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# Human Pheromones: What's Purported, What's Supported.

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**Summary:** Human pheromones are over-stated, or are they? Unfortunately, to most readers, listeners and viewers, ”pheromone” has come to mean sexual attractant. Chemical-based sexual attraction is present in many species; however, these influences have not been demonstrated in humans. Despite what is advertised on various web-sites, and even suggested in certain scientific, peer-reviewed publications, there are no published, scientifically-constructed, bioassay-guided studies that have lead investigators through the complex maze of compounds found on the human body to one or more elements that possess pheromonal activity. Compounds currently being used in experimental work and hawked on various websites as human pheromones, and marketed by major fragrance companies, have not been demonstrated to be pheromones when used at physiological concentrations. Steroids molecules such as $\Delta^{4,\ 16}$-androstadien-3-one (AND) and estra-1, 3, 5(10), 16-tetraen-3-ol (EST) have been *declared* to be human pheromones based upon the false premise that humans have a functional vomeronasal organ (VNO), which they don't. Consequently, selling and marketing of these fragrance materials as pheromonal products is not based upon valid information. This being said, human body odors do contain substances that affect mood and alter endocrine function. Hence, there is tremendous potential to be realized for anyone willing to invest the capital and time necessary to isolate compounds documented to be present in human body odor that affect changes in human physiology and behavior. Fine fragrances have traditionally been created and marketed with the allure of setting mood in both the wearer and receiver. A fragrance containing true human pheromones would be the first to have real experimental evidence to support these claims.

**Introduction:** In this paper we provide an overview regarding chemical communication in humans. A recent concise review article appearing in Nature (1) has summarized the 50 year history and science of chemical communication, employing pheromones, in both insects and mammals. The definitions and terms describing the various types of pheromones will be reiterated here as they apply to humans. Sufficient evidence has accumulated to demonstrate that humans do produce and receive pheromones; however, despite what is advertised on various

web-sites and even suggested in certain peer-reviewed publications (see below), there are no bioassay-guided studies that have lead investigators through the complex mixture of compounds found on the human body to one or more compounds with pheromonal activity. What we do know is summarized herein.

Before delving into the details it is best to define what we are talking about. Unfortunately, for many in the lay press and public, the word pheromone has taken-on one meaning, viz., that of sexual attractant. However, like cars, food and members of the opposite sex, pheromones come in several varieties, but, for each effect, can be reduced to a single compound or small set of compounds. In non-human mammals and humans several types of pheromones have been identified and defined. These include primers, releasers, signalers and modulators. **Primer** pheromones typically affect endocrine or neuroendocrine responses such as the onset of puberty, estrus/menstrual cycle timing and onset and pregnancy disruption. **Releaser** pheromones typically elicit a behavioral response. Sexual attractants are the most common examples of releasers. **Modulator** pheromones have been, thus far, uniquely described for humans (2): These are chemosensory cues that modulate affect or context of other people. **Signaler** pheromones have been discussed as chemical signals that provide a variety of information to the smeller: sex of the sender, reproductive status, age and dominance status of the sender. Much of this information about an individual is mediated by the individual's "odor print," which is a complex mixture of compounds and properly should not be classified as a pheromone.

These definitions are not without controversy, as has been pointed out, correctly so, by Wyatt (1). Applying the term pheromone, which was born from research with insect chemical communication (3), to more complex mammalian species has resulted in considerable discussion regarding definitions (e.g., 4). In this text we rely upon the definitions presented above and leave the controversy about properness of definitions for future discussion.

**Mammalian Chemical Communication:** It is widely recognized and demonstrated that odors play an important role in mammalian reproductive biology. In non-human mammals both primer and releaser pheromones have been discovered and identified (5-7). Most of the research has utilized rodents (see 6-8 for

reviews). Sources of the chemosignals vary. In rodents, male urine is an adequate source of many chemosignals (8), but in anestrus ewes the organic acids and several neutral components extracted from ram fleece stimulate lueinizing hormone (LH) release (9).

Primer pheromones also influence reproductive biology of nonhuman primates and have been well documented in Old World primates (10), such as chimpanzees and baboons (11, 12). More sensational were studies reported almost four decades ago that suggested that old world primates, female rhesus monkeys, produced releaser pheromones. The $C_2$-$C_5$ aliphatic acids present in the vaginal secretions of estrogen-primed female rhesus monkeys were reported to act as releaser-type pheromones (13, 14). These compounds were tagged with the label of “copulins.” Female rhesus monkeys scented with copulins, both naturally- or synthetically-derived, were reported to cause male rhesus monkeys to respond sexually and to mate with them. The behavioral responses were later questioned and could not be reproduced in a separate population of the same species (15). Nevertheless, this acid mixture was patented with claims that it promoted sexual attraction between humans (16). At least one major fragrance company may have put small amounts of this acid mixture into its perfume fragrances created during the early to mid-70's; however, a double-blind, placebo-controlled study with human couples showed no increase in sexual activity attributable to copulins (17). Despite these negative results “copulins” still live-on as sexual attractants for those “willing to believe” and who surf the net searching for instant fixes for their not-so-perfect-love-life (18).

**Human Chemical Communication:** The human body produces myriad odorants (19, 20). Different parts of the body smell different because of the difference in the type and number of skin glands, type and density of cutaneous microflora and available oxygen. Despite humans having several areas of the body that are capable of producing strong, distinct odors, e.g. underarms, mouth, feet, scalp and genitals, only the secretions from the axillae have been tested for possible pheromonal effects (if the anecdotal reports surrounding skin-derived “vomeropherins” [discussed below] are not included). Several studies have demonstrated that we produce, receive and are affected by pheromones. At least one example of each class of pheromonal effect has been reported for humans.

*Primer Pheromones:* Initially studies examined clinical end points, such as menstrual cycle length and synchronization, over long periods of time and in large populations of women. For example, these studies include examination of the menstrual synchrony effect first documented in an all-female living group (21) and later replicated by others in co-educational housing facilities (22, 23).

Male chemical stimuli also appear to alter menstrual cycle length and regularity. Women, who reported that they were in the company of men three or more times/week, tended to have shorter cycles than those who spent less time with males (21, 24). A follow-up study showed that women who had regular, weekly contact with males were more likely to show regular biphasic ovulatory-type cycles than were women who had sporadic or no contact with males (25). This study also suggested that sub-fertile cycles tended to show a shortened luteal phase rather than absence of ovulation. An inadequate luteal phase, i.e., < 12 days of hyperthermic basal body temperature, reflects a condition known as the “luteal phase defect,” a suggested cause of infertility in the United States (26, 27). In nonhuman mammals, such as rodents, estrus synchrony is mediated by airborne chemical signals (28).

The first study to present evidence that menstrual synchrony is mediated by axillary secretions was published in 1980 (29), but this study was criticized because it was not properly blinded and used limited numbers of subjects (30). Later, prospectively double-blind studies were done to determine whether menstrual cycle alteration was affected by odors from male and female donors (31, 32).

In a study employing male axillary extracts (31), women who had reported a history of aberrant menstrual cycles (< 26 or > 32 days) were randomly divided into two groups. The experimental group received applications of male axillary extracts to the upper lip three times a week, while the control group received similar applications of a placebo (the solvent ethanol). After 12 to 14 weeks, the experimental group showed a significantly greater proportion of normal-length (29.5 $\pm$ 3 day) cycles compared with the control group. In a parallel study employing female extracts (32), axillary secretions were collected from donor females, combined into 3-day lots, and applied sequentially three times a week to a randomly selected group of women who reported a history of normal length cycles (> 26 and < 32 days). A control group

received similar applications of a placebo (the solvent ethanol). At the time of the third menstrual cycle, the experimental group was significantly more similar in date of menses onset to the donor cycle compared with the control group.

While these findings are provocative and highly suggestive, they have been criticized on methodological and statistical grounds as well as for using small numbers of subjects (33-35). Nevertheless, a more recent study provided additional support for the idea that axillary compounds have primer-pheromone activity (36). The results of the experiments suggest that exposing women with normal menstrual cycles to axillary extracts from women in their follicular phase (the days following menses but several days prior to ovulation) shortens the recipient's menstrual-cycle length. In contrast, exposing subjects to axillary extracts collected near the time of ovulation of the donors lengthens the recipient's menstrual-cycle length. Interestingly, similar effects on estrous-cycle lengths have been noted in female rats exposed to the follicular and ovulatory odors of other female rats (37).

Using clinical end points such as menstrual cycle length and synchronization over multiple menstrual cycles has made it difficult to identify the mechanism(s) by which axillary extract components might work, or to isolate the causative agents. However, data from our laboratories demonstrate endocrine alteration and fairly rapid mood changes (see Modulator Pheromones below), which may be used as bioassays to isolate and identify human primer and modulator pheromones, respectively. These data have demonstrated that male axillary extracts, when applied to female volunteers, can alter the timing of the next lueinizing hormone (LH) pulse demonstrating the presence of primer pheromones in the axillary extract (38). Pursuit of the pheromone compound(s) has been stymied by lack of funding or interest on behalf of both government and industry sources. Consequently, identification of compounds that can be labeled as human primer pheromones has not been done in a systematic fashion by organic chemists in the same manner as has lead to success in the isolation and identification of insect pheromones.

Chemical signals from lactating women, which may also include compounds from the breastfeeding infants, affect timing and length of the menstrual cycle of other women who do not have children (39). Exposure to these compounds disrupted "homeostatic" regulatory mechanisms and increased variability of cycle

length. The authors speculate that such chemical signaling may regulate fecundity in and reproductive success in groups of women.

*Releaser Pheromones:* There is no solid evidence in the biomedical literature to support the claim that humans rely upon the presence of a sex attractant releaser pheromones. This should not be interpreted as a denial that such pheromones exist; they may, but their demonstration and identification has not yet survived, or even been attempted, at least in published information, in peer-reviewed, bioassay-driven studies. This also does not mean that releaser pheromones do not exist in humans. To the contrary, there is good evidence to show that a lactating mother produces a releaser pheromone that motivates and attracts the infant to the source, e.g., a breast pad previously worn by the mother (40). Evidence for other releaser responses is lacking.

*Modulator Pheromones:* The best evidence for this class of pheromone activity in humans is found in the work of the McClintock laboratory (2, 41) and in our research with male axillary secretions and their effects on female mood and LH pulsing (38). In the former, women without offspring were exposed to breast-pads from other women who were breastfeeding an infant. In the authors words: “we demonstrate that natural compounds collected from lactating women and their breastfeeding infants increased the sexual motivation of other women, measured as sexual desire and fantasies. Moreover, the manifestation of increased sexual motivation was different in women with a regular sexual partner. Those with a partner experienced enhanced sexual desire whereas those without one had more sexual fantasies” (41).

In our study, which exposed women to axillary secretions from males, we administered rating scales ranging from 1, which was labeled as ‘‘I am not at all …’’ to 7, labeled ‘‘I am extremely …” The … contained one of the following: energetic, sensuous, tense, tired, calm, sexy, anxious, fatigued or relaxed. Women were more relaxed and less tense during exposure to male axillary secretions than when they were exposed to the placebo.

Although, as noted above, changes in the mood/emotional state (particularly situations which evoke fear or anxiety) of individuals can change body odor (42, 43), it is not yet known whether these odorants, when presented to others, will induce a

similar mood or emotional state in the recipient. This information awaits the results of studies.

*Signaler Pheromones:* Many original publications and reviews (some of the latter by us) state that the best example of a signaler pheromone is the ability of the mother of a new-born to identify her infant by smell alone. This ability may in fact be based upon the unique “odor-print” that each of us possess. Tristram Wyatt has argued that this should not be included in the pheromone concept because one cannot isolate a single or small set of compounds that elicit the response (unpublished, personal communication with the authors): We have been persuaded.

Women may be signaling when they are fertile. A study of exotic dancers reported that women in the ovulatory phase of their menstrual cycle earned more in tips than when they were in the anovulatory phase (44). The authors suggested that chemical signals released by the women signaled the cycle-phase, which generated more interest in them. The dancers self-professed that any potential change in their own behavior was not responsible for the increased income, which was not independently assessed. While it remains unstudied, there are certainly many anecdotal claims that different stages of the menstrual cycle result in different odorant halos that can be detected by other animals, e.g., dogs, and other people; some of these compounds may provide signaler cues.

Age may be encoded in chemosensory information. A study from Japan suggested that 2-nonenal may be associated with advanced age (45), although this chemosensory-based signal could not be replicated in a population of US citizens (46). 2-Nonenal appears to be a skin-derived metabolite of marine fish consumption; hence, the Japanese population may be unique. We suggest replication with a population that does not consume a diet rich in marine species

There is a set of chemosignals that may cross definition boundaries. Some human-derived pheromones may act as both signaler and modulator pheromones, but the evidence for the latter is still lacking. Chen and colleagues (42, 47, 48) as well as Ackerl et al (43)have reported that a person’s body odor is perceptively altered during exposure to film clips that elicit anxiety or fear versus clips that contain comedic scenes (both relative to body odor when viewing a neutral film clip). These shifts in body odor may signal to others information about immediate environmental

situations that may impact upon the individual detecting the odor (e.g., there's danger). This has been demonstrated in rodents; rats will avoid an environment that has been suffused with chemical signals from other rats that have been stressed (49).

*Odor-prints:* Beginning with research with mice in the 1970's, findings began to emerge to implicate a role for the major histocompatibility complex (MHC; a large set of genes that regulate the immune system) in the production of individual-specific body odor (see 50, 51 for reviews). Later the MHC was demonstrated to have major impact on human body odor (52, 53). We now know that each individual's unique odor print results not only from the tremendous variability within the genes of the MHC complex but also from unspecified "background genes," as detailed in experimental animal models (54). Many of the genes have myriad forms (alleles); some in the thousands (55) resulting in a near zero chance that any two non-twin individuals have the same odor print. The odor print is a complex mixture of perhaps hundreds of compounds; hence, as noted above, it does not fit the definition of a pheromone. Odor prints do, however, appear to play a role in the choice of a mate (52; c.f., 56). Importantly, they also may provide chemosensory signals that are predictive of the underlying immune system.

Early reports on the influence of MHC on human mate choice noted that the odor print-based preference was for individuals whose MHC was different from that of the chooser (52). This led to speculation that the nose was leading the way in finding a mate whose immune system was different from the sniffer's immune system. Hence, any offspring from a mating between the two individuals would inherit a more variable, and hence more protective, immune defense than a mating between two individuals that had a very similar MHC.

Later work would come to show that maximal MHC differences between mates is not what people seem to be doing (53) even though commercial firms that have sprung up to genotype individuals for compatibility appear to emphasize maximal differences (e.g., 57). Instead, people appear to opt for an optimal difference that retains a genetic connection to the father (53). Indeed, a recent report demonstrates that the most successful marriages (as measured by fecundity) were

between 3rd and 4th cousins (58), although the authors did not address the MHC issue (59).

**Vomeropherins and the Human VNO***:* As we noted above, internet sites selling compounds claiming to be human pheromones, e.g. “copulins” and steroidal “vomeropherins,” abound, but actual science, focused on the identification of human pheromones, has lagged. Our studies of both human axillary chemistry and the effects of axillary constituents on human recipients, suggest a similarity between human axillary secretions and nonhuman mammalian odor sources, where, for both, lipocalins (proteins that transport small hydrophobic molecules such as such as steroids, bilins, retinoids, and lipids) interact with chemical signals used in pheromonal communication**.** Regardless, in our opinion, far more resources and time have been invested in the successful pursuit of insect and non-human mammalian pheromones. Identification of compounds that act as primer and releaser pheromones in non-human mammals, particularly in pigs (60) hamsters (61) and mice (5), have lead to the identification of several chemical structures and elucidated the role of lipocalin proteins (relatively small, 19-21 kilodaltons in size, with a lipid friendly cavity to hold lipophilic molecules) in the binding of volatile pheromone molecules to proteinaceous molecules (62).

With the exception of studies from our laboratories, numerous studies that have been published over the past decade (e.g., 63-67) have utilized synthetic, commercially available “putative human pheromones” consisting of either one or both of the steroids 4, 16-androstadien-3-one (androstadienone; AND) and estra-1, 3, 5(10), 16-tetraen-3-ol (EST). The labeling and use of these compounds as putative human pheromones are based on the false premise that humans have a functioning VNO (see below). These compounds were originally proposed as “vomerpherins” (defined as “compounds that stimulate the human vomeronasal organ”) based on their purported ability to stimulate the human VNO in a gender-specific fashion (68). This research was generated by scientists from Pherin Pharmaceutical Company and the University of Utah (63, 69-72). These compounds were said to have been isolated from human skin extracts by scientists from a related, predecessor company of Pherin, i.e., EROX (now Human Pheromone Sciences, Inc.); however, no data in either peer-reviewed literature or patents issued to EROX (63, 69-73) demonstrate

the isolation of these putative pheromonal compounds from a human source, e.g., axillae or skin, using a bioassay-guided procedure (or any other procedures!).

With the exception of studies from the above commercial groups, all experimental evidence accumulated by several labs has demonstrated that the adult human VNO is nonfunctional (74, 75). In addition, although AND has been shown to be present in human axillary secretions (76, 77), a demonstrated source of as yet unidentified human primer and modulator pheromones, as described above (36, 38), it is unclear how EST, which has only been reported in the urine from pregnant women in their third trimester (78), was identified as having pheromonal activity. Gower and colleagues examined the concentration and biogenesis of volatile axillary steroids (for review, see 79). In addition to AND, Gower and co-workers documented the presence and abundance of 5$\alpha$-androst-16-en-3$\beta$-ol (androstenol) and 5$\alpha$-androst-16-en-3-one (androstenone) in axillary secretions. These compounds also have been suggested by some to be human pheromones (for a review see 80). The steroid AND is often said to be “male-specific,” (e.g., 63), but it is not. Gower and colleagues used males almost exclusively in their studies. However, in one study, they reported the average level of AND across eight males to be 0.38 nanomole per microliter (nmol/μL; =102.6 nanograms [ng]) and 0.87 nmol/μL (= 234.9 ng) in the single female sample (76). Clearly, the average concentration of AND in males is not greater than that of the female. No other publication reports levels of axillary AND in male and female subjects. Further, its purported relationship to testosterone also is questionable. Experiments by Gower and associates (76, 77, 79) attempted the conversion of testosterone to AND by axillary bacteria: None were successful. In both the human and porcine testes, synthesis of the $\Delta^{16}$-androstenes (AND as well as other volatile steroids such as androstenone and androstenol) is independent of androgen formation. The precursors for AND and other 16-androstenes have been documented as progesterone and pregnenolone. Both are $C_{21}$ steroids that lose their $C_{17}$ side chains to form the $\Delta^{16}$ double bond (81).

Levels of AND used in numerous recent studies where behavioral and physiological effects were examined far exceed endogenous levels. For example, McClintock and colleagues (2, 82) used concentrations of commercially available AND (250 μM) that were more than 1, 000 times above reported axillary

concentrations (nanomolar; see 76) to demonstrate modulator pheromone effects, allegedly to “stimulate the (human) vomeronasal organ” (2). Subsequent work by Lundström et al. (83) demonstrated that the average olfactory threshold for AND is about 211 μM; in addition, using the concentration employed by Jacob and McClintock (2), Lundström et al. (84) reported a single effect on the mood of female participants (“more focused”) when a solution containing this concentration of AND was rubbed on the upper lip subjects. Shinhoara et al. (85, 86) also found that commercially obtained androstenol could alter LH pulsing when applied to the upper lip/nares region of female recipients at a concentration 1,000 times above endogenous axillary levels. Savic and colleagues (64, 65) as well as Sobel and co-workers (66), had subjects smell the headspace above up to 200 milligrams of neat, undiluted, crystalline AND while they recorded alleged pheromone-mediated differences in functional MRI images, mood, and physiological changes. This amount of AND is up to a million times greater than the nanogram amounts found in the human axillae!

The use of a concentration that far exceeds those found in natural sources, particularly in the absence of using lower concentrations, i.e., those closer to physiological levels, is counterintuitive and completely unsound. Indeed, presenting AND at such a high concentration is itself likely to produce its own effects. A biological effect should be examined using physiological levels of the natural substance. Under the conditions employed by the studies cited above, using $10^3$-$10^6$ times endogenous levels, many of the hundreds of olfactory receptors in the human olfactory epithelium may be recruited to respond. Under these conditions, we expect to see competitive inhibition of some receptors’ responses by others and responses by a subpopulation that typically would not respond at much lower, i.e., physiological, concentrations; hence, the summed effect would not be expected to resemble that seen by presenting the stimulus at natural concentrations.

In many, but not all, vertebrates the VNO is an additional structure located in the front part of the nose along the nasal septum (87). It has its own family of molecular receptor genes that are independent from the olfactory receptor gene family (88). Furthermore, many, but certainly not all, pheromonal responses originate by stimulating sensory receptors in the VNO (for a review see 7). This information is

then conveyed by a separate set of nerves to a region of the brain, the accessory olfactory bulb, which begins central processing (87). Perhaps based on the false assumption that mammalian pheromones must work via the vomeronasal organ, some have formulated the following logic: because humans exhibit pheromonal responses they must therefore have a functional VNO, which is a non sequitur.

In the past 15 years, considerable evidence has accumulated to demonstrate that 1) adult humans do have a VNO (e.g., 74, reviewed in 75), however; 2) it is devoid of sensory cells (88) and 3) does not have associated nerves making contact with the accessory olfactory bulb (89). These nerves, however, are present in the fetus, where they act as a lattice for migrating neurons containing LH releasing-hormone that originate in the nose and travel to their destination in the basal forebrain, e.g., the hypothalamus (90). Even if sensory cells were present, the genetic underpinning for transducing chemical information from chemosensory cues into electrical activity is nonfunctional because the TRPC2 gene, which encodes a protein that performs this function, is a pseudogene both in humans and in Old World primates (91). Also absent in adults is the accessory olfactory bulb (89). Hence, in humans, the VNO is the vestigial appendix in the nose. Does this mean that humans cannot respond to pheromones? Absolutely not! As is true for some pheromonal responses in other mammals, the olfactory system can be the route of information input to the brain (6).

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