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Next in the line of key historical articles of scientific impact in the medical literature is the paper on "Systemic Reactions to Stinging Ants" by Richard F. Lockey, MD, Distinguished University Health Professor, and Director, Division of Allergy and Immuology.

From Richard F. Lockey, MD

The "Systemic Reactions to Stinging Ants" paper was first sent to the *Journal of the American Medical Association*. It was rejected because "it was too regional". At that time, and even possibly to this day, there may have been prejudice against the South. Next, it was accepted by the *JACI* and was the first of its kind to nationally address systemic allergic reactions to stinging ants. Of interest is that I utilized the term "systemic allergic reaction" rather than "anaphylaxis", as it should be, since most of these patients did not have hypertension or trouble breathing secondary to their fire ant stings. Three ant species, *Solenopsis invicta*, *Solenopsis xyloni*, and *Pogonomyrmex barbatus* were involved in these reactions. Today, the main insect which stings individuals is the imported fire ant, *Solenopsis invicta*, which occupies the territory south of Delaware and extends to California. This paper triggered interest in fire hypersensitivity resulting eventually in *Solenopsis invicta* (imported fire ant) whole-bodied extract immunotherapy.

With warm regards,

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Systemic reactions to stinging ants*

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Four patients are described in whom immediate-type systemic allergic reactions occurred following stings by three different ant species. The reactions included diffuse urticaria, angioedema, dyspnea, wheezing, cough, and lightheadedness. The ant involved in each case was identified by an entomologist. The ant-hypersensitive patients were skin-tested and the results compared to two control groups: persons hypersensitive to honeybees, wasps, hornets, and yellow jackets; and normal nonatopic subjects. The three ant species responsible were Solenopsis invicta *Buren (imported fire ant),* S. xyloni *McCook (southern fire ant), and* Pogonomyrmex barbatus *F. Smith, (red harvester ant). The medical and ant entomology literature is reviewed in an area of insect hypersensitivity, which will undoubtedly command more widespread attention as the imported fire ant spreads its already extensive boundaries.*

Systemic allergic reactions from insect stings of the order Hymenoptera, contained in the superfamilies Apoidea (bees), Vespoidea (wasps, hornets, and yellow jackets), and Sphecoidea (solitary wasps) are common and have been widely publicized in the medical literature.[1-3] However, identical reactions secondary to ants (order Hymenoptera, superfamily Formicoidea) are less well known. Of the many separate species of ants in the world, the imported fire ant has most often been implicated as the cause of hypersensitivity reactions secondary to ant stings.[3-11] In most cases, documentation of the responsible insect is inadequate, i.e., based only on clinical history and clinical findings and not on identification of the offending insect. With few exceptions, documented deaths, the nature of the reaction, skin test results, results of treatment, and the natural course without treatment are equally unsubstantiated. Equally important is whether or not various species of ants are capable of hypersensitizing individuals, if cross-sensitivity occurs among the different species of ants, and if cross-sensitivity can occur in patients sensitized to other members of the order Hymenoptera. This paper describes four patients in whom systemic allergic reaction occurred secondary to stings by three species of ants, one case of which may have cross-sensitivity between wasps and the imported fire ant.

TERMINOLOGY

Most medical literature written on reactions to ant stings pertains to the imported fire ant. In previous medical literature, the imported fire ant in the

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United States was referred to as one species, *S. saevissima richteri* F. Smith. Two species have subsequently been separated, *S. invicta* Buren, and *S. richteri* Forel.[12]

Since there is no known important medical difference between the two species, the term *imported fire ant* used alone refers to either of the separate species. The imported fire ant species responsible for the systemic allergic reaction in this paper was identified as *S. invicta* Buren.

MATERIALS AND METHODS

Scratch and intradermal skin tests were performed using techniques described previously.[13] Commercial extracts used included *S. richteri* (imported fire ant), *P. rugosus* (red ant), yellow jacket, honeybee, wasp, hornet, and mixed stinging insect extract consisting of equal parts of the following species (honeybee [*Apis mellifera*]; yellow jacket [*Vespula pennsylvanica*]; wasp [*Polistes exclamans* and *P. annularis*]; yellow hornet [*Dolichovespula arenaria*]; black hornet [*D. maculata*]). The identity of the ant specimens collected for the commercial laboratory that supplied the extract were confirmed by an entomologist.[14] Scratch dilutions of $1:10^8$ to $1:10^7$ were used for all extracts. If no skin reactivity greater than 2+ occurred within 20 minutes, intracutaneous tests were applied in sequence, i.e., $1:10^8$ to $1:10^2$ for wasp, hornet, yellow jacket, honeybee, and mixed extract and 0.0005 protein nitrogen units (PNU) to 500 PNU for the ant species.

Scratch and intracutaneous controls were applied in all cases. Since some medications can interfere with skin tests up to 4 days, patients were required not to take medication one week prior to testing and patients were not tested within one month of their insect reaction.[15]

Seven control subjects, 5 male and 2 female, without a history of atopy, insect hypersensitivity, but all of whom had been stung without systemic allergic reaction by a wasp, yellow jacket, hornet, or honeybee and some of whom had been stung by ants, were skin-tested with all extracts (Table I). None of the controls had been stung during the previous 12 months. Three out of 7 reacted to the ant antigens; they had 2+ skin reactivity to the 50 PNU or 500 PNU strength. In addition, 5 out of 7 had 2+ or 3+ skin reactivity to $1:10^3$ to $1:10^2$ individual and mixed stinging insect extracts, and 2 were unreactive. Six patients, 5 male and one female, who had mild to very severe systemic reactions to a wasp, yellow jacket, hornet, or honeybee sting were skin-tested to all extracts within 3 months after the reaction occurred (Table II). One of the 6 had an atopic history, and all had been stung without consequence prior to the systemic reaction. All reacted 2+ or greater to intradermal individual or mixed Hymenoptera extract from $1:10^5$ to $1:10^2$ dilution. All but one reacted 2+ or greater to 0.0005 to 500 PNU of the ant antigen injected intradermally.

Ant specimens from the area where the stings occurred were brought to the Allergy Clinic at Carswell Air Force Base Hospital by the patients. They were examined by an entomologist of the United States Department of Agriculture Plant Protection Agency of Texas. Field identification surveys by the Animal and Plant Health Inspection Service, Plant Protection and Quarantine Program, United States Department of Agriculture of Texas, were made to confirm the presence of the species in the area in which the stings took place.

CASE REPORTS

Case 1

W. F., a 35-year-old white man, was stung on the foot by a single ant in his backyard. A 1 cm. wheal with erythema rapidly formed at the site of the sting. Approximately 20 minutes later, he noted the onset of generalized pruritis, urticaria, a swelling sensation in his upper airway passage, and mild wheezing. He took diphenhydramine 50 mg. by mouth, and within 20 to 30 minutes his symptoms began to resolve. Within 24 hours, a small pustule developed at the site of the sting. Extensive investigation was not carried

TABLE I. Controls. Summarized data and skin test results of persons reacting normally to

Initials	Age	Sex	History of sting by honeybee, wasp, yellow jacket, hornet	History of sting by ant	History of hypersensitivity	History of atopy
L. B.	42	Male	Yes	Yes	No	No
R. L.	32	Male	Yes	No	No	No
R. F.	25	Male	Yes	Yes	No	No
K. D.	20	Male	Yes	Yes	No	No
J. J.	37	Male	Yes	Yes	No	No
J. T.	23	Female	Yes	?	No	No
M. T.	27	Female	Yes	Yes	No	No

TABLE II. Summarized data and skin test results of persons hypersensitive to wasp, yellow

Initials	Age	Sex	History of allergy	Insect	Ant sting	Severity of reaction	Hypo-sensitiza-tion
B. A.	8	Male	0	?	Yes	Moderate-ly severe, general	Yes
W. W.	18	Male	0	Yellow jacket	Yes	Very severe, general	Yes
G. R.	42	Male	0	Honeybee	Yes	Mild general reaction	Yes
O. S.*	5	Male	0	Wasp	No	Moderate-ly severe, general	Yes
S. H.	14	Male	Asthma, no wheez-ing for 2 yr. prior to episode	Yellow jacket	No	Very severe, general	Yes
K. B.	12	Female	0	?	No	Very severe, general	Yes

*Complete tests not done.

Hymenoptera stings

Honeybee	Wasp	Yellow jacket	Hornet	Mixed stinging insect	Imported fire ant	Red ant
I.D. $1:10^2$ Neg.	I.D. $1:10^2$ Neg.	I.D. $1:10^2$ Neg.	I.D. $1:10^2$ Neg.	I.D. $1:10^2$ Neg.	I.D. 500 PNU Neg.	I.D. 500 PNU Neg.
I.D. $1:10^2$ Neg	I.D. $1:10^2$ Neg.	I.D. $1:10^2$ Neg.	I.D. $1:10^2$ Neg.	I.D. $1:10^2$ Neg.	I.D. 500 PNU Neg.	I.D. 500 PNU Neg.
I.D. $1:10^2$ 2+	I.D. $1:10^2$ 2+	I.D. $1:10^2$ 2+	I.D. $1:10^2$ 2+	I.D. $1:10^2$ 2+	I.D. 500 PNU 2+	I.D. 500 PNU 2+
I.D. $1:10^3$ 2+	I.D. $1:10^3$ 2+	I.D. $1:10^3$ 2+	I.D. $1:10^3$ 2+	I.D. $1:10^3$ 2+	I.D. 50 PNU 2+	I.D. 50 PNU 2+
I.D. $1:10^2$ 3+	I.D. $1:10^2$ 3+	I.D. $1:10^2$ 3+	I.D. $1:10^2$ 3+	I.D. $1:10^2$ 3+	I.D. 500 PNU Neg.	I.D. 500 PNU Neg.
I.D. $1:10^2$ 2+	I.D. $1:10^2$ 2+	I.D. $1:10^2$ 2+	I.D. $1:10^2$ 2+	I.D. $1:10^2$ 2+	I.D. 500 PNU Neg.	I.D. 500 PNU Neg.
I.D. $1:10^3$ 3+	I.D. $1:10^3$ 2+	I.D. $1:10^3$ 2+	I.D. $1:10^3$ 2+	I.D. $1:10^3$ 2+	I.D. 50 PNU 2+	I.D. 50 PNU 2+

jacket, hornet, or honeybee but not sensitive to ants

Honeybee	Wasp	Yellow jacket	Hornet	Mixed stinging insects	Fire ant	Red ant
I.D. $1:10^3$ 4+	I.D. $1:10^3$ 2+	I.D. $1:10^3$ 3+	I.D. $1:10^3$ 2+	I.D. $1:10^3$ 3+	I.D. 0.5 PNU 3+	I.D. 0.5 PNU 4+
I.D. $1:10^4$ 2+	I.D. $1:10^4$ 2+	I.D. $1:10^4$ 2+	I.D. $1:10^4$ 2+	I.D. $1:10^4$ 2+	I.D. 0.5 PNU 2+	I.D. 0.5 PNU 2+
I.D. $1:10^2$ 3+	I.D. $1:10^2$ 2+	I.D. $1:10^2$ 2+	I.D. $1:10^2$ 2+	I.D. $1:10^2$ 4+	I.D. 500 PNU 3+	I.D. 500 PNU 2+
I.D.* Neg. to $1:10^5$	I.D.* Neg. to $1:10^5$	I.D.* Neg. to $1:10^5$	I.D.* Neg. to 1:100	I.D. 2+ 1:100	I.D. 50 PNU 3+	I.D. 50 PNU 3+
I.D. 2+ $1:10^2$	I.D. 0 $1:10^2$	I.D. 2+ $1:10^2$	I.D. 2+ $1:10^2$	I.D. 2+ $1:10^2$	I.D. 500 PNU 0	I.D. 500 PNU 0
I.D. 2+ $1:10^4$	I.D. 2+ $1:10^4$	2+ $1:10^4$	I.D. 2+ $1:10^4$	I.D. 2+ $1:10^4$	I.D. 0.0005 PNU 3+	I.D. 0.005 PNU 3+

TABLE III. Summary—skin test results of ant-hypersensitivity case reports

Initials	Age	Sex	History of bee sting, etc.	History of ant sting	Atopy history	Ant responsible	Severity ant reaction
W. F.	35	Male	Yes	Yes	Yes	*S. invicta* Buren	Moderately severe
F. B.	14	Male	Yes	Yes	No	*S. invicta* Buren	Moderately severe
J. M.	4	Male	Yes	No	Yes	*S. xyloni*	Moderately severe
D. W.	9	Female	No	No	Yes	*P. rugosus*	Moderately severe

out until one year later, at which time the ants were identified as *S. invicta* (imported fire ant). A field trip confirmed the presence of this ant species.

Fifteen years prior to this episode, he was stung by a "red wasp," following which he developed generalized urticaria, pruritus, severe wheezing, dyspnea, lightheadedness, and was told by a friend that he was "blue." Subsequent stings by "bees" on at least two occasions resulted in severe local reactions. Previous ant stings, some of which could have involved the imported fire ant, were innocuous.

Since the above-mentioned ant sting, he has been stung by ants on three separate occasions without consequence. Two out of the three areas in which these stings occurred were areas in which *S. invicta* has not been reported. In none of these cases did the characteristic pustule of the imported fire ant appear at the site of the sting. He had a history of allergic rhinitis. A complete examination was normal. Skin test results are summarized in Table III. He was not tested with *P. rugosus* antigen.

He was started on 100 per cent stinging insect extract (equal parts of honeybee, wasp, yellow jacket, and hornet) and 100% ant extract (equal parts of *S. richteri* and *P. rugosus*).

Case 2

F. B. is a 14-year-old Mexican-American young man who was stung on the face and foot by approximately 20 ants. He experienced severe facial swelling, generalized urticaria, pruritus, nausea, wheezing, and shortness of breath within 30 or 40 minutes. He was treated with diphenhydramine 50 mg. intramuscularly and recovered without further sequelae. The following day, he had diffuse swelling of his lips, face, and left foot with approximately 20 discrete pustules scattered over these areas. There was no history of atopy. The physical examination was otherwise unremarkable. Previous stings by other Hymenoptera were unremarkable. Photographs of the ant identified it as belonging to the same genus as *S. invicta*, but could not confirm the exact species. A field trip one year later confirmed the presence of *S. invicta*. Skin test results are summarized in Table III. He was placed on 100 per cent imported fire ant extract.

Case 3

J. M. is a 4-year-old white male patient who was stung on his right foot by several ants. Within 10 minutes, he developed diffuse urticaria and pruritus with severe, continuous coughing. His mother noted no wheezing or dyspnea. He was treated within an hour with diphenhydramine 50 mg. intramuscularly. The generalized urticaria persisted unchanged for 24 hours, after which it gradually resolved. The right foot became severely swollen; however, discrete pustules were not noted by the mother. There was no known

H. B.	Wasp	Yellow jacket	Hornet	Mix	F. A.	R. A.
I.D. $1:10^7$ 3+	I.D. $1:10^7$ 2+	I.D. $1:10^7$ 1+	I.D. $1:10^7$ 1+	I.D. $1:10^7$ 2+	I.D. 0.05 PNU 2+	Not done
I.D. $1:10^4$ 2+	I.D. $1:10^4$ 2+	I.D. $1:10^4$ 3+	I.D. $1:10^4$ 2+	I.D. $1:10^4$ 3+	I.D. 0.005 PNU 2+	I.D. 0.005 PNU 2+
Not done	Not done	Not done	Not done	I.D. $1:10^2$ Neg.	I.D. 0.5 PNU	I.D. 0.5 PNU
I.D. $1:10^4$ 2+	I.D. $1:10^4$ 3+	I.D. $1:10^4$ 1+	I.D. $1:10^4$ 1+	I.D. $1:10^4$ 1+	I.D. 0.0005 PNU 2+	I.D. 0.0005 PN 2+

history of prior ant stings. He had been stung in the past by a wasp without consequence. The patient had a history of allergic rhinitis and urticaria with angioedema following a penicillin injection. The physical examination was unremarkable.

Ant specimens examined several days after the stings were identified as *S. xyloni* (southern fire ant). Two separate field trips revealed the same species of ants. *S. invicta* was not found in the vicinity where the stings occurred, and he lives in an area in which the imported fire ant has not been reported. A limited number of skin tests were performed because of the patient's age. They are summarized in Table III. Since *S. xyloni* extract is unavailable, he was started on ant extract (50 per cent *S. richteri* and 50 per cent *P. rugosus*).

Case 4

D. W. is a 9-year-old white female patient who was stung on the hand by two large red ants. Over the next 30 minutes, she developed moderately severe asthma and lethargy, which lasted for approximately 12 hours and was not relieved by oral bronchodilators. She had a history of asthma; however, she had not had any wheezing for at least one year prior to the above episode. She experienced no other symptoms. Initially, the sting sites were swollen to about the size of a quarter; however, they resolved over 24 hours. Pustules were not observed. She also had a history of allergic rhinitis with a family history of asthma. Her mother knew of no previous sting by any member of the order Hymenoptera. Ant specimens collected the day after the episode were identified as *P. barbatus,* or red harvester ant. A field trip was not recommended since the identification was felt to be assured and the imported fire ant had not inhabited the area where the stings occurred. Skin test results are summarized in Table III. Since *P. barbatus* extract is unavailable, she was started on 50 per cent *S. richteri* and 50% *P. rugosus.*

BIOLOGY OF THE IMPORTED FIRE ANT

There are approximately 20 species of ant in North America in the genus Solenopsis, most of which live in the South and Southwest.[16] They are commonly referred to as "fire ants" because of the painful sting they inflict. One of the most important ants in the genus Solenopsis are the imported fire ant species, which have been introduced into the United States from South America.[12, 17-19] The original imported fire ant species, previously referred to as S. *saevissima richteri* Forel, has now been suspected of being two separate species originating from separate areas of South America.[12] The first of two species to be intro-

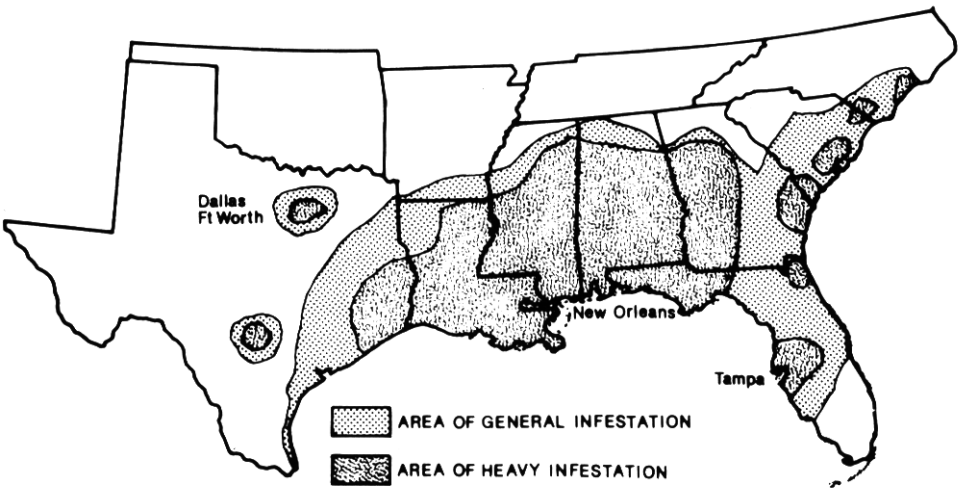

FIG. 1. Areas in the United States of imported fire ant infestation.

duced into the United States, S. *richteri* Forel, is thought to have originated from Uruguay and Argentina. It gained access at Mobile, Alabama, approximately 50 years ago, presumably by ships carrying cargo from South America. It is presently found only in a very limited area of north Mississippi and Alabama. The second species, *S. invicta* Buren was probably introduced during World War II from the Mato Grosso of Brazil. It is the dominant species that has spread over most of the South and into the southwest portion of the United States (Fig. 1).

The medical literature has always treated the imported fire ant as one species. Distinguishing morphologic features between *S. richteri* and *S. invicta* are discussed extensively elsewhere.[12] If a clinical difference does exist, it is unknown at this time. In most likelihood, they are both capable of causing systemic allergic reaction in humans. Their habits are similar, and since *S. invicta* was the species involved in the above case reports and is the more common of the two, most of the discussion pertains to it.

Positive differentiation of the major form of these species from other ants of the same genus (for example, *S. xyloni*, southern fire ant) can be important.[12, 20] This is based upon the number of mandibular teeth and the length of the antennal scape. The imported fire ant has 4 mandibular teeth, and its antennal scape extends beyond two-thirds the distance to the posterior margin of the head. In contrast, in the major form of *S. xyloni*, the southern fire ant, the mandible has 3 teeth, and the antennal scape does not extend beyond two-thirds the distance to the posterior margin of the head.[20] These ants inhabit similar ecological areas and have an almost identical appearance. In one case reported in this paper, J. M., *S. xyloni* was responsible for the systemic reaction rather than the imported fire ant.

The imported fire ant is a medium-sized ant. The alated queen is the new reproductive queen that is still unmated but will eventually leave the nest to

found a new colony. After the nuptial flight, she immediately breaks off her wings, and thus becomes the dealated mother queen that founded the colony and is a source of the eggs for it throughout the remainder of its life span.[21, 22] In addition, winged fertile males for mating and sterile wingless worker ants populate the nests. Two types of worker ants exist, the activity of which appears identical. The larger form, the major workers, are sterile females that can measure up to ¼ inch long. The smaller form are minor workers, also sterile females, measuring approximately ⅛ inch long. There can be considerable variation in the color of ants within one colony.

The imported fire ant normally infests a new area through a nuptial flight. However, the fertilized queen and viable colonies are also spread by man, who inadvertently distributes them over long distances. Mature colonies may contain from 100,000 to 200,000 workers with dozens of winged forms. Mounds may reach 40 or more cm. in diameter and 20 to 30 cm. in height.[23] They are constructed in cultivated fields, pastures, parks, lawns, meadows, in rotten logs and stumps, and occasionally under buildings. Once an area is populated, it continues to be infested unless the ants are poisoned or continuously disturbed.

The ants can be destructive and costly in several ways. They may damage the normal flora and become a nuisance to farm animals and to wildlife. Their mounds damage farm equipment, impede mowing and harvesting, and decrease property value. Federal and state assistance to control spread of the imported fire ant is available in some of the states through the Untied States Department of Agriculture.[19] Present control programs recommend the use of a bait containing 0.3 per cent dodecachlorooctahydro-1,3,3-metheno-2H cyclobuta (cd) pentalene (mirex), which can be broadcast over large areas from a plane.[24] There is considerable ecological and political controversy on the widespread use of this agent.[25, 27] The imported fire ant has also been reported to destroy other insects, possibly serving a useful role in the environmental system.[18] Therefore, the controversy increases when this is compared to the widespread use of mirex, which persists in the environment as a polycyclic chlorinated insecticide.[17, 27] The other two specimens of ants discussed in this paper are native to the North American continent and are less bothersome to humans since they are not as aggressive as the imported fire ant. The *S. xyloni* has its center of population in Texas with nests reported from South Carolina westward to California and as far south as North Florida. Its habits parallel that of the imported fire ant.[16] *P. barbatus* is one of about 25 species in the genus Pogonomyrmex. This particular species occupies Kansas, Oklahoma, West Texas, Old and New Mexico, Arizona, and Utah. Other members of the family occupy the southern half of the United States from coast to coast. They are less aggressive than members of the genus Solenopsis, although their sting can be equally painful.

DISCUSSION

Human skin responses and pathologic consequences secondary to the sting by imported fire ants in volunteers have been extensively studied.[9] The ant has been observed to initially fix itself to the skin with its mandibles, creating a

definite sensation of pain. It then arches its back at the peduncle, inserts its stinger, and maintains this position for up to 20 to 25 seconds. It may then withdraw the stinger, rotate in a pivotal fashion by maintaining its mandibles in the original position, and repeat the sting.

Pain elicited from the sting of the imported fire ant is not unlike that experienced from a bee sting. The intensity is usually not as great, and the painful reaction lasts only several minutes. The sting of *S. xyloni* appears to be even less painful. The sting of both species causes an immediate 25 to 50 mm. erythematous flare followed in a few minutes by a wheal, which may enlarge up to 10 mm. in diameter. Small prominences may persist for up to 2 hours. The *S. xyloni* sting will subsequently usually disappear; however, following the imported fire ant sting, vesicles containing clear fluid begin to appear in 4 hours. The fluid becomes cloudy over the next several hours. Within 24 hours, the pustules are unbilicated, surrounded by a red halo or large erythematous painful area. If left undisturbed, the pustule will remain 3 to 10 days before rupturing with subsequent crust formation. Pigmented macules, residual fibrotic nodules, and small scars may form at these sites. Although the sequence of events is fairly diagnostic of the imported fire ant sting, small pustular formation can occasionally follow the sting of *S. xyloni* and several other species of ants.[9, 28] Similarly, not every sting inflicted by *S. invicta* is associated with pustular formation, this appearing to be a function of the amount of toxin the ant has injected.[28] Both the patients stung by the imported fire ant reported in this paper, W. R., and F. B., had subsequent pustular formation with resolution over several days. J. M., stung by *S. xyloni*, and D. W., stung by *P. barbatus*, had immediate wheal-and-flair reactions with no subsequent pustular formation.

Histologically, in as early as 6 minutes, edema appears in the upper corium where the sting occurred. Epidermal edema can be demonstrated within 30 minutes with superficial dermal vessel dilation and slight lymphocytic, histiocytic, and plasma cell infiltration. Some necrosis is seen as early as 30 minutes. At 24 hours, the pustule contains many necrotic polymorphonuclear and lymphocytic cells with a thin roof composed of the stratus corneum and epidermal cells. Beneath the densely packed necrotic tissue forming the floor of the pustule are diffuse layers of polymorphonuclear cells, lymphocytes, and other cells. At 72 hours the pustule remains intact, at which time eosinophils and plasma cells can be visualized with the polymorphonuclear and lymphocytic cells. The central floor area of the pustule is obliterated with the cellular infiltrate extending into the underlying necrotic connective tissue.

The cellular infiltrate can extend in layers laterally and even deeper about the dilated blood vessels and nearby sweat glands. These changes appear to be exclusive to the imported fire ant and are more profound than the histologic findings associated with stings from most other insects.

Chemical and biological properties of the venom from the imported fire ant and *S. xyloni* have shown them to be remarkably similar to one another; however, they are unique among stinging ants.[29-33]

Venom alkaloids of 4 species, *S. geminata, S. xyloni, S. richteri,* and *S. invicta,* are characterized by the presence of various 2-6 disubstituted piperidines

in various amounts distinctive to the particular form.[32] These account for 97 per cent of the detectable substances in the poison gland secretion. These piperidine compounds, which have been prepared synthetically, have antibacterial activity against certain organisms and will produce local skin reactions following intradermal injection into rabbits.[31] They have no effect on the rat uterus and guinea pig ileum.[32] Based on available evidence, one cannot exclude the possibility that the piperidines act as haptens, thereby creating the hypersensitivity state demonstrated in the above cases. Cross-sensitivity with other Hymenoptera species, if it truly exists, would be difficult to explain if these chemicals were haptenic because of the uniqueness of these chemicals in the insect world. The lack of appreciable protein in the venom of genus Solenopsis is unusual based on present knowledge of insect and animal venoms. However, a small amount of polypeptide material with a molecular weight of 6,000 to 12,000 has been found in the venom sac extract of the imported fire ant.[32] The importance of this polypeptide is unknown; however, it theoretically could be the antigen responsible for ant sting hypersensitivity, and could explain possible cross-sensitivity with other Hymenoptera insects. In sharp contrast to the ant venoms, one to 10 antigens have been found in the wasp, yellow jacket, honeybee, and hornet species. Some of these cross-react with one another.[34] Physiologically active substances have not been found in the imported fire ant venom. In contrast, substances such as hyaluronidase, lecinthinase, histamine, serotonin, kinins, and acetycholine are found in venom of wasps, yellow jackets, honeybees, and hornets.[34]

The only immunologic studies performed with the imported fire ant demonstrated that extract of the whole ant, ant venom, and the hemolytic component of the venom contain a material that is immunologic and antigenically similar.[35] No immunologic data is available on piperidines or the polypeptide found in the venoms. No attempt has been made to see if cross-antigenicity exists among the wasp, yellow jacket, hornet, honeybee, and ant species.

Severe systemic reactions or fatal reactions from stings of bees, wasps, yellow jackets, and honeybees have been well documented.[1-3] Systemic reactions secondary to ant stings are also documented, however, fatal reactions appear much less common than with the above insects. Previous reports of reactions to ants are summarized in Table IV. Olive[5] reported on 300 cases of imported fire ant stings at Fort Benning, Georgia. Five had systemic reactions, 3 of whom were children in whom the exact number of stings was not recorded. One of the 5 received 6 stings, and another, 3 stings. A 1½-year-old child received 220 stings had no noticeable sequelae. In another case report, an inebriated male received 5,000 stings with no recorded toxic side effects.[10]

Seventy-five case reports of ant sting sequelae were reported in a survey made in the state of Texas.[6] Unfortunately, the species of ants involved in the reactions, the number of stings, and the exact nature of some of the reactions is unclear. Twenty-five of these patients had systemic reactions, 5 of whom were described as frank anaphylaxis. In a recent report of ant sting reactions, 2 patients developed systemic reactions to several ant stings.[7] One of these, a 9-year-old male, had systemic reactions at the ages of 7, 8, and 9, all of which

TABLE IV. Literature summarization of the reactions to ant stings

Investigators	Cases	Suspected	Lesion	Definite identification	Age
Smith, J. D., and Smith, E. B.[10]	1	IFA	Yes	No	49
Brown, L. L.[7]	2	IFA	Yes	No	48
		IFA	Yes	No	9
Olive, A. T.[5]	300, only 5 had reactions	IFA	Yes	No	3 children
		IFA	Yes	No	Middle-aged male
		IFA	Yes	No	Middle-aged male
		IFA	Yes	No	1½-year-old child
Micks, D. W.[6]	75	Large red ant—27 cases "Fire ant"—2 cases Unknown—46 cases	?	No	?
Parrish, H. M.[3]	4	? probably not IFA	?	No	?
Bowen, R. B.[4]	1	IFA	?	No	?
Helmly, R. B.[11]	1	*S. geminata*	Yes	Yes	?
Caro, M. R., et al.[9]	2	IFA	Yes	No	37
		IFA	Yes	No	64
Triplett, R. F.[8]	18	IFA	?	No	12 children 3 adults 3 teenagers

gradually increased in severity. Four fatalities were reported to have occurred secondary to ant stings in a nationwide survey.[3] There was no indication of the species of ant involved, the number of stings inflicted, or the medical details in the fatalities. A single case report of a fatality from 3 ant stings was also reported by Bowen.[4] The species of ant involved is unclear. It most likely was

Number of stings	Reactions	Deaths	Skin tests	Hyposensitization
5,000	0	0	0	0
3-4	Precordial pain, faintness, blurred vision, tachycardia, urticaria, angioedema	0	Yes—results reported positive to imported fire ant and other Hymenoptera	Yes
2	First occasion—age 7, crampy abdominal pain, blurred vision, angioedema, faint			
1	Second occasion—age 8, angioedema			
3	Third occasion—age 9, angioedema, urticaria, wheezing	0	Yes, only sensitive to imported fire ant	Yes
?	Marked edema, cyanosis, respiratory difficulties	0	0	0
6	Nausea, angioedema, urticaria	0	0	0
3	Fainted 3 times; hives and confusion	0	0	0
220	None	0	0	0
?	12 "systemic reactions": 7 fainting and/or vomiting, abdominal cramping, or urticaria 5 "anaphylaxis" manifested by shock, asthma, edema of face, lips, and glottis, massive generalized urticaria Others—local reaction	0	0	0
?	Unknown	4	0	0
3	Shock	1	0	0
5	Tearing, generalized itching, tightness in throat, urticaria, and angioedema of face, wheezing	0	Yes	0
20-25	Urticaria, angioedema, precordial distress, anxiety, laryngeal edema, nausea	0	0	0
20-30	Chest pain, tingling, dyspnea, anxiety	0	0	0
?	Generalized urticaria, angioedema, respiratory symptoms, nausea, vomiting, shock	0	0 Yes; see text	Yes

not the imported fire ant since the reaction occurred in North Texas before 1950, at which time this ant had not invaded this part of the country.[20] Helmly[11] reported one case in which 5 *S. geminata* stings resulted in a systemic reaction. Triplett[8] recently reported on 18 cases receiving hyposensitization for imported fire ant hypersensitivity. Most of these patients experienced generalized urti-

caria after being stung; however, one experienced severe respiratory symptoms and another, anaphylactic shock.

Skin testing to ant extract has been done only rarely. Brown[7] recorded two ant hypersensitivity cases in which one patient was skin-sensitive to imported fire ant antigen. The strength of the extract used and the degree of reactivity of the skin tests were not included in this report. Helmly[11] reported in his single case marked skin sensitivity to 500 PNU per cubic centimeter of imported fire ant extract, and a mild reaction to 500 PNU of mixed stinging insect antigen (honeybee, wasp, yellow jacket, and hornet). Both were given intradermally. Fifteen out of 17 tested intradermally by Triplett[8] to imported fire ant extract reacted as follows: 8 positive to $1:10^6$; 4 positive to $1:10^5$; 1 positive at $1:10^4$ dilution; 2 positive at $1:10^3$, and 2 were negative. Seven of these were tested to mixed stinging insect extract (wasp, hornet, yellow jacket, honeybee). All of these reacted. The strength of the mixed stinging insect extract to which they reacted is not noted.

The 4 systemic reactions that are reported in this paper were of moderate severity and presumably all involved an allergic and nontoxic response to venom, since other case reports have documented large numbers of stings without significant sequelae.[10] W. F. appeared to have developed systemic reactions to both wasp and the imported fire ant. This raises the interesting question whether or not cross-reactivity can exist between the above insect groups, especially since they are both included in the order Hymenoptera. Cross-sensitivity has not been documented; however, 2 cases in which systemic reactions to both bee or wasp and imported fire ant have been noted.[8] Cross-sensitivity could also exist in Case 1 in spite of the fact that subsequent stings by other stinging insects, other than wasps, resulted in large local reactions; and presumably species-different ant stings caused no reaction whatsoever. The latter two observations could mean that specific species sensitization occurred in both cases and that cross-sensitivity may exist between the two insects that caused the reaction, i.e., the "red wasp" and the imported fire ant. The second patient, F. D., had a moderately severe generalized reaction to approximately 20 ant stings. A hypersensitivity state most likely accounted for this response since other case reports have documented the benign nature of many more stings in humans.[5, 10] J. M. reacted to several ant stings; however, in this case, *S. xyloni* (southern fire ant), not the imported fire ant, was felt to be responsible for the reaction. D. W. was stung by two red harvester ants, species *P. barbatus*, resulting in an acute asthmatic attack. This was her first episode of bronchospasm for over one year and the most severe attack she has had during her lifetime. She has had no subsequent wheezing. Other reports of systemic reactions to these species of ants have not been recorded.

Several additional observations can be made from the literature and data presented in this paper. The differences between ant antigen skin reactivity in ant-sensitive individuals and wasp, hornet, honeybee, and yellow jacket–sensitive persons is not impressive. There does exist a greater degree of skin reactivity in both of these groups when compared to control groups. Unfortunately, species-specific ant antigen could not be obtained in all cases for testing or for treatment

in all of the ant-hypersensitive individuals. It is interesting to note that skin reactivity was similar in most cases with both ant antigens employed, whether or not it was the species responsible for the reaction. There also appears to be increased skin reactivity in ant-hypersensitive patients to the antigens of wasp, hornet, honeybee, and yellow jacket when compared to the control group. Skin reactivity to ant antigen cannot be used as a criterion for predicting a hypersensitivity state but only as a guide for beginning hyposensitization. Triplett[8] found similar findings with ant-sensitive individuals. Identical interpretation of skin test results are accepted practice in insect hypersensitivity to wasp, yellow jacket, hornet, and honeybee.[36, 37] The natural course in ant hypersensitivity is also unknown. The only extensive follow-up on ant-hypersensitive patients was reported recently by Triplett[8] in which 17 patients completed immunotherapy with aqueous imported fire ant extract. Eight of these patients were restung and none developed symptoms of a generalized allergic reaction. All four cases reported in this paper were started on an extract and tolerated hyposensitization without difficulty. None of them have been restung subsequently by the original offending insect.

In spite of the fact that ants, and particularly the imported fire ant, have been accused of being responsible for deaths of individuals, it is not well documented in the medical literature. Information is needed on additional documented case reports, identification of the species of ant responsible for the reaction, the natural history of ant hypersensitivity, identification of the antigen or antigens responsible for the hypersensitivity state, and whether cross-reactivity exists among the more commonly recognized Hymenoptera species such as wasp, honeybee, hornet, and yellow jacket. Answers to these questions will become increasingly important as the imported fire ant invades more and more territory of the continental United States.

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ADDENDUM

Subsequent to submission of this paper, 8 additional systemic allergic reactions due to stings of the imported fire ant have been seen. None have been fatal. It appears to be a greater problem in the Tampa Bay area than hypersensitivity to the usual Hymenoptera insects (honey bee, wasp, hornet, and yellow jacket).

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