A Stinging Commentary

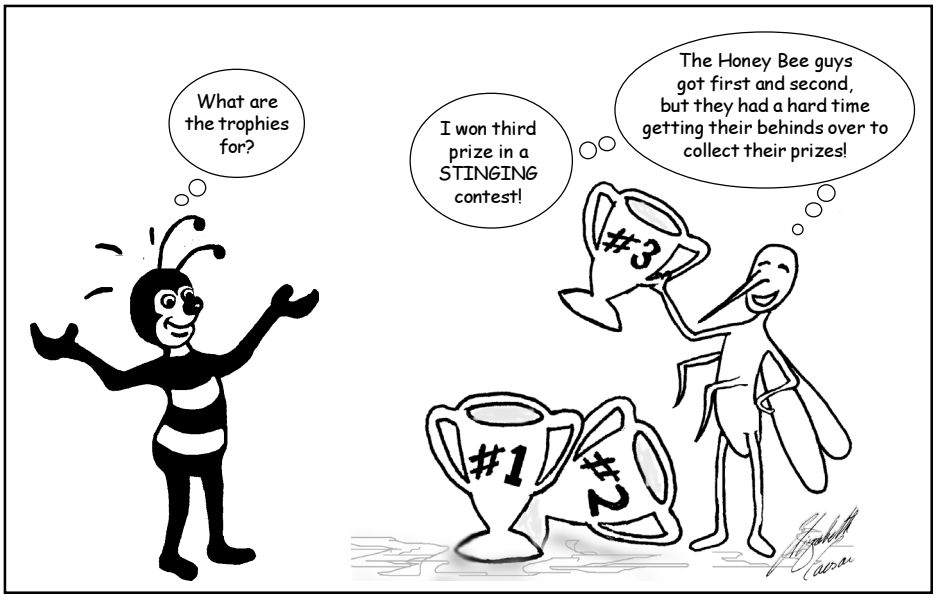
May Berenbaum

Although, as an entomologist, I'm embarrassed to admit it, there was a time when my own daughter Hannah was afraid of insects. Actually, she wasn't afraid of all insects—she was just fearful of what she referred to as "bees," by which she meant any striped buzzing multilegged creature other than the one in the Honey Nut Cheerios commercial.

The fear stemmed, I think, from witnessing a kindergarten classmate's hysterical response to being stung by a yellowjacket during an otherwise uneventful recess. Hannah and I spent many hours that summer reviewing the differences between bees and wasps, and by fall, her fear had been replaced by a better taxonomic appreciation of hymenopteran diversity, a healthy respect for yellowjackets, and a grudging admiration for honey bees. This is more than I can say for her first grade teacher, who was also afraid of "bees," and who never did learn the difference between bees and yellowjackets (despite Hannah's best efforts to educate her).

Even more embarrassing to admit as an entomologist is the fact that I'm a little afraid of most striped buzzing multilegged creatures myself (at least the ones in the order Hymenoptera—one advantage of years of graduate training in entomology is that at least I don't fall for syrphid mimics). I'm afraid of stinging hymenopterans for the same reason I'm afraid of, say, snarling pit bulls, tackle football games, and dentists with low-speed drills—I've never really been a big fan of pain.

That's why I was so happy to read a recent paper by Zubieta et al. (2003) in *Science*. These authors report their discovery of a polymorphism of the gene encoding an enzyme called catechol-O-methyltransferase (COMT). This enzyme is one of several that metabolizes catecholamines and in the process modulates function of dopaminergic



and adrenergic/noradrenergic neurons—among the neurons involved in pain perception. In homozygous mutant genotypes, called *met/met* (for methionine), in comparison with the normal *val/val* genotype, the activity of COMT is reduced 3-to 4-fold and consequently the content of enkephalin peptides (endogenous opioids) decreases. So does the capacity to activate μ opioid neurotransmission. So what, you ask? It turns out that μ opioid neurotransmitters mediate responses to pain.

I think it must take a particular type of personality (or maybe genotype) to conduct studies of pain perception. I had difficulty even reading the paper without cringing, much less carrying out the work. Zubieta et al. (2003) inflicted upon their human subjects what they called "a sustained pain challenge"—an injection of a saline solution into the jaw muscles. As one might guess, this is a painful experience. Subjects were asked to rate pain intensity experienced every 15 minutes and to fill out a questionnaire about their feelings.

I have no idea what inducement was offered to these volunteers who participated in this experiment. I can't imagine it was merely money; maybe it was a graduation requirement, or maybe the authors had compromising photographs of participants that they threatened to release to the newspapers.

In any case, individuals with the *met/met* mutant genotype scored highest on the measures of pain sensitivity; they were more sensitive to lower levels of pain, could withstand less pain, and reported more pain-related negative emotions. This study naturally resonated with me because at least it provides a shred of hope that my own pain aversion is an accident of birth rather than evidence of a lack of character. Granted, I have no idea what my genotype is at this locus, and frankly I'm afraid to find out.

The thing about arthropod stings that makes them so scary is not just that they

hurt—it's that they're actually designed to hurt. Arthropod venom is a fiendish mixture of pharmacologically active substances that for the most part serve no function in the life of the organism producing them other than to inflict pain on other organisms.

Inceoglu et al. (2003), for example, report that scorpions produce prevenom, a high potassium-salt and peptide combo that can alter potassium channels in neurons in such a way as to cause intense pain. It's not as if these components are the most lethal elements of venom—they're just incredibly painful. These authors conclude that this relatively metabolically inexpensive prevenom, consisting of mainly salts, can allow a scorpion to "make an impression by causing intense pain" (not unlike, when you think about it, Zubieta et al. did).

Bees do much the same thing but they up the ante—they target potassium channels with a small polypeptide called apamin. Several studies have shown that apamin, by selectively inhibiting calcium-activated potassium channels, can enhance learning, memory, and cognition and reverse amnesia (Ikonen and Riekkinen 1999). So not only do the stings cause pain; the honey bee (like some kind of sadistic ex-boyfriend or girlfriend who breaks up with you in order to marry your best friend) ensures that the individual stung will remember the pain for a long time to come.

One of the greatest challenges of pain research (greater even than dreaming up quantitatively repeatable ways to inflict pain) is to measure its intensity. Medical science sells devices such as dolorimeters and psychological instruments such as the visual analogue scale, verbal intensity scale, and the McGill Pain Questionnaire, (although it seems to me that if pain is sufficiently intense, the investigator may have a difficult time getting the subject to fill out a questionnaire.)

None of these tools seems ever to have been used to assess the algogenicity (pain-inducing capability) of arthropod stings. Fortunately, there is the Justin Schmidt index for that purpose. Justin O. Schmidt is a researcher in Tucson, Ariz. Several years ago, in an effort to understand the role of the sting in the evolution of sociality in Hymenoptera, Schmidt found it necessary to create a pain scale. For a 1984 publication, Schmidt developed a scale from 0 to 4, in which 0 was defined as the sensation of being stung by an insect that cannot penetrate human skin to 2, a familiar intermediate pain (honey bee), to 4, an intensely painful sting such as that inflicted by *Paraponera clavata*. For the numerically challenged, Schmidt et al also provided some verbal help. The end point of the scale, a sting from *Pogonomyrmex badius* was "likened to pain that might be caused by someone turning a screw into the flesh' or "ripping muscles and tendons." This scale was refined in 1986 (Schmidt et al. 1986), and subsequently, the ultimate pain index is in Schmidt (1990), in which pain ratings are provided for 78 species and 41 genera of Hymenoptera.

Although the 4-point scale remains the same, the verbal descriptions in the media have become more colorful. The sting of a sweat bee, for example, is described as "light and ephemeral, almost fruity. A tiny spark has singed a single hair on your arm." Fire ant stings are "sharp, sudden, mildly alarming—like walking across a shag carpet and reaching for the light switch"; and a bullhorn acacia ant inflicts "a rare piercing elevated sort of pain; someone has fired a staple into your cheek."

Staples in the cheek are not the endpoint in this continuum. A harvester ant's sting is "bold and unrelenting—somebody is using a power drill to excavate your ingrown toenail," a southern paper wasp's sting is "caustic and burning, with a distinctly bitter aftertaste—like spilling a beaker of hydrochloric acid on a paper cut," and a bullet ant's sting is "pure intense brilliant pain, like walking over flaming charcoal with a three-inch nail embedded in your heel."

The most impressive aspect of the construction of this index is that Schmidt has gone to great pains, as it were, to ensure the reliability of this index by charting his own personal perception of pain to create this index. Witness the methods section of his 1984 paper—"painfulness of venoms to humans was evaluated subjectively, mainly by the authors, to natural stings." In case you're wondering, I have it on good authority that these experiences were not actually compared to staple guns fired into cheeks or hydrochloric acid spilled into paper cuts. In any case, I'm betting that Schmidt is a *val/val* genotype when it comes to COMT. (He, on the other hand, modestly suspects he is only a *met/val*.)

Whatever his genotype, Schmidt has certainly earned the title of "King of Sting" as he was dubbed in an article in *Outside Magazine* (1996). The title "King of Pain," however, was already taken by that point in time. "King of Pain" was the title of a pop song that made it to No. 3 on the charts in 1983—an ode to the pain that can be caused by heartbreak. The chorus went:

I have stood here before
inside the pouring rain
with the world turning circles
running around my brain
I guess I'm always hoping
that you'll end this reign
but it's my destiny to be the king of pain.

Admittedly, there are no references to insect venom in the song (although there's a reference to dead salmon, a beached blue whale, and a butterfly trapped in a spider web), but it has to be more than a coincidence that the artist who recorded the best known pop song about pain was Gordon Sumner of The Police, who goes by the name of Sting.

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