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## Sixth-Sense Drugs May Improve Mood, Alter Hormones

Lynn Shapiro, Medical Writer



### Introduction

When physician and biochemist David Berliner left the University of Utah for a job at Alza Chemicals, he made sure his skin cell extracts were stashed safely in dry ice. Studying the composition of skin, Dr. Berliner had scraped it off the casts of skiers who had broken their legs in the mountains around Salt Lake City. He concentrated the skin cells and would occasionally let the extracts stand in open flasks in his lab.

He noticed whenever the flasks were uncapped his colleagues' moods brightened. "People started joking," Berliner recalls. "One usually serious German woman wanted to order pizza and play cards. So we all started playing bridge." Strangely, when Berliner put the flasks in the refrigerator, the bridge games stopped and the sober moods returned. This was in the early 1960s. The word "pheromone" had just been coined in 1959 after scientists isolated the female silkworm moth's "bombykol," the substance the male moth finds irresistible.

**Body odor may contain chemical cues that allow others to distinguish whether someone is feeling fear, anger or happiness.**

Berliner says he wasn't familiar with pheromones back then. It would be nearly 30 years before he unfroze his extracts and isolated the molecules that triggered his colleagues' camaraderie.

### Carrying Excitement

Pheromones (from the Greek word *pherein*, meaning "to transfer") are hormonal byproducts shed from skin cells that waft through the air, triggering brain and hormonal changes in a receptive individual of the same species. Other pheromones provide genetic information such as who's ovulating, who's dominant, who's next of kin.

In animals, pheromones are central to reproduction. A male pig breathes the testosterone metabolite called androstenol into a sow's face. She subsequently assumes the spread-



legged position called lordosis so the male can mount her.

"In humans, they won't make you dumbstruck as they do in animals and insects. But they definitely have an effect on the emotional and hormonal state of people," says University of Chicago biopsychologist Martha McClintock. In a 1998 *Nature* article, she offered what scientists consider the best proof to date that human pheromones exist.

### Anti-anxiety Pheromones

Although Berliner had identified the chemical composition of many pheromones by this time, he remained mum until his patent applications were secure. It was just this year (2000) that he published a paper showing that androstadienone--a testosterone byproduct found in male underarm hair, semen, and on the skin--has a powerful effect on female mood.

He has also isolated a female pheromone, estratetraene, which he says appears to stimulate male libido more than mood.

### Panic and Social Phobia

Meanwhile, Berliner has founded privately-held Pherin Pharmaceuticals, to modify pheromones for use as drugs. Last year, he struck a partnership with Johnson & Johnson to fund trials for two anti-anxiety agents--one for females and a second for males. Both are in phase I human trials. A pheromone-based PMS drug for nervousness and pain, funded by Organon, is in phase II trials.

"The drugs for panic and social phobia are powerful," he says. "Say you are going on a plane. You fear you'll have a panic attack. You take a sniff and the drug works immediately in picogram doses (one-billionth of a milligram) so it can prevent an attack before it occurs."

What's more, since pheromones are administered via a nasal spray and go directly to the hypothalamus--that part of the brain governing mood, appetite, and reproduction-- they never have to enter the bloodstream, so there are no toxic effects, Berliner says.

### Men Are Less Euphoric

In February (2000), McClintock found the two naturally occurring chemicals whose identities Berliner had discovered were "psychologically potent."

The tiniest dose of either steroid would prevent women's moods from slipping, she said. However, the steroids had the opposite effect on men. They became more depressed after taking a whiff of either the male or female scent.

Researchers at the Monell Chemical Senses Center in Philadelphia found that volunteers experienced relief from depression when exposed to underarm odors for less than 2 minutes. Foul odors were just as likely to produce happiness as were pleasant smells. What's more, human body odor may contain chemical cues that allow others to distinguish whether someone is feeling fear, anger or happiness, says Monell scientist Charles Wysocki.

"Pheromones could serve as fertility drugs for women who want to conceive and as contraceptives for those who don't."



## Hormone Regulators

Both Berliner and McClintock would like to capitalize on those sensory chemicals that change hormone levels. Pheromones that regulate ovulation could serve as fertility drugs for women who want to conceive and as contraceptives for those who don't, McClintock says, in a chapter on human pheromones in the book *Reproduction in Context*. (MIT 2000.)

Like Berliner, McClintock's fascination with pheromones goes way back. As a student at Wellesley College in 1971, she proved that the menstrual cycles of women living together tend to synchronize.

In 1998, she published a groundbreaking paper that proved that it is pheromones that control ovulatory "commands." She took the sweat from underarm pads worn by women who had not yet ovulated and swabbed them on the upper lips of study volunteers. The pre-ovulation pads accelerated the surge of luteinizing hormone (LH) that triggers ovulation, speeding up volunteers' cycles by as many as 14 days.

When exposed to sweat from women who were already ovulating, menstruation was delayed by up to 12 days.

In women, LH produces progesterone (spurring ovulation.) In men, it stimulates testosterone. Pheromones may also affect another sex hormone in women, called follicle-stimulating hormone (FSH), which stimulates estrogen.

Berliner is tinkering with the LH surge in males, hoping to find a prostate cancer treatment: He reports that when he gave a progesterone-like modified pheromone to males, their LH secretions dropped, and there was a later drop in testosterone. This is good news since prostate cancer patients must lower their testosterone levels to shrink tumors.

## The Sixth Sense

Despite Berliner's success, he is still considered a gadfly among mainstream scientists. That's because he insists that pheromones are detected not by the regular sense of smell but by a receptor called the vomeronasal organ (VNO), literally a sixth sense.

Medical textbooks still state flatly that the VNO--two pits and cone-shaped sacs buried in each nostril--is vestigial in humans, so it no longer provides a neural hotline to the hypothalamus.

However, when Berliner finally unfroze his skin cell extracts in 1990 and asked University of Utah neuroscientist Luis Monti-Bloch, to test them, he was convinced the medical establishment was wrong.

Using a patented device, Monti-Bloch found that smelly substances produced no effect in the VNO whatsoever. Only Berliner's skin extracts made the sixth sense spark. At the same time, heart and breathing rate slowed, body temperature rose, and when androstadienone was applied to the VNO, women chilled. This proved to the two men that the VNO is much more than a vestige.

## Pheromones May Dictate Choice of Mates

Women choose mates with immune system types unlike their own in order to give offspring a varied and robust immune system, according to Carol Ober, a University of Chicago geneticist. And when people with the same immune system type marry, a woman is more likely to suffer a miscarriage, Ober says.

She found that despite low genetic variability among the Hutterite Brethren, a small, socially closed religious community in South Dakota, married couples are likely to have different immune system types, indicating that they avoid marrying partners with the same major histocompatibility complex (MHC), the immune system genes that distinguish between "self" and "other."

People can also discriminate human MHC type from compounds left on worn T-shirts. According to Swedish researchers, women rated the odors of MHC-dissimilar men as more pleasant than those with an MHC similar to their own.

However, women on the Pill--which mimics pregnancy--preferred T-shirt odors with MHCs similar to their own: Presumably these MHCs suggested men like their fathers and brothers, who would presumably stick around to help raise her offspring.

While androstenol is a sex lure for pigs, for people it appears to be a territorial pheromone that makes even 21<sup>st</sup>-century men take heed. When androstenol was sprayed on toilet doors and movie seats, women used those spaces freely. Men, however, avoided those spots, unconsciously obeying a "No trespassing" sign presumed to have been left by another male.

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