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Scent Brush of a Male Moth

Bugs, Behavior, and Biomolecules: The Naturalist's Guide to the Future

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Thomas Eisner

Exploration and Discovery

My interest in *Utetheisa ornatrix* dates back to an occasion some forty years ago when I saw an individual of this beautiful multicolored moth species fly into a spider's web. I fully expected the spider to make a meal of its catch, but not so. The moment the moth struck the web the spider darted toward it, only to refrain from biting it and to proceed to cut it loose. Systematically, by use of its fangs and palps, the spider cut each of the silken strands that were imprisoning the moth, until the moth fell free.

I was soon to learn that this was no freak event. I offered *Utetheisa* to a diversity of spiders, including orb-weavers, wolf spiders, and jumping spiders, and found that they all rejected the moth. *Utetheisa* was decidedly distasteful, and so was its larva. When I offered *Utetheisa* caterpillars to wolf spiders, the spiders consistently refused to take them.

Eventually, working with my wife Maria and my students, and with my friend Jerry Meinwald and his associates from Cornell's chemistry department, we discovered why *Utetheisa* is unpalatable to spiders. As a larva, *Utetheisa* feeds on leguminous plants of the genus *Crotalaria* that contain highly bitter toxins called pyrrolizidine alkaloids (PAs). *Utetheisa* larvae are unaffected by PAs and are able to incorpo-

rate the compounds without having to detoxify them. They retain the chemicals systemically through metamorphosis, with the result that the adults themselves come to possess the compounds.

We proved that it is the PAs that give *Utetheisa* its bad taste. We were able to raise *Utetheisa* in the laboratory on a PA-free diet, thereby generating moths that lacked PA. Such moths, which were perfectly normal in other respects, proved palatable to spiders. We also showed that crystalline PA, when added to the surface of insects ordinarily eaten by spiders, renders such insects decidedly less acceptable.



Figure 1: A male *Utetheisa* moth wiping its everted scent brushes against the female in courtship.

Utetheisa transmits PAs to its eggs. Eggs laid by *Utetheisa* that we raised on the PA-free diet were themselves PA-free, and, as a consequence, vulnerable to attack. Eggs endowed with PA, in contrast, proved unacceptable to ants, green lacewing larvae, ladybugs, and parasitoid wasps.

Utetheisa adults have a life span of three to four weeks. The female, over that period, lays hundreds of eggs. How, we wondered, does she manage to protect them all? Does she have enough PA stored in her body to provision her entire brood? The answer is that she is not, in fact, ordinarily sufficiently endowed, but that she is able to obtain supplementary PA by mating. The *Utetheisa* female is promiscuous, and she receives PA from each male with the sperm package. The number of partners that a female takes over her lifetime is astonishing. Under natural conditions, in established populations of the moth, females mate, on average, with eleven males. Prima donnas may take more than twenty partners. I know this because the female *Utetheisa* keeps a sort of diary of its ex-

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ploits. The *Utetheisa* female retains a vestige of each sperm package it receives, a small tubular remnant that stays with it for life. These vestiges, each a *carte de visite* from an individual male, can be accessed by dissection of the female, and counted. Having on average as many as eleven partners clearly indicates that the female *Utetheisa* makes every effort to exploit the male's gift-giving capacity.

Utetheisa differs in the quantity of PA it sequesters as larvae, and as a consequence has varying PA content as an adult. For the female, which is dependent on receipt of PA from males, it is of some importance to know how much PA a prospective mate holds in store, since this may determine the magnitude of the nuptial gift she receives. Interestingly, the female *Utetheisa* puts the males to the test during courtship. The females assess the males' PA load and mate selectively with males richest in PA, ensuring thereby that they will be more generously provisioned. And how can females tell that a male has a higher quantity of PA? It turns out that the male gives off a scent, a pheromonal signal, by which he reveals his alkaloid load. He emits that signal from two brush-like structures that he everts during close-range precopulatory interaction with the female. The pheromone, hydroxydanaidal (HD), is derived by the male from PA, in quantity proportional to his PA load. Therefore, by favoring males more intensely scented with HD, females are guaranteed receipt of larger amounts of PA. It turns out that males selected for high HD content are also physically the largest, which has important consequences for *Utetheisa*, because body size is heritable in this moth. Thus, by mating selectively with strongly scented males, females are assured that their offspring will be larger – that their sons will be more competitive in courtship and their daughters more fecund. Evidently, by being "choosy," the female *Utetheisa* benefits both phenotypically and genetically.

Interesting also is the mechanism by which *Utetheisa* males and females ensure that they

find one another. In *Utetheisa*, as in moths generally, it is the female that attracts the male. She does so in conventional fashion, by emission of a pheromone, a mixture of unsaturated hydrocarbons, that she produces in a pair of glands that open on the abdominal tip. We observed early on that the female *Utetheisa*, during the hour or so after dusk when she broadcasts her pheromone, undergoes a conspicuous throbbing of the abdomen. Thanks to the efforts of Bill Conner, a student in my laboratory at the time, we learned that this throbbing is the visible concomitant of a rhythmic compression and decompression of the pheromonal glands that causes the contained secretion to be emitted in pulses. The advantage that the female derives from such discontinuous delivery of attractant appears to be economic. By pulsing, the female may be able to cut back on the amount of pheromone released.



Figure 2: Caterpillar of *Utetheisa* inside a seed pod of its *Crotalaria* food plant.

Courtship in *Utetheisa* is evidently a fine-tuned affair. Chemical signaling is the rule of the game, both in the initial attractant phase of the behavior, and in the subsequent interactive phase, when the female assesses the male. Is the mating strategy of *Utetheisa* unusually complex? Most probably not. Other insects are bound to be discovered that have equally sophisticated sexual communicative systems. Are chemical signals likely to play major roles in these other species as well? Most probably. Chemical interaction is the most common form of sexual interaction in animals of all kinds. Studies of animal courtship are therefore likely to remain multidisciplinary and to continue to be dependent on the collaboration of behaviorists, ecologists, neurobiologists, and chemists.

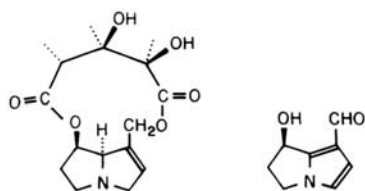


Figure 3: A pyrrolizidine alkaloid (left) and its pheromonal derivative, hydroxydanaidal.

My research on the chemical ecology of insects has been supported since 1959 by the National Institutes of Health (grant AI02908), and more recently also by funds from Johnson & Johnson. A more comprehensive account of our work on *Utetheisa ornatrix* can be found in my recent book, *For Love of Insects* (Harvard University Press, 2003).

Jerrold Meinwald

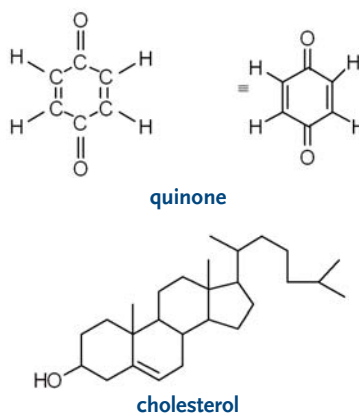
Chemical Elucidation

When Tom Eisner walks across the Harvard Yard and through the small patch of woods en route to the Academy, he sees what most of us do not see: a bush with all its leaves perfectly intact; a millipede being attacked by ants, bathing itself in a brown secretion; a spider releasing a beautiful moth from its web. And he asks himself questions that many of us might not ask: Why haven't some herbivores eaten these leaves? Does the millipede's secretion provide a useful defense against ant attacks? Why is this spider forgoing what would appear to be an attractive feast?

These are a naturalist's questions. They can be answered by following up on the field observations, bringing the subjects into the laboratory, and designing appropriate behavioral experiments. Only slightly less obviously do they turn out to be chemical questions as well. Their pursuit at the molecular level can yield unexpected insights into such basic biological phenomena as how organisms defend themselves and how they communicate with one another.

But the chemist's world is not the naturalist's. One important difference is the matter of scale; the chemist's world is very much smaller, in the sense that its basic entities are molecules rather than cells, organisms, populations, or ecosystems. Thus, the molecules of *p*-benzoquinone (hereafter simply "quinone"), which serves to repel ants, or of monocrotaline, a typical plant-produced pyrrolizidine alkaloid that can render *Utetheisa* unpalatable, have dimensions of about a millionth of an inch. The mo-

lecular formula of quinone is $C_6H_4O_2$, meaning that its molecules are composed of six atoms of carbon, four of hydrogen, and two of oxygen. But their composition alone does not adequately define what quinone is. It was only in the mid-nineteenth century that chemists realized that molecules also have specific structures and shapes. In order for a molecule to be quinone, its twelve constituent atoms need to be bonded to one another in one specific way. Figuring out how the atoms are connected in any given compound – determining its structure – can be a daunting task. For compounds of the complexity of cholesterol or morphine, it required several chemists' lifetimes of research. In the case of quinone, a relatively simple structure, the process was much quicker. The correct arrangement (of the large number theoretically possible) is an almost regular hexagon of carbon atoms, with one oxygen attached to the carbons at each of two opposite corners, and one hydrogen attached to each of the four remaining carbon atoms. This structure is usually written in a more abstract style, as shown below. For more complex molecules, such as cholesterol, such shorthand representations are easier to write, read, and remember.



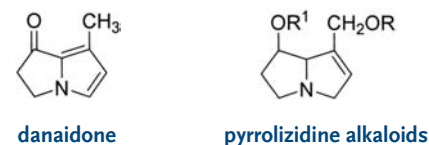
How small these molecules are can be gathered from a simple thought experiment. Imagine an espresso spoon about half full of bright yellow crystals of quinone (approximately 1 gram). A back-of-the-envelope calculation tells us that this sample contains about 6×10^{21} quinone molecules. If we were to count them at a speed of ten per second, it would take us 6×10^{20} seconds. With about 4×10^7 seconds in a year, we would finish counting in $(6 \times 10^{20}) / (4 \times 10^7)$ or 1.5×10^{13} years. If we assume the universe is 15 billion (1.5×10^{10}) years old, we conclude that the task of counting a gram of quinone molecules would require a *thousand times the age of the universe!*

The invention of logic capable of determining the structures of molecular entities this small was one of the great intellectual achievements of the nineteenth century. But despite many

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major advances in ultraviolet and infrared spectroscopy, nuclear magnetic resonance spectroscopy, mass spectrometry, and X-ray crystallography during the twentieth century, structure determination remains one of our great challenges. Its importance stems from the fact that the physical, chemical, and biological properties of any compound depend entirely on its molecular structure.

Structures also suggest origins and relationships. For example, when we examined the male pheromonal secretion of a Trinidad danaid butterfly, *Lycorea ceres*, we discovered danaidone. We were immediately led to speculate that this compound might be derived from a plant alkaloid, on the basis of the clear architectural similarity of the insect- and plant-derived structures. Subsequent research with related butterflies from Florida and East Africa confirmed this speculation. This research might be considered a prelude to the much richer *Utetheisa* story that Tom Eisner has outlined.



I want to end by saying a few words about spiders, supporting actors in the *Utetheisa* story. With almost forty thousand described species, spiders constitute the second largest group of terrestrial animals, and they are all thought to be capable of paralyzing their prey with their venoms. Recent drug candidates developed from spider venom components block neuronal nicotinic acetylcholine receptors, increase parathyroid hormone secretion, and inhibit atrial fibrillation, a common chronic cardiac arrhythmia. However, since less than 1 percent of spider venoms have been studied chemically, they present an intriguing opportunity for future research. Doctors Frank Schroeder, An-

drew Taggi, and Matthew Gronquist in my laboratory have been looking recently for novel chemical entities in spider venoms, and they have used a new experimental approach that avoids the loss of information concerning unexpected or unstable components.

Conventionally, natural products are subjected to some sort of chromatographic purification or separation before an attempt is made to determine the structures of the individual components that comprise them. Both gas-liquid chromatography and high-pressure liquid chromatography provide the remarkable ability to separate highly complex mixtures of natural products into dozens or even hundreds of individual components. However, these procedures can also result in the loss or decomposition of some particularly interesting constituents. But with the use of one- and two-dimensional NMR spectroscopic analysis before any separation is attempted, followed by mass spectrometric studies, this loss of information can be avoided. Using this approach, we have characterized a new family of venom components whose molecules are built from nucleic acid bases, sugars, and sulfate groups. It will be exciting to study the biological properties of these novel compounds once we have synthesized them.

A final point to make is that the same chemical principles apply whether we are studying insect pheromones, steroid hormones, neurotransmitters, antibiotics, or flavors and fragrances. That is to say, in chemical research the biological context temporarily vanishes. Chemists studying nature seek to isolate biologically significant substances, to determine their structures, to synthesize compounds of interest, to discover origins and metabolic pathways, and to understand mechanisms of action – all at the molecular level. Ever more powerful experimental techniques have accelerated these endeavors enormously in the last few decades, and have enabled us to do with micrograms or even nanograms of material what might have required gram quantities fifty years ago. The cure for pancreatic cancer that E. O. Wilson muses might turn up in an Andean beetle might be found by analyzing a single specimen. Even the ultimate objective of working with single molecules is coming into sight. It is inevitable that chemists will continue to think smaller and smaller as we progress through the twenty-first century.

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John Hildebrand

Neural Processing

Since reading the books of Jean-Henri Fabre when I was a schoolboy, I have been fascinated by chemical communication in insects and especially the “perfumes,” or sex pheromones, that female moths release to attract mates. Early in my independent research career, I decided to study the behavior of the responding male moths and the sensory neural mechanisms – the “brains” – responsible for it. To facilitate neurobiological explorations, I needed moths that were both easy to rear in the lab and very big. Advice from my colleagues Fotis Kafatos and Jim Truman, then at the Harvard Biological Laboratories, guided me to the ideal species for my purposes: the sphinx moth *Manduca sexta* (tobacco hornworm). As soon as I saw it, I knew that *Manduca* would be good for my purposes, and my coworkers and I have been working on those beautiful creatures since that day thirty-two years ago.

Manduca is a powerful flyer, and its large size and feeding behavior can fool a casual observer into mistaking it for a hummingbird. In the warm, humid evenings of summertime, throughout much of the territory from the northern United States to Argentina, one can observe both male and female *Manduca* hovering near tubular white flowers and feeding on their nectar. That in-flight refueling enables the moths to do what really matters to them: to reproduce. A female needs chemical energy to produce eggs, to synthesize and release the sex pheromone in order to attract a mate, and then to fly to and deposit her fertilized eggs on appropriate host plants. A male has to find a receptive female by means of pheromone-modulated flight to the unseen source of the seductive chemical message.

Much is known about the behavior of male moths in response to the sex pheromones released by conspecific females and about the “calling” behavior of the females. (Behavioral studies of *Manduca* by my group, and especially Wendy Mechaber, Mark Willis, and the late Ed Arbas, have built upon previous masterful work on other species by many leading investigators, including Tom Baker, Ring Cardé, John Kennedy, Ernst Kramer, Wendell Roelofs, and their coworkers.) A calling female, typically positioned on a plant, extends her ovipositor (located at the tip of her abdomen) to expose the intersegmental cuticle from which the sex pheromone, produced in underlying glands, evaporates. That volatile signal is carried down-

wind, forming a sex-pheromonal plume that may extend many meters from the moth. The pheromone is not uniformly distributed within the plume, nor does it form a concentration gradient. Instead, it is present in filaments and blobs of pheromone-bearing air interspersed with relatively clean air. The pattern is similar to that of a lit incense stick, where one can see the filaments of smoke emanating from the burning tip.

At a time when the boundaries between disciplines are disappearing, it is gratifying and exciting to savor the rich benefits to be derived from the integration of the study of animal behavior, chemical ecology, and neurobiology.

A flying male *Manduca* that happens to intersect the pheromone plume detects the species-specific chemical signal and typically sets out to locate the female releasing it. He does so by orienting and flying upwind in a characteristic zigzagging manner. He receives intermittent stimulation, owing to the discontinuous distribution of the pheromone within the plume, and the resulting spatiotemporal pattern of stimulation is necessary for the male moth to respond to the chemical message. The pheromone activates a counterturning flight program, and with each “hit” from a filament of the pheromone, an upwind thrust is superimposed on that flight pattern. When the male moth inevitably strays out of the invisible and meandering plume, and therefore ceases to receive frequent pulses of the pheromone, the anemotactic zigzagging flight that was triggered and sustained by the pheromone gives way to a different pattern of behavior activated by the loss of the pheromonal stimuli. Upwind flight thus gives way to stationary counterturning that usually brings the moth back into contact with the plume, and then upwind pheromone-modulated flight resumes. The net result of these behavioral responses to detecting, and losing, the pheromone signal is to follow the plume to its source. As the male approaches the calling female, changes in the character of the pheromone filaments let him know that he is close. When he reaches his goal, he hovers near the female, contacting her and landing, and mating at last.

The sex pheromone that exerts such powerful control over the male's behavior is a mixture, and the essential signal is the blend of components. Chemical analyses performed by our colleagues Karl Dahm and James Tumlinson and their coworkers revealed that the sex pheromone of *Manduca sexta* is a mixture of as many as eight 16-carbon aldehydes. Of those, two are necessary for the oriented flight from a distance, and although not optimal for eliciting that behavior, an appropriate mixture of those two components is sufficient to do so. They are E₁₀,Z₁₂-hexadecadienal and E₁₀,E₁₂,Z₁₄-hexadecatrienal. For simplicity, hereinafter I will refer to these components as *A* and *B*.

My coworkers and I are especially interested in trying to understand how moths detect a behaviorally significant volatile chemical stimulus like this simple pheromone mixture and how they process sensory information about it in the central nervous system (CNS), eventually to generate the observed behavioral responses. From previous pioneering research by Dietrich Schneider and his protégés, particularly Jürgen Boeckh, Karl-Ernst Kaissling, Ernst Priesner, and R. Alexander Steinbrecht, we knew that the antennae of male moths possess male-specific sensory hairs, or sensilla, innervated by olfactory receptor cells (ORCs) that are exquisitely narrowly and sensitively "tuned" to detect the components of the conspecific female's sex pheromone. That has proved to be the case for *Manduca* as it is for the species they studied. A large fraction of the approximately three hundred thousand ORCs in one male *Manduca* is dedicated to the detection of sex-pheromone components. Action potentials (spikes) in activated ORCs signal the presence of components *A* and *B* to the brain. The temporal pattern of pulses of the pheromone received by the ORCs is represented by bursts of spikes, and information about the concentration (intensity) of each component is encoded in the instantaneous frequency of spiking in those bursts in the responding ORCs.

For us, a particularly interesting challenge is to unravel the neural circuitry and physiological mechanisms responsible for processing sensory information about chemical – and in the present case, sex-pheromonal – stimuli in the CNS, and ultimately to explain how those messages influence behavior. (Many coworkers have contributed to my group's efforts along these lines over many years, among them, notably, Scott Camazine, Tom Christensen, Bill Hansson, Thomas Heinbockel, Uwe Homberg, Ryohei Kanzaki, Jane Roche King, Hong Lei, Steve Matsumoto, Wolfgang Rössler, Josh Sanes, Anne Schneiderman, Leslie Tolbert, and Brian Waldrop.)

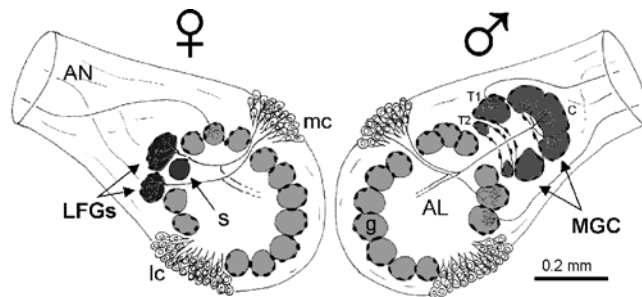


Figure 1. Diagrammatic representations of an antennal lobe (AL) of female (left) and male (right) adult *Manduca sexta*, showing the antennal nerve (AN), the lateral (lc) and medial (mc) groups of neuronal cell bodies, "ordinary" glomeruli (g), and the sexually dimorphic glomeruli – the macroglomerular complex (MGC) in the male AL, including cumulus (C) and toroids (T₁, T₂), and the three female-specific glomeruli (LFGs and S).

Antennal ORCs send their axons through the antennal nerve into the antennal lobe (AL) of the deutocerebrum in the brain (figure 1). The neuropil of each AL contains a characteristic array of glomeruli, which are condensed knots of neurites and synapses and the sites of massive convergence of ORC axons on far fewer AL neurons. Indeed, the primary olfactory centers in the brains of most animals that have differentiated olfactory systems – from arthropods such as *Manduca* to mammals including mice and mankind – characteristically exhibit glomeruli. In insects, there is a species-specific number of glomeruli, and in moths the array includes sexually dimorphic glomeruli. Flanking the glomerular neuropil of the AL are groups of neuronal cell bodies; in *Manduca*, there are three such groups (lateral, medial, and anterior) totaling about twelve hundred neurons. All the glomeruli (sixty-three in *Manduca* ALs, including three sexually dimorphic glomeruli) and some of the AL neurons are identifiable in an insect's AL, which contributes to making insects experimentally favorable for studies of olfaction and olfactory control of behavior.

Each ORC axon projects to and terminates within a single glomerulus, where it makes synaptic connections with neurites of AL neurons. Thus the glomeruli are the sites of primary synaptic processing of sensory information about olfactory stimuli. AL neurons belong to three broad classes: local interneurons (LNs), projection or output neurons (PNs), and centrifugal modulatory neurons. Each of those classes is further divisible into a variety of types of neurons based on attributes such as cellular morphology, physiological functions, and neurochemical phenotype. Most LNs have wide-field arborizations in most or all glomeruli, most lack axons extending outside the AL, and most, if not all, mediate inhibitory synaptic interactions within and among glomeruli. The most thoroughly studied PNs have arboriza-

tions confined to a single glomerulus and an axon projecting to higher-order olfactory centers in the protocerebrum.

ORCs in the male moth's antenna tuned to sex-pheromone components *A* and *B* send their axons to two of the three male-specific glomeruli, which in *Manduca* are large and characteristically shaped and together are called the macroglomerular complex (MGC). *A*-specific ORCs project to "toroid I," a donut-shaped glomerulus, while *B*-specific ORCs send their axons to the "cumulus," which is a globular, multi-lobed structure resembling a cumulus cloud. When the male's antenna intersects a filament of pheromone-laden air, both *A*- and *B*-specific ORCs are stimulated essentially simultaneously, so that primary afferent information about these two essential components reaches the MGC glomeruli at the same time.

We have learned a great deal about neural processing of sex-pheromonal information in *Manduca* and certain other species of moths by means of intracellular recording from, and staining of, individual neurons associated with the MGC and higher-order way stations in the olfactory pathway of the brain. In particular, "listening in" to the responses of MGC PNs to antennal stimulation with *A* or *B* or with mixtures of *A* and *B* has informed us about what is accomplished through synaptic processing in a given glomerulus. We have learned, for example, that although "the mixture is the message," sensory information about the qualitative presence and concentration of the individual pheromone components is processed through parallel labeled lines in the AL and onward into the protocerebrum. At the same time MGC PNs and, more strikingly, certain protocerebral neurons exhibit dramatically blend-specific responses that signal the salience of each component, *A* or *B*, when in the presence of the other. Particular MGC PNs of this kind have an enhanced ability to follow the discontinu-

ous pulses of pheromone that occur because of the filamentous nature of the plume, and are essential for triggering and sustaining the male moth's characteristic behavioral responses.

Our explorations of the male-specific olfactory pathway dedicated to the sex pheromone have taught us much about how that critically important natural signal is detected and processed through the CNS, ultimately to influence the flight behavior of the receiver. At the same time, we have used this specialized olfactory subsystem as a sort of keyhole through which to view a bigger landscape of olfaction. We expect that the principles and mechanisms we have uncovered in studying the MGC will prove to be exaggerated versions of the principles and mechanisms that operate in and among other glomeruli, and therefore will guide us to greater understanding of general issues in olfaction in insects and other animal taxa alike.

It is also clear that investigations of olfactory neurobiology and neuroethology sometimes can lead to discoveries in the realm of chemical ecology; we think of the approach as "reverse chemical ecology." By first probing the olfactory "tuning" of ORCs and their CNS targets, we can identify compounds in the environment – derived from conspecifics, hosts, or other sources of importance to the animal in question – that are likely to be behaviorally significant for that creature. Probing the brains behind behaviors influenced by chemosensory stimuli in the environment can teach us how the chemical components of a stimulus contribute to an animal's behavior, and how sensory signals can exert control over motor outputs

of the animal. Neurobiological explorations can even lead to discovery of unforeseen stories in chemical ecology. At a time when the boundaries between disciplines are disappearing, it is gratifying and exciting to savor the rich benefits to be derived from the integration of the study of animal behavior, chemical ecology, and neurobiology.

The exciting and important advances that have been achieved through the application of contemporary tools of molecular genetics and cell biology to olfactory systems in the last two decades have explained, or confirmed earlier findings about, early events in chemosensation at the level of receptor cells and their projections to the CNS. Much of what has been learned through that approach, however, has reinforced and extended earlier findings made by means of powerful physiological and anatomical methods. Now the challenge is to understand how the inputs are processed by higher-order neural circuits to achieve recognition, comparison, integration, and learning of and adaptive behavioral responses to olfactory stimuli in the environment. The effort to discover how the brain works with the inputs will benefit greatly from molecular approaches, but must also emphasize experimentation with other powerful tools such as the methods of imaging, single- and multi-unit physiological recording, neural circuit analysis, computational modeling, and rigorous behavioral studies. Although Yogi Berra unquestionably got it right when he observed that "there's nothing as hard to predict as the future," we can predict with assurance that what lies ahead in this domain of science will be exciting.

My group's research has been supported by funding from NIH, NSF, USDA, DoD, and Monsanto, and most recently by NIH grant DC-02751 and NSF grant IBN-0213032. For further reading on this subject, see the following publications and the references cited in them: T. A. Christensen and J. G. Hildebrand, "Pheromonal and host-odor processing in the insect antennal lobe: how different?" *Current Opinion in Neurobiology* 12 (2002): 393–399; T. A. Christensen and J. White, "Representation of olfactory information in the brain," in T. E. Finger, W. L. Silver, and D. Restrepo, eds., *The Neurobiology of Taste and Smell*, 2nd ed. (New York: Wiley-Liss, 2000), 201–232; J. G. Hildebrand, "King Solomon Lecture – Olfactory control of behavior in moths: central processing of odor information and the functional significance of olfactory glomeruli," *Journal of Comparative Physiology A* 178 (1996): 5–19; J. G. Hildebrand and G. M. Shepherd, "Molecular mechanisms of olfactory discrimination: converging evidence for common principles across phyla," *Annual Review of Neuroscience* 20 (1997): 593–631; and T. D. Wyatt, *Pheromones and Animal Behaviour: Communication by Smell and Taste* (Cambridge: Cambridge University Press, 2003). ■

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Figure 1 in John Hildebrand's article © by John Hildebrand.



Jerrold Meinwald, John Hildebrand, Academy President Patricia Meyer Spacks, and Thomas Eisner



Frank Westheimer and Rose Frisch (both, Harvard University)