Bee Stings

Immunology, Allergy, and Treatment

Part I of Two Parts

by BUDDY MARTERRE, MD

Although it's part of the business, few of us actually look forward to being stung. As beekeepers we need to know about the various reactions to bee stings and be responsible to ourselves, family, neighbors and friends in regard to bee stings. I hope this article will serve some of those purposes and be informative to both the beginner beekeeper and the most experienced scientist. The first part will cover insects that sting, honey bee stings in particular, bee venom biochemistry, precautions and sting prevention, the management of beekeeping emergencies, and basic immunology and allergy. The second part will cover sting reaction types and treatments, allergy testing and desensitization results, and specific recommendations for beekeepers.

Hymenoptera stings

The order Hymenoptera includes ants, bees, hornets, and wasps, many of which inflict stings (Table 1). Although solitary bees, such as sweat bees and carpenter bees, can inflict a sting, the risk of an allergic response to their venom is low because they are both unaggressive and the amount of venom they inject is low. More aggressive, primitively social paper wasps, yellow jackets, bald-faced hornets and European hornets from the Family Vespidae (Figures 1 – 4) – as opposed to eusocial honey bee workers from the Family Apidae – can sting more than once. If the flying stinging insect that inflicts a sting is unidentified, most often (unless the sting is still present

Figure 1. Wasp (*Polistes* sp.), *Buddy Marterre, MD*

Figure 2. Yellow Jacket (*Vespula vulgaris*), *courtesy of Jarmo Holopainen*

Figure 3. Bald Faced Hornet (*Dolichovespula maculata*), *courtesy of Chris Wirth*

Figure 4. European Hornet (*Vespa crabro*), *Buddy Marterre, MD*

Table 1
Hymenoptera Species with Venoms for Immunotherapy

Vespidae Wasps			
	Vespinae		
		Vespula	**ground-nesting yellow jackets**
		Dolichovespula	**aerial yellow jackets**
		Vespa	**hornets**
	Polistinae		
		Polistes	**paper wasps**
Formicidae Ants			
	Myrmicinae		
	Solinopsis		**fire ants**
Apidae Bees			
	Apinae		
	Apis		**honey bees**

Figure 5. Imported Fire Ant (*Solenopsis invicta*), *courtesy of Deyrup and Cover, antweb.org*

in the victim) the culprit was not a honey bee. Sting incidence in America varies with region. Yellow jackets are more populous than honey bees in the north, wasps are more prevalent in the southwest, and fire ants are more prevalent in the southeast. Imported fire ants - Family Formicidae, genus *Solenopsis* - also have a sting apparatus (Figure 5). And their venom is the most potent venom known in the animal kingdom! A general approximation of flying insect sting incidence throughout the US is yellow jackets (*Vespula* and *Dolichovespula*) 50 %, honey bee (*Apis*) 25 %, paper wasp (*Polistes*) 15 %, bumble bee (*Bombus*) 5 %, and European hornet (*Vespa*) 5 %.

Honey bee stings

Bees sting defensively – when their hive, nest, or mound is thought to be under attack. For example, foraging bees will only sting if directly injured when they are away from the hive. Mature, adult, female worker bees in the hive deploy the sting from its sheath in response to alarm pheromone. This chemical messenger release is usually accompanied by a short 'buzz' and an astute beekeeper may even smell the banana oil-like pheromone. Guard bees are attracted to dark colors, contrast (like hairlines), certain body odors (and perhaps the carbon dioxide you exhale), all drawing them toward your face and eyes. Certain perfumes, cosmetics, and banana oil may mimic alarm pheromone. Vibrations and fast movements further aggravate the situation.

Stinging bees flex their abdomens to jab the sting into their target. The honey bee sting (unlike the sting of other insects) has a barb which leaves it attached to its victim - complete with venom sac (Figure 6). The sting apparatus is also covered by muscles which continue to thrust the sting further into the victim. The venom then travels down through the hollow, hypodermic needle-type shaft (Figure 7). ninety % of the venom sac empties in the first 20 seconds. Alarm pheromone (highly volatile isopentyl acetate and other alcohols and esters) is released from the attached Koschevnikov gland, leaving the victim marked for further injury. In this way, many old guards can be recruited in an exponential defensive response when their hive is being threatened. And of course, the primary perceived threat is you – the beekeeper!

Figure 6. Honey Bee Stinging an Arm, *courtesy of Zachary Huang, PhD*

Honey bee queens have more poorly developed barbs than workers on their longer stings. The queen sting apparatus has a stronger attachment to their abdomen and queens do not produce alarm pheromone. They reserve their stings for other queens, but have larger venom sacs than workers, and can sting multiple times. Worker bees die in the process of stinging, as their sting and sometimes other abdominal contents are extruded.

Bee (and other insect) venom biochemistry

Each European bee venom sac contains about 140 micrograms of venom (only about 100 micrograms per Africanized bee venom sac), but the average venom delivered is a dose of about 50 micrograms. Needless to say, there are a lot of very potent chemicals in bee venom that are bad for you (Table 2). Many of these chemicals are peptides (small protein chains) and enzymes (larger proteins that facilitate biochemical reactions). Together they cause the reaction that your body has to the sting (pain, swelling, itching, redness, etc). Some of these chemicals (or the body's response to them) can also initiate very rapid reactions. An example would be the clotting cascade, which forms a clot within minutes of a cut. Many of these proteins are also recognized as foreign by the human immune system (antigens) and lead to allergic reactions in some individuals.

Figure 7. Sting Apparatus, *courtesy of Zachary Huang, PhD*

Table 2
Honey Bee Venom Biochemistry

Melittin *
Phospholipase A2
Apamin *
Hyaluronidase
Acid and Alkaline Phosphatases
Mast Cell Degranulating Peptide *
Histamine, Dopamine, Norepinephrine
* unique to honey bees

Forty – fifty percent of honey bee venom is mellitin. Mellitin is a chemical that is unique to bee venom and is a cytolytic, which means that it directly bursts cells. It contributes to itching and swelling, and is the primary cause of the sting's pain. Mellitin can also dilate blood vessels, leading to low blood pressure. ten – twelve percent of honey bee venom is Phospholipase A2 (the most potent allergen). Phospholipases are enzymes that help mellitin destroy cell membranes (cell membranes have lots of phospholipids in them). Apamin is also unique to bee venom (3 %) and is a neurotoxin – it is toxic to nerve conduction. Hyaluronidase (2 %) is an enzyme that breaks down hyaluronic acid, which is one of the components of connective tissue or the tissue in between your cells that hold you together (like little microscopic tendons). Hyaluronidase contributes to the "spread" of the reaction. Phosphatases are enzymes that break off the phosphate portions of high-energy chemicals. Frequently these phosphate molecules begin cascades of other, very inflammatory biochemical reactions in your body (like the clotting cascade). Mast cell degranulating (MCD) peptides do just what they're named for – they cause the mast cells in your body to release the many biochemicals (including histamine) in their granules. Mast cells will be covered more in the immunology section later. Histamine causes 'leaky' capillaries and contributes to the familiar wheal and flare reaction (slightly raised red area that itches) in allergic or atopic individuals.

Venoms from hornets (*Vespa*), aerial yellow jackets (*Dolichovespula*), ground-nesting yellow jackets (*Vespula*), and paper wasps (*Polistes*) lack mellitin, phospholipase A2, acid phosphatase, apamin, and MCD peptide. Their venom contains 10 - 25 % phospholipase A1 and

B as well as antigen 5, which honey bee venom does not contain, however. The proteins in the venoms of individual yellow jacket and hornet species (subfamily Vespinae) are quite similar. This leads to a lot of cross reactivity in the human immune response to them. Thus, venoms for testing hypersensitivity and immunotherapy desensitization are typically available separately for honey bees, wasps, and 'mixed vespids'.

Precautions and sting prevention

Good technique can reduce the number of bee stings you receive (Table 3). Realize that the 'mood' of the hive can be affected by many things, such as season, weather, and many factors that may only be apparent to the bees. A long time ago I gave up trying to predict the mood of the five females I live with, much less the 50,000 females in a bee hive! Therefore, don't assume that a given hive will be gentle just because it had a good temperament the last time you inspected it. Also, if you are a suburban beekeeper (like me), only keep very gentle bees near your house. And inquire as to your neighbor's possible venom allergies.

Work hives on warm, sunny, calm days.

Table 3
Precautions and Sting Prevention

Wear white and ALWAYS WEAR YOUR VEIL
Avoid using perfumes and eating bananas
USE SMOKE judiciously
Work slowly and deliberately
Remove and smoke stings ASAP
Wash your bee suit and gloves frequently

Cold, windy conditions and impending thunderstorms make for irritable bees. Approach bee hives from the back. Do not stand in their flight paths. Wear white and ALWAYS WEAR YOUR VEIL. Avoid using perfumes and eating bananas before bee work. Use smoke judiciously, but use it almost every time you work in a hive's brood nest (queen inspections very soon after introduction and quick, gentle feeding operations are exceptions). Work slowly and deliberately, avoiding quick movements and hive vibrations. Remove stings quickly without squeezing them and smoke the stings as soon as possible. And wash your bee suit (and gloves if you use them) frequently – particularly if you've received a bunch of stings!

Management of emergencies

It's better to be prepared for a major battle and not have one than to only prepare for a minor skirmish and experience a major war. What do you do if you drop or knock over a hive and there are more angry, stinging bees than you ever thought possible coming at you? Table 4: Close the hive if you can (easily). Cover up. Get your smoker and smoke yourself (if it's still lit). Calmly walk at least 20 yards away into some brush. Evergreens are particularly good at distracting bees. Walk. Do not run (unless you can run a 5 minute mile)! Don't swat bees. Don't return to the scene of the crime until you and the bees have calmed down (this takes about 10 or 20 minutes for the bees – I can't say for you)!

Table 4
Management of Emergencies

Close the hive if you can
Cover up
Kill any bees inside your veil
Get your smoker
Walk at least 20 yards away into brush (evergreens)
Return when calm (20 minutes)

If a bee gets inside your veil, kill it before it can sting your face. If you don't have a veil on (heaven forbid) and bees are flying into your face, close your eyes and walk away (and get your veil). If you have a bunch of bees inside your veil (more than two or three), take it off, cover your face and let them sting your hands. And remember, every sting leaves you marked for more!

Immunology and allergy

The human immune system is highly complex. Its basic function is to recognize and destroy foreign tissue (like bacteria or viral-infected cells). In order to do this, it must not only recognize proteins that belong to the body (self), but distinguish these from proteins that don't belong (non-self). The specialized white blood cells in the immune system that do this are called lymphocytes. Lymphocytes utilize complex protein receptors on their surface to recognize self and non-self and they generate two integrated responses to foreign proteins (such as those from bee venom). One effector arm of the immune response is the production of antibodies and the other is the production of other controlling and effector lymphocytes.

Antibodies are produced by B lymphocytes and are large complex proteins called immunoglobulins (Ig). Immunoglobulins or antibodies have a hypervariable region that fits around a small piece of a foreign protein (antigen) like a lock fits over a key. The fit is even more specific than a key and lock, however, because it is in three dimensions and also includes charge affinity (areas of negative charge on the antigen line up with areas of positive charge in the cleft of the antibody). There are many different classes of antibodies, but the primary class in the bloodstream that is involved with a 'normal' immune response is IgG and the class that is involved with an allergic or hypersensitivity response is IgE.

The controlling cells of the immune response are called T lymphocytes. They recognize the foreign antigen with receptors on their surface (very much like antibodies) and can induce B cells to make

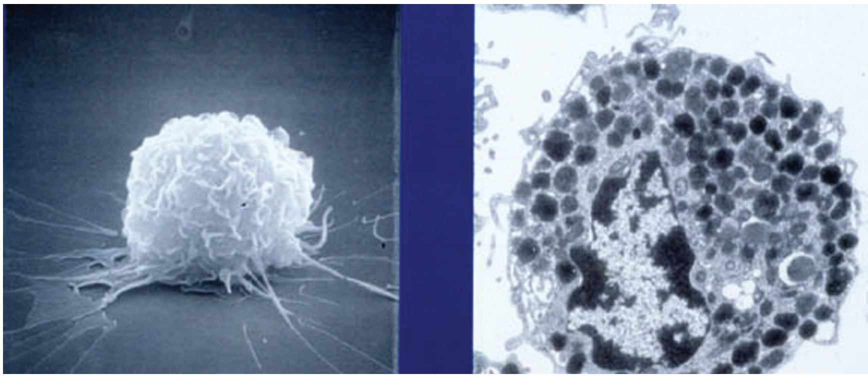

Figure 8. Electron Micrographs of Mast Cells with Granules Left is scanning em, Right is transmission em (showing granules), *courtesy of Soman N Abraham, Duke University Medical Center*

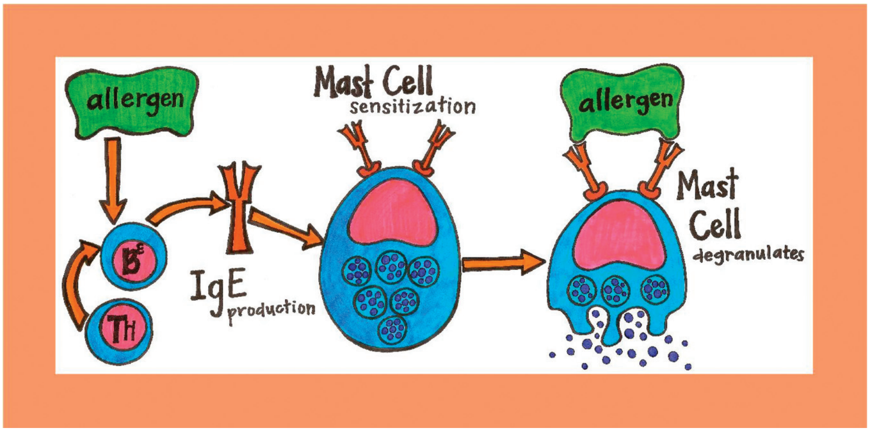

Figure 9. Diagram of Allergic Immune Response, *by Rachel Alexandra Marterre*

specific antibodies to the antigen. Their response may include recruiting other cells to destroy it (using chemical messengers called cytokines – similar to pheromones in a bee hive) or by directly attacking the foreign antigen themselves. In both the case of antibody production by B cells and T lymphocyte generation, memory cells (both B and T) are generated that can then recognize the foreign antigen decades later. This is how immunity to a virus or bacteria or venomous sting can last a lifetime, even though exposure to it may have been years before or even in childhood.

The effector cells that are recruited by the T cells and the antibody classes that B cells make differ with different people, even in response to the same foreign antigen. The cytokine messenger profiles (that recruit other effector cells) also differ from individual to individual. Thus, some individuals may make allergic IgE antibodies to bee venom antigens even though most people make non-allergic IgG antibodies.

An allergic response to a venom antigen (now called an allergen) is also quite complex. It begins with IgE antibodies and mast cells. Mast cells are already present in the sting site (Figure 8). Mast cell surfaces are loaded with IgE antibodies that may react with many different types of antigens or allergens. After venom is injected into the skin, at least two IgE antibodies on the surface of a mast cell each react with the venom allergen, causing the immediate release of preformed substances in the granules of the mast cell, as well as the production of other new substances. Refer to the Figure 9 for a basic diagram of an allergic immune response. And recall, the mast cell degranulating peptide in bee venom can cause this reaction all by itself – even without a typical allergic response! With just a few stings, mast cell degranulating peptide's effects are only local, but with hundreds of stings the venom dose can cause toxic effects.

Once activated, mast cells release a lot of very potent preformed chemicals from their granules immediately, including histamine, proteases (enzymes that destroy proteins or initiate other cascades), heparin (an anticoagulant), and chemicals that attract eosinophils (another allergic effector cell) (Table 5). These primary mediators are released within minutes and their effects on the human body begin very quickly. Histamine dilates blood vessels, makes them leaky, and activates the endothelium (or lining of the capillaries). This leads to local edema (swelling), warmth, redness, and the attraction of other inflammatory cells to the site. In large amounts, it can drop blood pressure, and cause rapid swelling of the airway (leading to stridor or an inability to breathe) and constrict bronchial tubes (causing an asthmatic 'attack'). Histamine also irritates nerve endings (leading to itching or pain).

Table 5

Mast Cell Granule Contents and Products

- Histamine, Serotonin
- Enzymes (that destroy proteins or initiate cascades)
- Heparin (anticoagulant)
- Eosinophil Chemotactic Factor of Anaphylaxis
- Neutrophil Chemotactic Factor
- Leukotrienes
- Prostaglandins
- Cytokines (which recruit other inflammatory cells)

Upon activation, mast cells also begin to synthesize secondary chemicals which have more delayed effects including prostaglandins, leukotrienes, and cytokines. Some of these secondary chemicals (particularly the cytokines) are responsible for the late phase of allergy, which typically begins 2 – 4 hours after the insult. The prostaglandins and leukotrienes – like histamine – also cause bronchial constriction, dilation of blood vessels and leaky capillaries, but their onset is hours later and their effects more long-lasting. Aspirin can actually exacerbate these effects by causing more leukotrienes and fewer prostaglandins to be produced by the mast cells. The cytokines which are made and released by the mast cells are primarily responsible for the late phase of anaphylaxis. They attract other effector cells of allergies, like eosinophils, basophils, and neutrophils (which significantly contribute to allergic responses). Once these processes get initiated, they can snow-ball in a hurry and cause a lot of problems very quickly. Again, if the allergic reaction becomes systemic (throughout the entire body), it is called anaphylaxis.

That's enough science for one article. In part two, we'll discuss sting reaction types and treatments, allergy testing and desensitization results, and specific recommendations for beekeepers.

About the author

I've had allergies all my life. I became very interested in bees while I was in college at Virginia Tech. But the beekeeping course I wanted to take interfered with biochemistry lab (my major), so instead I took graduate courses in immunology. After medical school and a general surgery residency, I did a fellowship in and then practiced transplant surgery. So while I learned and practiced more immunology (by transplanting 'foreign' organs), my personal experience with bee stings was still lacking. After my fellowship, I married an experienced intensive care nurse, who is now a certified pulmonary-allergy nurse. Then, I finally became a beekeeper and am now a Master Beekeeper in North Carolina. I have large local reactions to bee stings – and have experienced quite a few of those! Being concerned about my risk of more serious reactions, I went back to the immunology and allergy journals. Then, last year, I had an anaphylactic reaction (fortunately not to bee stings, but to salmon – which I had eaten many times before)! Thus, I am a doctor, a beekeeper, *and* a patient. In addition to all the photo credits, I'd also like to thank two excellent allergists for their review of this article: Aneysa Sane, MD from Wake Forest University Medical Center, and Larry Williams, MD from Duke University Medical Center.