.[95] Interestingly, patients evaluated in Texas had the highest reactivity to fire ant skin tests with positive reactions in 31% of patients with no history of fire ant allergy. The prognostic significance of having detectable specific IgE to fire ant is unknown and prospective studies are clearly needed. In the aforementioned study by Hoffman, 2/5 nonallergic patients with positive fire ant RAST's subsequently experienced large local reactions after fire ant stings.[83]

In Triplett's report on immunotherapy for fire ant allergic patients, he noted that 15/17 patients had positive skin tests to a whole-body extract, however the other 2 patients were not tested at high enough concentrations.[96] Lockey reported 3/3 patients with systemic reactions to fire ants had positive skin tests.[26] Rhoades reported the results of skin testing 86 patients with systemic reactions to fire ants and 95% had positive skin tests but the technique of skin testing varied since this was a collection of patients from different allergists.[53] Several studies have compared skin testing with whole-body extracts and venom skin testing and overall have shown that venom testing is superior. James et al. first reported on the use of hand-milked venom for skin testing and compared it to skin testing with whole-body extracts.[78] *S. invicta* venom skin testing was positive in 15/18 (83%) allergic patients while *S. invicta* whole-body extract was positive in 14/18 (78%). However using the whole-body extract mix including *S. invicta* and *S. richteri* 100% of allergic patients were detected. Strom et al. similarly found that whole-body extract skin testing was positive in 82% of patients with systemic reactions to fire ants while testing with venom was positive in 94%.[48] Paull et al. in College Station compared skin tests with whole-body extract and venom, RAST with whole-body and venom and also performed inhibition assays.[97] They found good correlations between skin testing with both extracts and RAST with both extracts and also showed extensive cross-reactivity between whole-body extracts and venom based on their ability to inhibit each other in RAST inhibition studies. They also observed that fire ant venom was about 10 times more potent than whole-body extracts. Butcher et al. demonstrated significant differences in RAST with whole body RAST positive in only 48% while venom RAST was positive in 79% of allergic patients.[98] However, this study was flawed in that it included patients with histories of large local reactions only and skin testing was not performed in all patients. Bahna et al. has performed the only evaluation of children with fire ant allergy using both skin testing and RAST.[99] In this study of very

young children aged 15-39 months who had systemic reactions to fire ants, skin testing with whole body extract was positive in 18/19 (95%). RAST testing with venom was better than with whole-body extract in that it was positive in all allergic children with no overlap with controls, in contrast to other studies. Interestingly, the single child with a negative whole-body skin test had a positive whole-body RAST and the highest venom RAST of the entire group. Whole-body RAST demonstrated that 26% of allergic children were in the control range. Another finding in this study was that fire ant allergic children had higher levels of specific IgE on RAST than allergic adults. Stafford et al. also compared both skin testing and RAST with whole-body and venom. [100] Skin test results with both whole-body extract and venom was equal in its ability to detect clinical sensitivity but venom RAST was significantly better than whole-body RAST.

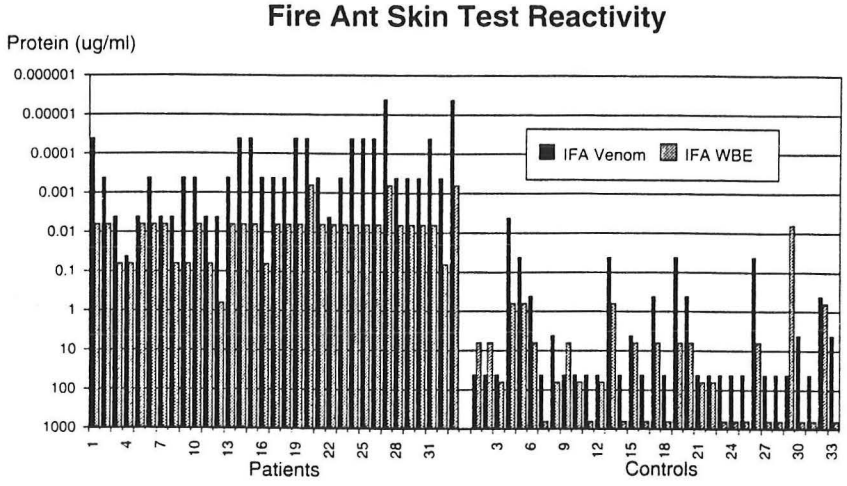

Figure 9. Bar graph showing the results of skin test reactivity based on protein concentration shown in $\log_{10}$ scale in patients and controls.[101]

Finally Stafford et al. reported on the results of an IND study of commercially produced fire ant venom.[101] This study was unique in that the investigators analyzed both whole-body extracts and venoms for total protein and Sol i 2 and Sol i 3 content. As might be expected, the whole-body extract contained a larger total protein content than venom, likely due to the relatively large amounts of extraneous body proteins in the whole-body preparations. The Sol i 2 content was similar between 2 different whole-body extracts from different manufacturers but Sol i 3 content differed by 2 fold. These 2 antigens were found at similar levels in fire ant venom. When normalized for total protein content, skin testing to venom was 10 times more potent than whole-body extract skin testing (Fig. 9). However, there was no appreciable difference in skin test reactivity between venom and whole-body extracts on the basis of Sol i 2 or Sol i 3 content. Skin testing with high concentrations of whole-body extract caused delayed large local reactions in 53% control subjects whereas venom testing at the highest concentration had no adverse effects. As shown in previous studies, allergic patients had higher reactivity to venom RAST than whole-body RAST.

More recent studies have evaluated different *in vitro* methods of diagnosing fire ant allergy. A venom ELISA assay has been shown to be equivalent to venom RAST.[102] Two studies have evaluated the use of the Pharmacia CAP system in fire ant allergy. The Pharmacia CAP system may be more advantageous than conventional RAST in allergy to inhalants,[103] food,[104] and insect

venoms.[105] This may be due to the increased binding capacity of the CAP solid phase which can bind three times more protein than the classic cellulose disk. Using this CAP system, whole-body extract specific IgE yielded similar results to venom RAST and ELISA which is in contrast to most other conventional whole-body extract RAST's.[106] More recently a venom CAP assay was shown to out perform the whole-body CAP assay.[107]

In summary, several conclusions can be made regarding diagnostic tests for fire ant allergy:

1) Skin testing to the commercially available imported fire ant whole body extract is very sensitive and will be positive in nearly all patients with a history of systemic reactions to fire ants.

2) Skin testing to imported fire ant venom is equally if not more sensitive than whole-body extract testing, has higher specificity and is associated with less delayed reactions from skin testing. Currently, imported fire ant venom is not commercially available.

3) *In vitro* tests for fire ant allergy are generally not as sensitive as skin testing, but may be considered in patients with good histories and negative skin tests. RAST using the Pharmacia CAP system is the preferred method. If fire ant venom becomes commercially available, venom would be the preferred antigen.

4) The incidence of imported fire ant specific IgE in endemic areas is approximately 25-30% and therefore these diagnostic tests must be used in the context of the history and cannot be used solely to determine therapy.

MANAGEMENT OF STING REACTIONS

Pustular lesions from fire ant stings will resolve spontaneously without any specific therapy. Since many victims scratch and excoriate these lesions, secondary infections may occur and have been reported in 54% of those seeking medical attention for fire ant stings.[47] Therefore, repeated cleansing of the site with soap and water, avoiding excoriations and prompt treatment of secondary infections is recommended. Efforts to minimize pruritus such as antihistamines, topical anesthetics and corticosteroids may also be employed. Several treatments have been studied to determine their effect on sting reactions. Caro et al. applied topical corticosteroids, antibiotics, and topical antihistamines to sting lesions immediately after stings and daily for several days thereafter and none of these therapies prevented the development of pustules.[46] Parrino et al. studied the effects of topical corticosteroid and parenteral corticosteroid and epinephrine therapy after stings in rabbits without effect and even prophylaxis with topical and parenteral corticosteroids was ineffective.[108] Meat tenderizer and topical aluminum sulfate have also been applied topically after fire ant stings without effect.[109,110] Other anecdotal treatments recommended for other stinging insects including topical vinegar and salt solution and tincture of iodine have been untested.[111]

Large local reactions are manifested as extensive erythematous, painful swellings with pruritus and persist for several days. They may be confused with secondary infections but can be differentiated by the fact that large local reactions develop within hours of the sting. Medical management consists of elevation of the affected extremity and antihistamines and systemic steroids

in severe cases.[8] Antibiotics are not necessary.

Systemic reactions to fire ant stings range in severity from generalized urticaria to life-threatening reactions with bronchospasm, laryngeal edema, and hypotension. Anaphylactic reactions should be managed as medical emergencies and treated the same as other forms of anaphylaxis. Patients with a history of systemic reactions should be given injectable epinephrine for self-administration such as an EpiPen and should self-administer this at the onset of systemic symptoms after a subsequent sting. Furthermore, all patients with a history of systemic reactions to fire ant stings should be referred to a board certified allergist for diagnostic testing and evaluation for immunotherapy.

IMMUNOTHERAPY

Allergen immunotherapy has been extremely successful in treating patients at risk for insect anaphylaxis. Initially immunotherapy to bees and vespids was performed with whole-body extracts with anecdotal success. In 1978, Hunt et al. discovered that treatment with whole-body extract was no different than placebo but venom immunotherapy reduced systemic reactions to subsequent stings from 58% to 5%.[112] Subsequent studies have shown that venom immunotherapy reduces the risk of systemic reactions to stings to less than 1-2%.[73,113] In contrast to these other Hymenoptera, imported fire ant venom is not commercially available and a whole body extract is the only extract presently available. However, unlike bee and vespid whole-body extracts, fire ant whole body extract contains significant amounts of the relevant allergens. Based on data of the Sol i 3 content, a quality 1:10 wt/vol fire ant whole-body extract has been estimated to contain about 30-45 μg/ml of total antigenic protein and therefore a maintenance dose of immunotherapy of 0.5 cc should deliver 15-22 μg of venom protein.[93] Analyzing data from another study[101] reveals that a conservative estimate based on Sol i 3 content of 56 μg/ml of total protein in a 1:10 wt/vol extract would similarly deliver 28 μg venom protein in a 0.5 cc 1:10 wt/vol maintenance dose. Large worker ants who were hand milked have been shown to contain 0.12 μg venom protein per ant.[82] This is likely larger than a typical sting, since these were larger ants who were milked until no more venom was expressed. This amount of protein is markedly less than found in a typical bee sting which delivers approximately 50 μg protein per sting. Since most patients are stung by an average of eight fire ants per sting episode, and each sting delivers less than 120 ng venom protein, this dose has been estimated to be sufficient for protection.[8]

Immunotherapy using whole-body fire ant extracts has been evaluated in only a few studies, none of which have been placebo controlled. Triplett was the first to report results with immunotherapy using a maintenance dose of 0.5 ml of 1:100 wt/vol and noted a 100% success rate in 18 patients with generalized allergic reactions, 8 of whom were re-stung in the field without reaction.[96] Rhoades et al. reported their experience with 92 patients on fire ant immunotherapy for systemic reactions.[53] The maintenance dosage was variable but was in the range of 0.5 cc of a 1:10-1:50 wt/vol whole-body extract. Nineteen patients were re-stung in the field and about half were re-stung more than once. Two of these 19 patients had systemic reactions while re-stung on immunotherapy. Both patients had been re-stung several times and only on one occasion did they have a recurrence of a generalized reaction. Both of these reactions were mild systemic reactions and one occurred prior to reaching the maintenance dosage. Three other patients have been reported as immunotherapy treatment failures and suffered systemic reactions while on maintenance immunotherapy.[114,115]

	Immunotherapy group	Untreated group
No. of patients	65	11
Age range	2-76 (mean: 37)	23-61 (mean: 42)
Sex (M:F)	22:43	7:4
Initial IFA sting history		
Reaction type		
Generalized cutaneous	24 (37%)	1 (9%)
Generalized life-threatening	41 (63%)	10 (91%)
No. multiple anaphylaxis	9 (14%)	1 (9%)
Study evaluation		
No. without subsequent stings	18	5
No. with repeat stings	47 (112 events)	6 (11 events)
Reaction type*		
Generalized cutaneous	0	2
Generalized life-threatening	1 (2.1%)	4

*p value comparing 1/47 to 6/6 is <0.00001.

Figure 10. Demographics and results of field re-stings in fire ant allergic patients treated with immunotherapy and untreated controls.[116]

Finally, Freeman et al. performed a retrospective study but they used untreated fire ant allergic patients as controls.[116] Sixty-five patients with systemic reactions to fire ants agreed to immunotherapy while 11 patients who refused immunotherapy were used as controls. The untreated group tended to have a higher female to male ratio (2:1 vs. 1:2 in treated group) and a larger percentage had life-threatening reactions (91% vs. 63% in treated group) as opposed to only a generalized cutaneous reaction (Fig. 10). At the time of the review, all of the 65 immunotherapy treated group were on a maintenance dosage of 0.2-0.5 ml of a 1:20-1:100 wt/vol imported fire ant whole-body extract with a total duration of immunotherapy ranging from 6 months to 18 years. Field re-stings were reported in 47 immunotherapy treated patients (112 re-sting episodes) with one patient (2.1%) reporting anaphylaxis. In contrast, 6 of the 11 untreated patients had field re-stings (11 re-sting episodes) and all (100%) had systemic reactions at least once, with 4/6 having anaphylaxis. Lastly, Freeman et al. performed intentional sting-challenges on 30 immunotherapy treated patients and none had systemic reactions. Four untreated patients did not undergo sting challenge since each continued to have substantiated anaphylaxis after field re-stings. Combining these three studies, 3/74 patients (4%) who were treated with fire ant whole-body extract immunotherapy and suffered re-stings while on immunotherapy had systemic reactions and 2/3 were mild. This data does not take into account the fact that many of these patients were repeatedly stung so likely the risk of systemic reaction/sting episode is even lower; 0.9% in Freeman's study. This data is very similar to the data with Hymenoptera venom immunotherapy where the risk of systemic reaction in treated patients who suffer re-stings is about 2% or less.[73,113]

In the absence of placebo controlled studies, the true efficacy of immunotherapy with imported fire ant whole-body extract is unknown. The natural history of imported fire ant sensitivity has not been determined, and therefore one may argue that patients treated with immunotherapy would have become non-reactors overtime. The data by Freeman, while limited to a small number of patients suggest that patients may not lose their sensitivity over time. This data also suggest that the reaction rate in untreated fire ant allergic patients is about 55% which is similar to other Hymenoptera data. Patient selection for fire ant immunotherapy is also not entirely clear. Only

patients with a history of generalized reactions should be considered for immunotherapy. However, immunotherapy may decrease large local reactions as well. Rush immunotherapy to fire ants has recently been shown to reduce the wheal and induration to subsequent intentional fire ant sting by 55% and 76% respectively after 3 months of immunotherapy.[117] In children with generalized cutaneous reactions to stings from bees and vespids, immunotherapy is not indicated since subsequent stings have < 10% systemic reaction and most of these systemic reactions are milder than the initial sting reaction.[118] Whether this is the case for children sensitive to fire ants is unclear. The duration of fire ant immunotherapy is also unclear. A recent position statement from the American Academy of Allergy, Asthma and Immunology recommended that for patients receiving Hymenoptera venom immunotherapy, 3-5 years is usually sufficient but may be continued indefinitely in patients with very severe reactions.[119] Freeman and colleagues have performed sequential intentional fire ant sting challenges in patients after stopping whole-body immunotherapy for 3 months, 18 months, and 5 years. Seventeen patients who had received immunotherapy for a duration of 2-19 years with a mean duration of 7.7 years had intentional fire ant sting challenge at least 3 months after discontinuing therapy.[120] Seventy-seven percent had negative skin tests one year before but at the time of challenge 76% had positive skin tests. Only one patient reacted to the sting challenge with 94% having no reaction. This initial group was again studied after being off immunotherapy for at least 15 months at which time 15 patients were available.[121] At this evaluation, 80% had positive skin tests and 2/15 patients had systemic reactions; both had only mild cutaneous symptoms. For their final re-evaluation, 9 patients were available after being off immunotherapy for approximately 5 years.[122] At this time, 89% had positive skin tests but no patients had reactions to sting challenge. Freeman recommends continuing maintenance immunotherapy for at least 3-5 years.[123]

Reed and Butcher evaluated the utility of measuring fire ant specific IgG and IgG_4 levels in patients on immunotherapy.[124] Their study revealed that fire ant venom IgG or IgG4 was no different in immunotherapy treated versus untreated patients with reactions ranging from large locals to systemic reactions. Just as in other Hymenoptera allergy,[125,126] measurement of specific IgG has little role in determining response to immunotherapy.

In view of all the uncertainties surrounding fire ant immunotherapy, a recent survey of 329 allergists in Southern states was performed to determine how fire ant allergy is managed by practicing allergists.[127] Ninety-seven percent of respondents used immunotherapy to treat fire ant allergy. A wide range of maintenance doses were reported but the median dose was 0.5 ml of a 1:100 wt/vol extract. Nineteen percent of respondents reported at least one case of a treatment failure suffering cutaneous or more severe reactions while on maintenance immunotherapy. Based on clinical experience, most authorities consider a maintenance dose of 0.5 ml of a 1:100 wt/vol to be protective for most patients.[8] This dosage would contain venom protein equivalent to at least 12-18 stings. However since fire ant whole-body extracts are not standardized to a specific amount of venom protein and there is variability in the protein content in commercial extracts, I prefer to treat patients with the highest tolerated dose which is usually between 0.1-0.5 cc of a 1:10 wt/vol extract.

Although the precise duration and dosage of venom immunotherapy required for protection from sting reactions has not been established, reaching a maintenance dosage is a reasonable endpoint to achieve protection. Using conventional immunotherapy schedules with weekly injections, a maintenance dosage is often not reached for at least 6 months during which time the

patient is vulnerable. The development of rapid (rush) immunotherapy protocols allows patients to be rapidly desensitized to a cumulative protective dosage in a period as short as 90 minutes![128] Rush immunotherapy to imported fire ants has also been reported using protocols as rapid as 1-3 days.[129-132] Parker et al. have reported their experience with 67 patients undergoing rush immunotherapy and have found that a 2-3 day protocol is associated with a markedly lower incidence of systemic reactions than a 1 day protocol (4-5% vs. 50%). A very similar reaction rate was observed by Tankersley et al. in their recent report on a 2 day rush immunotherapy protocol with 42 patients.[132] Premedication with prednisone, H_1 and H_2-antagonists has also been shown to reduce systemic reactions in rush immunotherapy to aeroallergens in children.[133] My own experience with rush immunotherapy to fire ants using premedication is that it is very well tolerated by patients with primarily cutaneous reactions only and can successfully achieve a maintenance dosage in 2 days. Anecdotally I have had more systemic reactions in patients receiving rush immunotherapy to aeroallergens for rhinitis and asthma than to rush fire ant immunotherapy for anaphylaxis.

I should also note that immunotherapy with ant venom has been used in rheumatoid arthritis. Based on the anecdotal observations of a Bolivian patient as well as some South American rheumatologists a double-blind study using venom from the ant *Pseudomyrmex sp.* was conducted and found to improve some parameters including the number of swollen joints and the swollen joint index.[134] Little is known about the venom constituents of this ant species but some studies by these same authors indicate potent in vivo anticomplementary activity.

PREVENTIVE MEASURES

A few practical measures to avoid fire ant stings should be recommended to fire ant allergic patients:[8]

1) Avoid going outdoors barefoot or wearing sandals.

2) Wear gloves and protective footwear while gardening.

3) Wear long sleeves when landscaping.

4) Do not intentionally disturb fire ant mounds.

5) Be cautious in picnic areas, along roadsides, near refuse containers and when hiking.

6) Treat home areas with bait insecticides to kill active mounds and prevent development of new mounds.

FIRE ANT CONTROL MEASURES

Many methods have been tried to control imported fire ants, but no method has been successful in permanently eliminating ants from an area. The control of an ant colony ultimately depends on killing the queen. A worker population can be nearly decimated but the colony will survive and multiply if the queen lives. If foraging ants are killed too quickly by a compound, before they can bring the toxic bait back to the colony, this method will also fail. A variety of factors can

influence treatment efficacy including soil type, soil moisture content, temperature, mound height and shape, and the percentage of worker ants away from the nest at the time of treatment.[30] Imported fire ants construct the largest mounds when the soil is wet and/or cool. During hot, dry weather the ants move deeper into the soil to obtain a favorable temperature and moisture environment and thus making it more difficult to contact the workers and queen.

In the 1950's and early 1960's, treatments with residual or contact insecticides such as chlordane, heptachlor, and dieldrin were extensively used to control imported fire ants.[30] Between 1957-1962, thousands of acres were treated resulting in numerous reports of adverse environmental effects to a variety of organisms. In the early 1960's, mirex was developed by the USDA and hailed as a means to control fire ants over large areas of land with minimal environmental effects.[135] Mirex consisted of a granular carrier (corncob grits) onto which a food attractant (soybean oil) containing the toxicant was absorbed. The bait was applied with ground or aerial equipment, usually at the rate of 1.25 lb/acre.[30] The lack of a chemical residue allowed fire ants to reinfest treated areas requiring repeated applications. Between 1967-1975, over 45 million hectares were treated.[7] It soon became apparent that mirex biodegraded very slowly in the environment and this led to a court injunction in 1970 filed by the Environmental Defense Fund and the Committee for Leaving the Environment of America Natural (CLEAN).[7] This injunction was denied in 1971,[136] but was followed by public hearings called by the newly formed EPA. Allied Chemical Corporation eventually decided to discontinue the formulation of mirex. A study of adipose tissue from cadavers and surgical patients estimated that 10.2% of the southern U.S. population had detectable mirex levels but the clinical significance of these levels was unknown.[137] In 1978, mirex bait registrations were canceled by the EPA. In the mid-1970's the EPA again began an accelerated search for delayed-action toxicants to replace mirex. The first agent that proved to be very effective against imported fire ants was an amidinohydrazone that was eventually formulated with soybean oil and corn pellet bait under the trade name of Amdro.[30]

Four strategies are currently used to control fire ants: 1) broadcast bait applications, 2) individual mound treatments, 3) combination of broadcast baiting and individual mound treatments, and 4) barrier and spot treatments.[41] Broadcast baits apply insecticides incorporated into an attractant or bait. Most bait products contain slow acting toxicants (e.g., hydromethylnon, abamectin, and fenoxycarb) dissolved in soybean oil, a preferred food source for ants, that is then absorbed into corn grits. A broadcast application eliminates the need to find mounds and relies on foraging ants to bring back the toxin to the rest of the colony and the queen, which when fed either dies or is unable to reproduce, killing the colony. Broadcast baiting is less labor intensive than individual mound treatment and is less expensive per acre. Disadvantages of bait applications include: lack of specificity for fire ants; baits dissolve when in contact with water and are then irretrievable by foraging ants; retrieval of baits is temperature dependent (70-95°F optimal soil surface temperature for foraging); and baits are slow-acting taking between 2-10 weeks depending on the type of insecticide. Individual mound treatment may eliminate colonies quicker than via broadcast treatments but all queens must be killed and it requires the identification of all mounds individually. Both chemical and nonchemical methods have been employed for individual mound treatment. Chemical methods include insecticides formulated as baits, drenches, granules, dusts, aerosols or liquid fumigants. Contact insecticides are not effective for large-scale control, are not specific for fire ants and rapid reinfestation is common after use.[18] Care must be taken to avoid disturbing the mound, since the colony may be alerted and take the queen deeper into the mound beyond the reach

of the toxin. While effective, some of these products, especially fumigants and injectants are dangerous if not handled properly. Nonchemical methods include applying boiling water, burning the nest with flammables such as gasoline and physically excavating the nest. The combination of the two strategies uses the efficiency of broadcast baiting and the rapid action of individual mound treatment and is the recommended approach to control fire ants outdoors. Baits should be broadcast first to reduce the number of colonies and then several days should be allowed for the foraging ants to bring the bait back to the colonies prior to individual mound treatment. Fall applications of bait work best. I have included as a supplement to my protocol, "The Texas Two-step Method" which has been advocated by the Texas Imported Fire Ant Research & Management Plan as the recommended method for fire ant control for homeowners and provides excellent tips on bait and individual mound treatment. Finally, barrier and spot treatments contain active ingredients such as acephate, bendiocarb, carbaryl, chlorpyrifos, diazinon, isofenphos, propoxur, permethrin and resmethrin that kill ants on contact.[41] These products are usually sold as sprays or dusts and are applied around building foundations and equipment to create a barrier to ants but will not eliminate colonies.

Common insecticides for fire ant control

Trade Name	Pesticide	Control
	Baits	
Amdro®, Combat®	hydramethylnon	moderate-slow
Raid®, Ascend®	abamectin	moderate-slow
Award®, Logic®	fenoxycarb	slow
Distance®	pyriproxyfen	slow
Extinguish™	methoprene	slow
	Mound Treatments*	
Insecto Formula 7®	pine oil suspensions	slow
Diazinon	diazinon	fast
Dursban®	chlorpyrifos	fast
Organics Solutions®, etc.	pyrethrins	immediate
Orthene® Fire Ant Killer	acephate	moderate
Spectracide® Bug Stop	permethrin	fast
Sevin®	carbaryl	moderate
Bonide Rotenone 5	rotenone	slow

*Baits containing hydramethylnon and abamectin also can be used as mound treatments.

Current research on fire ant control is being aimed at biological control measures. Populations of imported fire ants in the U.S. appear to be free of pathogens.[138] In South America, a few pathogens have been isolated from native fire ants including microsporidia, and a neogregarine species but the importance of these organisms on limiting fire ant populations is unknown.[30] *Thelohania solenopsae* is a protozoan (microsporidium) pathogen that is an obligate intracellular pathogen of fire ants in South America and infects the fat body of workers, males, and queens.[139] Workers transmit the pathogen to the queen through food exchange and she consequently lays fewer eggs which are all infected. Preliminary field studies on *S. richteri* in Argentina indicated that decreasing mound volume and sexual broods was associated with an increasing presence of this pathogen.[140] *Thelohania solenopsae* is currently being studied at imported fire ant test sites in Florida, Arkansas, Oklahoma, Louisiana, South Carolina and Tennessee. Three groups of parasitic arthropods affect South American fire ants. *Solenopsis daguerri* is a workerless social parasitic ant

that has been found in association with *S. richteri* in Uruguay.[30] The queens "yoke" themselves to the fire ant queen permanently by grasping her between the head and thorax and fire ant workers then care for the parasitic queen and her progeny preferentially. These parasitic ants are usually found in only 4% of colonies in Uruguay and have not been found in association with *S. invicta*. Euchartid wasps have also been associated with fire ants but their influence on population control is unknown. Recent attention has focused on the third type of arthropod parasite, the phorid fly. At least 18 species of *Pseudoacteon* phorid parasitoids attack fire ant species, many are host-specific and appear to have different daily activity patterns.[141,142] The phorid fly lays its eggs inside the heads of worker ants. The developing larva feeds on tissues in the host-ant's head and brain. After 3 weeks, the ant's head falls off and the adult fly emerges from it a few weeks later.[143] Although only a small percentage of worker ants from a colony are parasitized, the flies can have a dramatic effect on behavior of the whole colony. Phorid flies hover less than a centimeter in front of an ant and to oviposit, turn 180°, dart quickly down and insert the ovipositor in the foramen behind the ant's head. In response to the phorid flies, ants hide, assume defensive postures or are chased up to a meter from the foraging trail thus significantly affecting behavior and reducing competitive dominance with other ant species.[142] Phorid flies in Texas have been observed to prevent foraging behavior in the native fire ant, *S. geminata*, but imported fire ants in the U.S. are free of native phorid parasites.[144] Phorid flies are currently being studied as a natural defense against imported fire ants in Texas and Florida. Studies in Central Texas using *Pyemotes tritici*, the straw itch mite, proved it to be an ineffective biological control agent.[145] *Beauvaria bassiana* is a genetically engineered fungus being studied as another biological control agent for fire ants. Other research strategies are aimed at identifying pheromones and attempting to manipulate the natural behavior of ants such as influencing worker ants to "defend" the colony by destroying the queens.

UNANSWERED QUESTIONS

Although significant knowledge has been acquired in the field of fire ant allergy, many important questions remain including:

1) What is the natural history of fire ant allergy?

2) Do patients with large local reactions have an increased risk of subsequent systemic reactions?

3) What is the prognostic significance of having fire ant specific IgE?

4) Are patients with cutaneous only reactions at significant risk of more severe reactions with future stings?

5) What is the true efficacy of fire ant immunotherapy with whole-body extracts?

6) Will fire ant venom be commercially available for testing and immunotherapy?

7) Will fire ant venom immunotherapy be more effective than whole-body extract therapy?

8) What is the optimum dosage and duration of fire ant immunotherapy?

9) How far will the imported fire ant spread?

CONCLUSIONS

The imported fire ant has become an established pest in the Southern U.S. and is expected to spread even further in the coming years. The future of hybrid fire ants is unknown but they are expected to be able to spread further north due to their increased cold tolerance. Since imported fire ants have spread to Puerto Rico and *S. geminata* to Guam, there is speculation that they may spread into southern and temperate Europe where other Solenopsis species currently live.[18] Eradication efforts have not been effective at preventing the relentless march of these ants. Clearly, further research is needed to help control these predators. With their continued spread, more people will become exposed and suffer medical consequences from fire ant stings, including life-threatening allergic reactions. While significant knowledge has been attained in the field of fire ant allergy, large gaps exist especially in regards to immunotherapy. While the prospect of commercially available fire ant venom for diagnosis and treatment is appealing, the limited market demand may prevent the availability of fire ant venom. Patients with a history of systemic reactions to fire ant stings should still be referred to a board-certified allergist for testing and potential treatment with whole-body extracts. Finally, it is worth remembering that a fire ant's sting is much worse than her bite!

Queen Invicta
(Fire Ant Invincible)
Lyrics by Bill Oliver

She stepped off of the boat in Mobile, Alabama
Sometime back in the thirties from her home in deep Brazil
She had six legs and a stinger, fire in her eyes
And the ability to recreate herself a billion times

She didn't plan to come here, to become chaotic
Imported and exotic, she came against her will
She stalked the Southern states, from Florida to Texas
Gained a reputation as the Queen Ant of the Hill

And they call her Queen Invicta
Fire Ant Invincible
Nothing here could stop her
Predator or chemical

The horror stories then grew, like nutria and kudzu
Nobody knew what to do, to stop the fiery tide
And they sprayed the land with chlordane
They sprayed the land with Heptachlor
They sprayed the land with Mirex, but the ant refused to die

Puzzled entomologists, chemists and biologists
Bureaucrat apologists still wondered what to do
For climbing up the food chain, came Heptachlor and chlordane
The fire ants would remain, the chemicals would, too

Refrain

Pesticides persistent, created ants resistant
Eliminated natural foes, going about their business
The cure employed to hit them became worse than the symptom
The efforts to eradicate threatened the whole system

So they banned the searing spray, and they banned the deadly dust
Before they bring the Silent Spring springing up on us
This much we can say, the ant is here to stay
The final bill of over-kill is much to high to pay

Refrain

You who live in cities, cultivated neighborhoods
Fire ants, it's understood, may come and take their stand
The males that die in nuptials, the queens that come in multiples,
The fire ant, combustible, is hard to understand

In backyards it's no picnic, but think before you panic
This isn't the Titanic: don't give up the land

The poison preparations, blind exterminations
Research the implications, analyze your goal
Reactions based on bedlam may only serve to spread them
To some extent accept them, search for safe control

They call her Queen Invicta
Fire Ant Invincible
In our quest to stop her
Let us first be sensible

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Texas Agricultural Extension Service
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The Texas Two-step Method:

Do-it-yourself Fire Ant Control for Homes & Neighborhoods

Texas Imported Fire Ant Research & Management Plan

Texas Agricultural Extension Service
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Good news! Fire ants can be controlled with persistence, patience and the right plan. The Texas Two-step Method gives excellent control of fire ants with less cost and bother than other methods. Just as important, it's safe and easy to do. Two-step pesticides can be found in any nursery, garden center or hardware store. When properly applied, this method causes little risk to people, pets or the environment.

Let Them Eat Bait

The first step is to broadcast a fire ant bait—a product containing a food plus an insecticide—over the whole yard. When collected by worker ants, bait particles are carried back to the colony and shared with the queen and other ants. Less pesticide is needed with baits, because this kind of delivery is so efficient.

Baits work best when scattered lightly over the whole yard. Hand-held seed spreaders are ideal for applying fire ant baits. The Cyclone Seed Sower® and the Ortho Whirlybird® are typical units. Set the spreader on the smallest opening and make one pass over the area to be treated. This should apply the recommended rate (1 to $1^1/_2$ pounds per acre for most products). Push-type fertilizer spreaders put out baits too quickly.

Be patient. Baits work slowly. Products containing hydramethylnon work the fastest, controlling ants within 2 to 6 weeks. Insect growth regulator baits (like fenoxycarb, pyriproxifen and methoprene) usually require 8 to 10 weeks. The advantage of growth regulators is that they need to be reapplied less often when treating areas larger than an acre.

Apply baits at the right time. Baits are effective only when fire ants are actively searching for food. Ants remove baits from the soil surface within a few hours if baits are applied during peak foraging times. Fire ants forage when the soil surface temperature is between 70 and 95 degrees F, May to September, in most of Texas. Fall applications work well to reduce fire ant numbers the following spring. During winter, fire ants forage little and rarely pick up baits.

Use a hand-held seed spreader to apply fire ant bait.

Common insecticides for fire ant control

Trade Name	Pesticide	Control
	Baits	
Amdro®, Combat®	hydramethylnon	moderate-slow
Raid®, Ascend®	abamectin	moderate-slow
Award®, Logic®	fenoxycarb	slow
Distance®	pyriproxyfen	slow
Extinguish™	methoprene	slow
	Mound Treatments*	
Insecto Formula 7®	pine oil suspensions	slow
Diazinon	diazinon	fast
Dursban®	chlorpyrifos	fast
Organics Solutions®, etc.	pyrethrins	immediate
Orthene® Fire Ant Killer	acephate	moderate
Spectracide® Bug Stop	permethrin	fast
Sevin®	carbaryl	moderate
Bonide Rotenone 5	rotenone	slow

*Baits containing hydramethylnon and abamectin also can be used as mound treatments.

Getting the most from baits

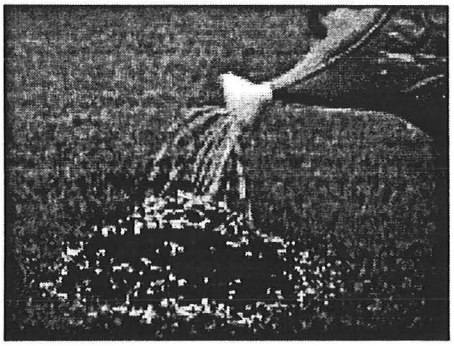
- Apply baits when ants are foraging. To see if ants are active, place a small amount of suitable food (hot dog or potato chip) next to a mound. If ants begin removing the food within 30 minutes, it's a good time to treat.
- In summer, apply baits in the evening. During the cool of evening, ants will quickly discover and carry off baits. If applied during the day, in extreme heat, baits quickly lose their effectiveness. Also, ants do not forage during the day.
- Use only fresh bait, preferably from an unopened container. Once opened, baits should be used quickly. Opened containers may last only a few weeks. Unopened containers stay fresh for up to 2 years.
- Test baits for freshness before using. Sprinkle a small amount next to an active mound. If the bait is fresh, ants will begin removing it within 30 minutes.
- Apply baits when no rain is expected for at least 8 hours. This reduces the risk of their being washed away.

Treat the Mounds

The second step is to treat problem ant colonies—those needing immediate attention—using a mound treatment. Mound treatment is a way of destroying one colony at a time. It is the fastest way to get rid of individual colonies. It's not necessary to treat all fire ant colonies with mound treatments after applying a bait. Limit *Step Two* treatments to mounds located next to house foundations, in high-traffic areas or other trouble spots.

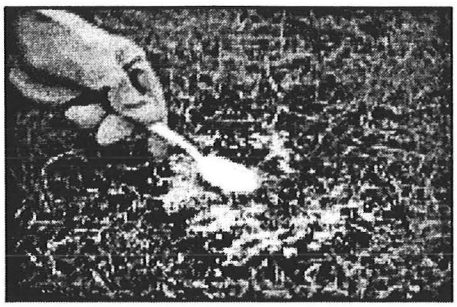
Options

- *Granular products* contain an insecticide that releases into the soil, usually when drenched with water. Sprinkle the recommended amount of product around and on top of the mound. When directed on the label, sprinkle 1 to 2 gallons of water over the granules with a watering can. Sprinkle gently to avoid disturbing the colony and washing the granules off the mound.



Most granular products contain an insecticide that releases into the soil when drenched with water.

- *Liquid drenches* are pesticides mixed with water first and then applied directly to the mound. As with granules, 1 to 2 gallons of water is needed per nest. Always wear chemical resistant, unlined gloves to protect your skin when handling liquid concentrates, and follow label safety directions.
- *Acephate* (Orthene®) is an effective dry dust treatment that does not require added water. Sprinkle lightly and evenly over the entire mound. Avoid disturbing the colony during application. This can cause the ants to vacate a mound. It's best to keep pets away from treated mounds until the dust is gone.



Dry dusts are convenient and easy to apply.

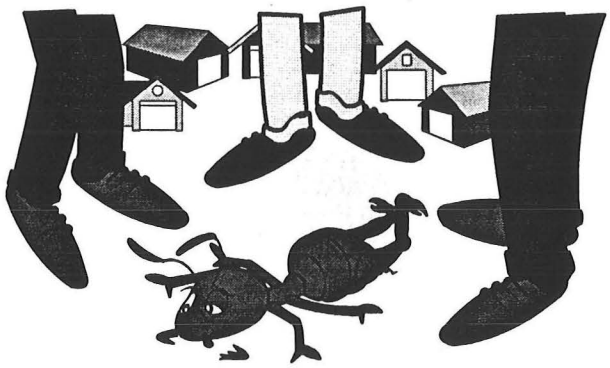
- *Baits* are slower than most other mound treatments, but they can be used for treating colonies next to sidewalks and curbs. Nests in such sites often extend under the concrete, making them difficult to treat with other methods.
- Several *"organic"* or *plant-derived* products will control fire ants. Products containing pyrethrins (e.g., Organics Solutions™ Fire Ant Control) are effective and fast-acting. They should be mixed with water and poured on the mound. Organic products may cost more and act more slowly than conventional pesticides.
- *Boiling water* (about 3 gallons per mound) also can eliminate fire ant colonies. However, this method can be hazardous to the person carrying the hot water. Boiling water poured on grass or over plant roots also can be lethal to the plants.
- *Shoveling* can be used to disturb or move unwanted fire ant colonies from gardens, compost piles and other sensitive sites. Wear rubber gloves and liberally dust your gloves and a shovel with talcum powder. Talcum powder creates a slippery surface that ants cannot climb. Captured colonies can be dispatched by carefully dousing with soapy water.

Have a Fire Ant Block Party!

Consider the Two-step Method as a reason for a block party. By joining with neighbors, you may reduce your costs, improve control and have fun at the same time! There is less chance for re-infestation if adjoining yards are treated. That means fewer treatments.

If you and your neighbors prefer not to apply pesticides yourselves, or want to ensure that treatments are applied uniformly and on time, consider a professional pest control company. Some companies even may offer discounts to households in neighborhood treatment programs.

For more information on how to organize your own neighborhood block party, visit the fire ant Website at http://fireant.tamu.edu or check with your county Extension office. Other insect information is available on the Web at http://entowww.tamu.edu and http://agcomwww.tamu.edu.



The information herein is for educational purposes only. Reference to commercial products or trade names is made with the understanding that no discrimination is intended and no endorsement by the Texas Agricultural Extension Service is implied.

Respect Our Environment!

- **Never use gasoline or other petroleum products for fire ant control!** Although gasoline kills fire ants, it is extremely flammable and dangerous—both to you and to the environment.
- **Don't leave insecticide granules on streets** or sidewalks after application, as these will wash into storm sewers.
- **Follow label directions** when disposing of extra pesticides and containers. Never pour leftovers down the drain. This can contaminate streams and can endanger aquatic life. Use all insecticides before discarding the containers.

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