BIOCHEMISTRY

THE SCENT OF YOUR THOUGHTS

Although we are usually unaware of it, we communicate through chemical signals just as much as birds and bees do

By Deborah Blum

Deborah Blum won a Pulitzer Prize in 1992 and is author most recently of *The Poisoner's Handbook: Murder and the Birth of Forensic Medicine in Jazz Age New York*. She first learned about pheromones by watching her father, an entomologist, extract them from ants.

THE MOMENT THAT STARTED MARTHA MCCLINTOCK'S SCIENTIFIC CAREER WAS A WHIM OF youth. Even, she recalls, a ridiculous moment. It is summer, 1968, and she is a Wellesley College student attending a workshop at the Jackson Laboratory in Maine. A lunch-table gathering of established researchers is talking about how mice appear to synchronize their ovary cycles. And 20-year-old McClintock, sitting nearby, pipes up with something like, "Well, don't you know? Women do that, too."

"I don't remember the exact words," she says now, sitting relaxed and half-amused in her well-equipped laboratory at the University of Chicago. "But everyone turned and stared." It is easy to imagine her in that distant encounter—the same direct gaze, the same friendly face and flyaway hair. Still, the lunch-table group is not charmed; it informs her that she does not know what she is talking about.

Undaunted, McClintock raises the question with some graduate students who are also attending the workshop. They bet that she will not be able to find data to support her assertion. She returns to Wellesley and talks this matter over with her undergraduate adviser, Patricia Sampson. And Sampson throws it back at her: take the bet, do the research, prove yourself right or wrong.

Three years later, now a graduate student, McClintock publishes a two-page paper entitled "Menstrual Synchrony and Suppression" in the journal *Nature*. (*Scientific American* is part of Nature Publishing Group.) It details a rather fascinating effect seen in some 135 residents of Wellesley dormitories during an academic year. In that span, menstrual cycles apparently began to shift, especially among women who spent a lot of time together. Menstruation became more synchronized, with more overlap of when it started and finished.

Today the concept of human menstrual synchronization is generally known as the McClintock effect. But the idea that has continued to shape both her research and her reputation, the one that drives a still flourishing field of research, is that this mysterious synchrony, this reproductive networking, is caused by chemical messaging between women—the notion that humans, like so many other creatures, reach out to one another with chemical signals.

It has been harder than expected to single out specific signaling chemicals and trace their effects on our bodies and minds as precisely as entomologists have done for countless insect pheromones. But in the four decades since McClintock's discovery, scientists have charted the influence of chemical signaling across a spectrum of human behaviors. Not only do we synchronize our reproductive cycles, we can also recognize our kin, respond to others' stress and react to their moods—such as fear or sadness or "not tonight, honey"—all by detecting chemicals they quietly secrete. As researchers learn more about this web of human interaction, they are helping to bridge an arbitrary dividing line between humans and the natural world.

ANIMAL KINGDOM CHEMISTRY

THE VERY INTRIGUING IDEA of animals sharing invisible chemical cues has a long and illustrious history, at least as far as other species are concerned. The ancient Greeks talked enthusiastically of the possibility that female dogs in heat might produce some mysterious secretion capable of driving male dogs into a panting frenzy. Charles Darwin, pointing to several famously smelly species, proposed that chemical signals were part of the sexual selection process. Throughout the late 19th

IN BRIEF

Evidence suggests that humans unconsciously exchange chemical messages that help to synchronize women's menstrual cycles, signify the presence of kin, and convey moods such as stress or fear. **The signals** may be akin to the pheromones found in hundreds of animal species, including mammals.

Researchers are isolating the compounds secreted by humans and attempting to decode their physiological and psychological effects.

Illustration by Noma Bar

century the great French naturalist Jean-Henri Fabre puzzled over evidence that the siren call of chemistry could stir winged insects into determined flight.

Still, it was not until 1959 that the science really began to gain traction. In that year Adolf Butenandt, a Nobel laureate in chemistry, isolated and analyzed a compound that female silk moths release to attract males. Butenandt dissected the insects and painstakingly extracted the chemical from their microscopic secretion glands. He collected enough to crystallize it so that he could discern its molecular structure by x-ray crystallography. He called the compound "bombykol," after the Latin name for the silk moth.

It was the first known pheromone, although the term did not yet exist. Shortly after, two of Butenandt's colleagues, German biochemist Peter Karlson and Swiss entomologist Martin Lüscher, coined that name out of two Greek words: *pherein* (to transport) and *horman* (to stimulate). They defined a pheromone as a type of small molecule that carries chemical messages between individuals of the same species. The compounds must be active in very tiny amounts, potent below a conscious scent threshold. When released by one individual in a species and received by another, the two researchers wrote, they produce a measurable effect, "a specific reaction, for instance, a definite behavior or a developmental process."

Since then, an astonishing array of pheromones—the best known and established class of chemical-signaling molecules exchanged by animals—have been found in insects, not just in silk moths but in bark beetles, cabbage looper moths, termites, leaf-cutter ants, aphids and honeybees. According to a 2003 report from the National Academy of Sciences, entomologists "have now broken the code for the pheromone communication of more than 1,600 insects." And pheromones serve many more purposes than simply attracting mates: they elicit alarm, identify kin, alter mood, tweak relationships.

By the late 1980s pheromones had also been found to influence a wide spectrum of noninsect species, including lobsters, fish, algae, yeast, ciliates, bacteria, and more. As this new science of chemical communication grew—acquiring the more formal name of semiochemistry, from the Greek *semion* (meaning "signal")—scientists extended the search to mammals. Almost immediately they ran into resistance from their colleagues.

"In the 1970s and 1980s people would jump at you if you said 'mammalian pheromone,'" recalls Milos Novotny, director of the Institute for Pheromone Research at Indiana University. "They'd say, 'There's no such thing: mammals are not like insects. They're too evolved and complex to be spontaneously responding to something like a pheromone.'"

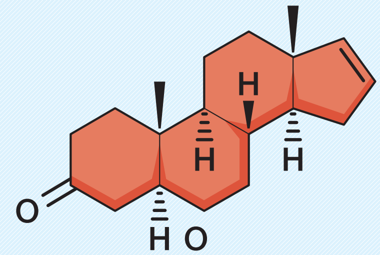
But by the mid-1980s Novotny had not only identified a pheromone in mice that regulated intermale aggression, he had synthesized it. Such compounds were also verified in rats, hamsters, rabbits and squirrels. And as the list lengthened, it also became apparent that mammals' pheromones were very like—if not identical—to those found in insects. As an example, most researchers cite the stunning work of the late Oregon Health and Science University biochemist L.E.L. "Bets" Rasmussen, who showed in 1996 that a sex pheromone secreted by female Asian elephants is chemically identical to one used by more than 100 species of moths for similar purposes of attraction.

McClintock had proposed a similar idea in 1971 in her pioneering paper on menstrual synchrony. "Perhaps," she wrote then, "at least one female pheromone affects the timing of other female menstrual cycles."

ODOROUS LANDSCAPE

MCCLINTOCK, NOW 63, is sitting in a small, sunny room occupied by filing cabinets, computers, racks of stoppered vials and tubes, and scent sticks—all contributing to a faint, slightly sweet chemical aroma—and a dark-haired graduate student named David Kern. ("All the other graduate students would climb over my dead body to get in this room," he says.) McClintock's lab is at the University of Chicago's Institute for Mind and Biology, of which she is a founding director. She wears a tweedy jacket over a bright, patterned shirt, and she is thinking over a question: How far has the science of semiochemistry traveled since that day, some four decades ago? The case for human chemical communication has been made, she says, and "our goal is to tackle identifying the chemical compounds. And then we can refine our understanding of what fundamental roles they play."

That task is anything but easy. Human body odor is estimated to derive from about 120 compounds. Most of these compounds occur in the water-rich solution produced by the sweat glands or are released from apocrine, or scent, glands in the oily shafts of hair follicles. The apocrine glands concentrate the most under the arms, around the nipples and in the genital regions.



The steroid androstadienone is a promising candidate for a human pheromone. It has been shown to influence cognition, stress hormones and emotional responses.

It is a complicated landscape, made even more complicated by our use of what researchers refer to as exogenous compounds, such as soap, deodorants and perfumes, as Johan Lundström of the Monell Chemical Senses Center in Philadelphia points out. And yet Lundström marvels at how adeptly our brains sort through this chemical tangle. Neuroimaging work done at his lab finds a 20 percent faster response to known human chemical signals compared with chemically similar molecules found elsewhere in the environment. "The brain always knows when it smells a body odor," Lundström says.

This capacity is already present in infancy. Numerous studies in humans have shown that, as is true in animals, mothers and infants are acutely attuned to each other's scent. This scent knowledge is so precise that babies even prefer the parts of clothes worn by their mother (and their mother only) touched by sweat compounds. The recognition, interestingly, is more acute in breast-fed infants than in those raised on baby formula.

"We're still just mapping the influential compounds from those that are not," Lundström says. "I don't think we're dealing with one single compound but rather a range of different ones that may be important at different times." Pheromones operate under the radar, he says, and they influence—but do not necessarily completely control—numerous behaviors. "If

Illustration by Brown Bird Design

we compare these with social cues, they may be less important than the obvious ways we communicate," Lundström says. But, he adds, the ability probably aided survival as we evolved, keeping us more closely attuned to one another.

Psychologist Denise Chen of Rice University also argues that this kind of chemical alertness would have conferred an evolutionary advantage. In her research, she collects odor samples from individuals while they watch horror movies. Gauze pads are kept in viewers' armpits to collect sweat released during moments of fear. Later, the pads are placed under volunteers' nostrils. For comparison, Chen has also collected sweat from people watching comedies or neutral films such as documentaries.

One of her early experiments found that participants could tell whether the sweat donor was fearful or happy at the time the sweat was produced. The subjects' guesses succeeded more often than they would by pure chance, especially for fear-induced sweat. Chen followed up with research showing that exposure to "fear sweat" seemed to intensify the alarm response—inclining participants to see fear in the faces of others. These exposures even enhanced cognitive performance: on word-association tests that included terms suggestive of danger, women smelling fear sweat outperformed those exposed to neutral sweat. "If you smell fear, you're faster at detecting fearful words," Chen explains.

In a study currently in press, she and Wen Zhou of the Chinese Academy of Sciences compared the response of long-time couples with people in shorter-term relationships. Those results indicated—perhaps not surprisingly—that the longer couples are together, the better the partners are at interpreting the fear or happiness information apparently encoded in sweat. "What I hope that people will see in this is that understanding olfaction is important for us to understand ourselves," Chen says.

And evidence continues to accumulate that unconscious perception of scents influences a range of human behaviors, from cognitive to sexual. In January, for instance, a team of scientists at Israel's Weizmann Institute of Science in Rehovot, led by psychologist Noam Sobel, reported that men who sniffed drops of women's emotional tears felt suddenly less sexually interested in comparison to those who smelled a saline solution. Sobel found a direct physical response to this apparent chemosignal: a small but measurable drop in the men's testosterone levels. The signal may have evolved to signify lower fertility, such as during menstruation. More generally, the discovery may help explain the uniquely human behavior of crying.

HARD SCIENCE

A MAJOR GOAL now is to identify the key chemicals that convey signals surreptitiously and to learn much more about how the body detects and reacts to those signals. George Preti, a Monell chemist, has mapped out a research project that would include tracking these messengers by analyzing sweat and apocrine secretions and studies of hormone levels in those who sniff the chemicals. "We've yet to identify the precise signals that carry the information," Lundström agrees. "And if we want a solid standing for this work, that's what's needed next."

McClintock also sees this as a priority. In recent years she has focused on building a detailed portrait of one of the more potent known chemosignals, a steroid compound called androstadienone. She believes that this particular small molecule is potent enough to meet the requirements of being called a human pheromone: it is a small molecule that acts as a same-species chemical signal and influences physiology and behavior. Over the years labs, including McClintock's and Lundström's, have found that this particular compound shows measurable effects on cognition and that it can alter levels of stress hormones such as cortisol and evoke changes in emotional response.

In one recent study McClintock and her colleague Suma Jacob of the University of Illinois at Chicago explored androstadienone's propensity to affect mood. They mixed a trace amount into the solvent propylene glycol and then masked any possible overt odor with oil of clove. They then exposed one study group to a solvent containing the compound and another to a plain solvent. Subjects were asked to smell gauze pads containing one version; they were told only that they were participating in olfaction research. All the subjects went on to fill out a long and tedious questionnaire.

Overall, the subjects exposed to androstadienone remained far more cheerful throughout the 15- to 20-minute test. A follow-up study repeated the same process but included brain imaging as well. The neuroimages showed that brain regions associated with attention, emotion and visual processing were more active in those exposed to the chemosignaling compound. McClintock sees this as a classic pheromonal effect, the kind that she speculated about decades ago.

Even so, she and other researchers continue to carefully talk of "putative" pheromones. Humans are complicated, and any causal links between specific chemicals and changes in behavior are hard to demonstrate conclusively. Indeed, no one can say for certain yet what chemical or chemicals account for McClintock's original discovery, the synchronization of women's menstrual cycles. Even the phenomenon itself has proved somewhat elusive: it has been confirmed in numerous follow-up studies but contradicted by others, and it is still not accepted unanimously by the scientific community.

Much of the discussion centers on what exactly is being synchronized—perhaps timing of ovulation, perhaps length of cycle. A review of human data from the 1990s by the father-and-son team of Leonard and Aron Weller of Bar-Ilan University in Israel found that synchrony sometimes occurs and sometimes does not. "If it exists," Leonard Weller reported, "it is certainly not ubiquitous."

Although she still retains the assertiveness of her college days, McClintock agrees that the effect is subtler than she thought at first. But she also believes that the critics tend to miss the more important point: that evidence for chemical communication between humans has steadily accumulated since her study. And that it is not surprising that our chemical messaging is turning out to be as intricate as every other form of human communication. SA

MORE TO EXPLORE

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