This Week's Citation Classic®

Habermann E. Bee and wasp venoms. *Science* 177:314-22, 1972.
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A few years ago, ingredients of venoms were dismissed as mere curiosities without relevance for general biology. Today, the view has changed. Teleologically, venomous animals practice high-level biochemical pharmacology; they have evolved a series of very active, specific, pharmacologically and chemically novel drugs that may be useful in elucidating basic mechanisms of central nervous system (apamin) or membrane (melittin, phospholipase A, mast cell degranulating-peptide) functions. [The *SCI*® indicates that this paper has been cited in over 440 publications.]

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I would never have dared to offer a review article to *Science* had I not attended a colloquium on toxins during an International Congress of Biochemistry in the late 1960s. What I presented there about Hymenoptera and, in particular, bee venom had not yet entered the mainstream of anglophone literature, although I had published on and reviewed the topic since 1951. When a participant, S. Udenfriend, encouraged me to write down a summary for *Science*, I took a chance. The resulting review covered about 20 years of continuing, largely unnoticed work. At least partially, its high citation rate may have a simple bibliographic reason: the original papers had been presented in internationally recognized journals, but in the German language.

The publication was and is attractive for two reasons. First, I subjected bee venom to a complete analysis both biochemically and pharmacologically, while other venoms had served as the source of just a single constituent. Attention was also given to the cooperative actions of the various components. My work on bee venom led to the distinction between enzymes and toxins devoid of enzymatic activity and to the functional resynthesis of some particular effects of the venom by recombination of the separated components.[1] Thus, general rules emerged from my preoccupation with an esoteric topic.

Second, the publication in *Science* generated interest in the properties of the individual peptides that we had described and sequenced. As it turned out, all of them became useful tools in biology. *Melittin*, which is the main peptide component, bored me as a pharmacologist because it was active on every system tested. However, its unique amphipathic structure makes it a model for peptide incorporation into and interaction with biomembranes.[2] *Apamin* belongs to the few peptides with a prominent centrally stimulating effect in animals. It blocks a subtype of CA^{2+}-dependent K^+-channels specifically and with high affinity. An endogenous equivalent of apamin in pig brain has even been postulated.[3] *Mast cell degranulating peptide* (MCD-peptide) was introduced as a histamine releaser, with due reference to B. Fredholm's work.[4] Later on we and others focused on its central effects, and now it serves as a tracer for a class of K^+-channels.

The publication in *Science* marks the zenith of my work with insect venoms. Later I shifted to different (bacterial) toxins,[5] while others took over those from Hymenoptera.[6] The contents of the publication survived my interest in insect venoms and even my name. Such uncoupling is the ultimate proof for acceptance of one's work by the scientific community. Nevertheless, I have to admit my mixed feelings at a conference about 10 years ago when I was just 51 years old. A young scientist had spotted my name in the list of participants just before he started his talk about bee venom peptides. He commenced: "I am particularly happy that Dr. Habermann is still among us." I thoroughly shared his opinion.

1. **Neumann W & Habermann E.** Beiträge zur Charakterisierung der Wirkstoffe des Bienengiftes. (Characterization of the active principle of bee venom). *Naunyn-Schmied. Arch. Pharmacol.* 222:367-87, 1954. (Cited 75 times since 1955.)
2. **Vogel H & Jähnig F.** The structure of melittin in membranes. *Biophysical J.* 50:573-82, 1986.
3. **Fosset M, Schmid-Antomarchi H, Hugues M, Romey G & Lazdunsky M.** The presence in pig brain of an endogenous equivalent of apamin, the bee venom peptide that specifically blocks Ca^{2+}-dependent K^+ channels. *Proc. Nat. Acad. Sci. USA* 81:7228-32, 1984.
4. **Fredholm B.** Studies on a mast cell degranulating factor in bee venom. *Biochem. Pharmacol.* 15:2037-43, 1966.
5. **Habermann E & Dreyer F.** Clostridial neurotoxins: handling and action at the cellular and molecular level. *Curr. Topics Microbiol. Immunol.* 129:93-179, 1986.
6. **Piek T,** ed. *Venoms of the Hymenoptera. Biochemical, pharmacological and behavioural effects.* London: Academic Press, 1986. 570 p.