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ChemoSense

EDITORIAL

Human Chemical Communication

By Graham Bell

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Insects do it, elephants do it. Pigs and domesticated dogs do it. Noel Coward would never have refused a chance to do it. So let's do it? Let's communicate.

There is no doubt that humans communicate using chemicals: think only of the uses of perfume through the ages. But do we leave biological odour trails or scent marks or waft out "come-hithers" from our scent glands? And if we do, who is receiving these messages and with what effect?

This issue reviews the state of thinking on human pheromones. Evidence is growing that humans are receiving and using chemical messages from each other. They have the means to send and receive signals. In our lead article, Wysocki and Preti of Monell, review the concepts and scientific evidence to support or refute definitions of pheromones, in terms of chemistry, human physiology and behaviour.

And while the science is being done, the perfume and flavour industries are convinced of the potential of their products, as shown by our useful guide to human perfumes presented by Krishnamurthy of IFF.

We wish Don Barnett and Peter Barry a happy retirement and in sustaining their valuable chemosensory efforts.

Human Pheromones: Oxymoron, Marketing, Maya, or Meaningful Messages?

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In the academic and biomedical communities, mention of human pheromones brings forth mixed reactions. To some the concept is foreign to the extreme. Arguments akin to the following can be heard: *Microsmatic humans have advanced well beyond reliance upon chemical communication for social order. Insects, yes, that's where it all began; vertebrates, including some mammals, yes, because chemicals have been identified for pigs, mice and elephants; but not for humans.* Furthermore (the argument continues), *humans do not have a functioning vomeronasal organ (VNO) and a VNO is necessary to detect pheromones* (we will attempt to dissuade the reader from this non sequitur).

Others embrace the concept to the extreme. Although Rodriguez and Mombaerts (2002) cautioned about misuse of their results, the identification of VNO receptor genes in the human genome has lead others to argue that *since humans have intact V1R-like receptor genes, they must use them to detect pheromones.*

In another area, especially on the Internet, hawkers of "human pheromones" try to bring in

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INSIDE:

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Human Pheromones:

Oxymoron, Marketing, Maya, or Meaningful Messages? continued

big bucks. Herein may lay the reason why some in the academic and biomedical communities reject human pheromones. Many have been misinformed about the true nature of pheromones.

In this review, we will A) define the various types of pheromones; B) discuss how pheromones function; C) explore the evidence for human responses to pheromones; D) introduce candidate human pheromones; E) briefly review the sensors in the nose that can detect pheromones, including those found in humans; F) argue that no single detection system is devoted to pheromones; and G) discuss the relationship between human pheromones and the VNO.

A. What Is a Pheromone?

In the original definition provided by Karlson and Lüscher (1959), pheromones are "substances which are secreted to the outside by an individual and received by a second individual of the same species, in which they release a specific reaction, for example, a definite behavior or a developmental process." The original pheromone was a single compound, bombykol, which is released by the female Silk moth *(Bombyx mori)* to attract the male to mate. Now, however, it is possible to purchase many types of putative human sex ("releaser"; discussed below) pheromones. They go by such names as *The Edge, Scent of Eros™, Alter-ego, Pheromone Additive*, and many more.

Unfortunately, even for insects the original definition now fails. As examples, in some situations the chemicals must be many and in the appropriate ratio to be effective; there is cross-species communication, to the extent that some predators emit the female sexual signaling pheromone of its prey, attracting the unknowing male to become a meal; the "specific reaction" may not be specific and may be dependent upon context. Furthermore, the definition, which included "releaser" (of behavior) and "primer" (of developmental process) , has been expanded to include two additional classes, viz., signaler (provides information) and modulator (alters the probability of an outcome) pheromones.

How Do Pheromones Function?

At present, many recognize four categories of pheromones, viz., primers, releasers, signalers and modulators. Each will be discussed briefly.

1. Primers. Primer pheromones typically affect endocrine or neuroendocrine responses. Examples include: the onset of puberty, which can be determined in part by exposures to the chemical signals of adults of the opposite sex; synchrony of estrous or menstrual cycles in females, by exposure to chemical signals from the females; suppression of estrus by exposure to the chemical signals of females living in high density; in some species, induction of ovulation by chemical signals from males; pregnancy failures by exposing females to the chemical signals of strange males; and surges in testosterone in males exposed to the chemical signals of females.

2. Releasers. Releaser pheromones typically bring on a behavioral response. Sexual attractants, i.e., sex pheromones on the Internet, are the most common examples of releasers, but not in humans (discussed below). The first mammalian pheromone to be chemically identified, androstenone (and perhaps, too, its alcohol cousin, androstenol) is a releaser pheromone. It is present in the saliva of boars. When a sow that is in heat smells androstenone, she assumes the lordosis spray of androstenone from a can of *Boar Mate®,* in the direction of the sow, is sufficient to release the behavior.

3. Signalers. Signaler pheromones are most likely the most numerous. These chemical signals provide information to the smeller. Whether any consequence ensues is typically irrelevant. The types of information are myriad. There is excellent evidence that animals, using chemical signals alone, can extract information about the sex of the sender, the status of the reproductive cycle if the sender is a female, the age of the animal, its dominance status if a social structure is maintained, its health and what it recently ate, and, importantly, the individual identity of the sender. This last chemical signal is known as the odor-print of the individual and is determined, in large part, by the set of genes that regulates the immune system, the major histocompatibility complex (MHC; Yamazaki, Singer and Beauchamp, 1998-99). Variation in MHC is so extreme that in nature no two individuals (unless they are identical twins in humans or analogous siblings in non-humans) share the same MHC-type. Hence, other than the noted exceptions, no two individuals share the same MHC-determined odor-print.

4. Modulators. most other pheromones, originated from the concept of modulator pheromones was introduced following initial work with humans (McClintock, 2000). There is evidence to suggest that fluctuations in human odor linked to emotional states (Chen and Haviland-Jones, 1999, 2000; Ackerl et al., 2002). McClintock (2000) proposed that this chemosensory information modulates one's context of other people, e.g. smelling an emotion influences one's own emotive state.

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Introduction to Fragrances

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Introduction

Perfumes have been used in various forms since the beginning of civilisation. The word "perfume" is derived from the French word "parfum" which originated from the Latin "per"-through and "fumes"- smoke. A perfume is precisely defined as "a sweet smelling liquid" for personal use and a fragrance as "a sweet scent" which has a broader applications, however the terms are often used interchangeably.

There are at least 5,000 perfumes and fragrances currently commercially available around the world. These products are sold under approximately 900 brands and sales companies (Boelens & Boelens, 2001). Every year, about 200 new fragrances appear on the market.

This article gives an overview of fragrance, which is the product of an important and growing global industry.

History of Perfumes

The story of perfumery reflects the history of human civilisation. In all cultures since antiquity, the original use of aromatic materials was ceremonial, religious, therapeutic or aesthetic.

In the West, the Egyptians, ancient Greeks, Hebrews, and Romans were familiar with perfumes.

The Egyptians used perfume in their temples and annoint the statues of their gods. The dead were embalmed in decay-resistant and perfumed substances. The available substances were gum resins, oleoresins, woods & flowers.

The Greeks burnt perfumes at religious festivals, births, marriages & funerals. Perfumes were believed to relieve pains.

Perfumes were also part of daily life in the Roman Empire.

The Middle Ages saw almost no fragrance activity in the West, as supplies of aromatic materials from the rest of the World were unavailable. However, the conquest of Venice by Constantinople opened the West to the perfume trade again, and Italy became the centre of the perfume industry.

Technology began to have impact on fragrances with the introduction of distillation by Islamic scholars, and the production of ethyl alcohol. Eau de cologne, introduced in 1710, marks the beginning of modern perfume creation.

The history of modern perfumery starts with the introduction of synthetic chemicals. Chemistry started to take its present form in the 1830s, and the decade around 1875 witnessed a flowering of technology that revolutionised the fragrance industry.

The nineteenth century saw the development of a number of methods to extract fragrance materials from natural substances. The south of France had the greatest concentration of fragrance activity.

Throughout the twentieth century, synthetic chemicals increasingly became the major components of most fragrances. Fragrance use increased in household products such as laundry detergents and fabric softeners after World War II. Fragrances also became a major marketing component of personal care items such as shampoos and deodorants.

Changes in society and marketing arose simultaneously with the growth of technology. Fashion designers added signature fragrances to their lines of clothes and accessories.

Some important historical highlights are summarised in Table 1 (Herman, 2002).

Table 1: Highlights in the History of Fragrance

1800 B.C.	Perfume made by maceration (Mesopotamia)
Circa 350 B.C.	First book on perfume (Theophrasus of Athens)
Circa 1000	Distillation of rose oil (Ibn-Sina)
Circa 1202	Venice conquered Constantinople brings perfumes back to the West
Circa 1320	Distilling alcohol with serpentine cooler (Italy)
1370	Hungary Water introduced
1533	Perfumery brought to France (Caterina de'Medici)
1573	Perfume brought to England – perfumery encouraged by Elizabeth I
1710	Eau de Cologne (by Farina family)
1771	Yardley founded
1775	Houbigant founded
1826	H.Hennel (England) synthesised
1827	Guerlain founded
1895	Solvent extraction of fragrance materials by Robiquet (France)

Source: Herman (2002)

Creation of a Perfume

Perfume creation is an art and not a science. A perfume is like a painting or a piece of music, except the artist's (perfumer's) palette is replaced with fragrant essential oils.

Perfume creation starts with a concept or image. Once the concept is decided the process moves to identifying ingredients that would fit the concept. The perfumer studies every aspect of the concept and achieve perfection by trial and error. This process can be long.

Historically, all perfumes were made using natural materials. However, a modern fragrance is a complicated blend of natural and synthetic ingredients, maybe 300 - 400 different ones. Each ingredient affects the others in often unpredictable ways.

Most modern perfume companies use "keys", which are compounded blends that replace expensive naturals or products that are illegal.

Introduction to

Compounds made by major perfume companies typically contain "captives", that is, aroma chemicals or blends made for internal use and not made available to outside companies. This makes duplication of the product much more difficult.

There have been numerous great perfumers. Some are mentioned in Table 2.

Table 2 - A Few Noteworthy Perfumers

Perfumer	Perfume
Ernest Beaux	Chanel 5, Cuire de Russie, Soir de Paris
Sophia Grosjman	Eternity, Spellbound, Tresor & many others
Jean Kerleo	Mille, Eau de Patou, Sublime, Voyageur
Guy Robert	Madame Rochas, Dioressence, Gucci No.1, Amouage
Edmand Roundnitska	Diorissimo, Femme, Eau Sauvage & many others

Source: Boelens & Boelens (2001)

Fragrance Ingredients

All ingredients used to create a perfume fall into one of three categories - 1) Naturals 2) Chemicals and 3) Bases

The naturals are obtained from plants or animals. These are complex mixtures of odorous substances. The characteristic odor of a single material is called a "note". An "accord" is the blend of several "key" notes, which make up the main character of a fragrance.

Natural ingredients from animal origin include:

Musk - Musk Deer; Ambergris - Sperm Whale; Castoreum - Castor Beaver; Civet - Civet Cat

Some natural ingredients from plant origin are:

Patchouli - Leaves; Vetiver - Roots; Cinnamon - Bark; Rose - Flowers; Cedarwood - Woods; lemon - Fruit Peels; Coriander - Seeds; Styrax - Resins; Pepper - Berries; Citronella - Grasses

Chemicals are obtained through synthesis. They offer consistency in supply and quality, provide a means for higher creativity with odours not found in nature, and are less expensive than naturals.

Bases are "ready made" accords. They substitute for naturals and provide characteristic fantasy notes. Bases are used where odours cannot be obtained from nature, and to replace rare, expensive or unsafe natural materials.

Forms of Fragrances

The finished fragrance oil is often dark, heavy and not very volatile. A carrier is necessary for the perfume to perform well. Carriers can be product bases e.g. detergent powder, fabric softener, shampoo etc.,or alcohol (ethanol) for fine fragrances.

Fine fragrances exist in three forms: Perfume, Eau de Toilette, and Cologne.

Perfume contains the highest level of fragrance oil (20-30%) and is the strongest and longest lasting.

Eau de Toilette contains a lower level of fragrance oil (10-18%) and has slightly less strength & tenacity.

Cologne contains the lowest percentage of fragrance oil (5-10%) and may contain some water, which softens the scent. It is the oldest form of fragrance, originating in Cologne, Germany.

Structure of Fragrances

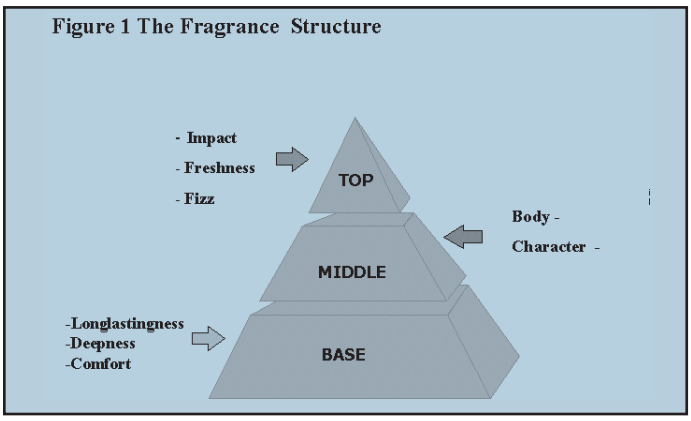
Every perfume is unique and could be made with as many as one thousand ingredients. The ingredients themselves vary in staying power and come to the fore at different stages of the perfume's "life" on the skin (The H & R Book,1985). Perfumers distinguish between:

The Top Note. This is the initial impression of a fragrance. Light, fresh & floral elements form the top note. Examples of top note materials are citrus oils, ester-volatile chemicals (floral-fruity notes) and volatile essential oils.

The Middle Note. This connotes the body/character of a fragrance. Warm, floral, fruity, spicy elements form the middle note. Examples of middle note materials are most essential oils, absolutes, most floral or spicy elements & aldehydes.

The Base Note. This delivers the depth/foundation of the fragrance and has the most lasting effect .Rich, sweet, woody, animalic notes form the base note. Example of base notes are resinoids, musk & other animal products, woody chemicals/essential oils, mossy & balsamic products.

A typical fragrance structure is shown in Fig 1.



Classification of Fragrances

Various classifications of perfumes have been published over the years. Edwards published "Fragrances of the World" and classified about 2,700 fragrances (Edwards, 2001).

At IFF, fragrances are assigned to their respective fragrance families. The women's fragrances are classified into six main families - Citrus/Eau Fraiche, Floral, Chypre, Floriental, Oriental & Musk. The families floral, floriental and oriental are further subdivided as shown below:

Fragrances continued

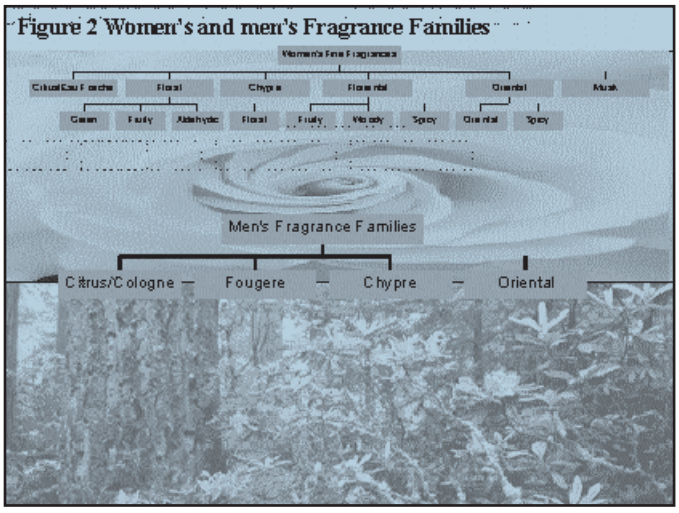
Floral: Floral green, Floral fruity, Floral aldehydic and Floral floral.

Floriental: Floriental fruity, Floriental woody and Floriental spicy

Oriental: Oriental oriental, and Oriental spicy.

The men's fragrances are classified into four main families: Citrus/Cologne, Fougere, Chypre and Oriental.

The women's and men's fragrance families are shown in Figure 2.



Description of Fragrances

Fragrances are usually described in terms of "notes" (similar to "notes" in music). Firstly, the fragrance is assigned to its fragrance family (e.g. Floral). Then, within this family, one identifies the top notes, middle notes and finally, the base notes.

Fragrance Applications

Beside application as fine fragrances, fragrances have important applications within the fast moving consumer goods industry especially in fabric care, personal care, personal wash and home care. A further application of fragrances is their use as malodor counteractants and masking agents.

Benefits of Fragrances

Fragrances are powerful emotional ingredients. Pleasure, wellness, and sensuality are strong, universal human desires and emotions Since 1982, IFF has pioneered the concept of an Aroma Science program, studying the effects of fragrance and fragrance ingredients on human emotions. IFF developed tools to demonstrate how to build fragrances that fit a desired emotional outcome and product concept. Some are described below:

- Mood-MappingTM techniques identify individual fragrance combinations affecting specific human emotions (Warren & Warrenburg, 1993)
- Mood Mapping database of over 1,500 perfumery materials, accords, and finished fragrances.
- Consumer Fragrance Thesaurus allows insights derived from consumers to the perfumer's desk, speeds the development of a new fragrance and focuses on the most fruitful directions (Warrenburg, S. 1999)
- Measurement of stress-reducing effects of fragrance
- Measurement of the effect of fragrance on social interactions and developing social-enhancing fragrances

There are numerous benefits of fragrances available in literature. Some positive effects claimed for fragrances are on creativity, memory, social behavior, work environment & performance.

More recently, IFF has been studying the effect of pheromones on human sexual attraction. A pheromone is a form of chemical communication between members of the same species. The preliminary findings within IFF indicate that pheromones incorporated into a suitable fragrance could enhance sexual "chemistry" between couples.

Conclusion

Fragrances are a key component of many consumable products. Fragrance is what drives the sale of many cosmetics and toiletries, and marketers aims to produce a range of fragrance variants in order to satisfy the breadth of consumer preferences.

The fragrance market is further enhanced by the increase in production of cosmetics and toiletries worldwide and the growing interest in aromatherapy. Growth is expected to continue with the aging population in the developed world and increased per capita income in the developing world.

What basically started out as a masking agent for unpleasant odors and a means to heal and seduce has turned into a highly competitive, multi-billion dollar industry. It is estimated that the global demand for flavors and fragrances is expected to grow 5.4 percent per annum to US$18.4 billion in 2004 (The Freedonia Group, Inc.).

Acknowledgements

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Photographs: Graham Bell

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Human Pheromones:

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A. Is there Evidence for Human Responses to Pheromones?

Figure 1 summarizes the interpretation of the available evidence that addresses human responses to pheromones. All available examples are not included because of space limitations.

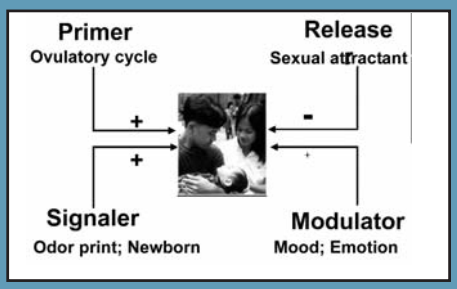

Figure 1. Summary of biomedical evidence for human pheromones. Key: + = strong evidence; + = weak evidence; - no evidence.

1. Primers. In humans, several studies have indicated that interpersonal relations among women and between men and women may alter reproductive physiology, suggesting the presence of primer pheromones. These effects include menstrual synchrony among women, first documented by in all-women groups (McClintock, 1971) and later replicated in a variety of other situations (for reviews see McClintock, 2000; Wysocki and Preti, 2000).

Russell and colleagues (1980) were the first to present evidence suggesting that menstrual synchrony could be mediated by axillary (underarm) secretions. Results of additional studies suggested that axillary secretions from donor women could be used to bring other women into synchrony with the donors (Preti et al., 1986). Male axillary secretions also appear to affect women with a history of irregular cycle lengths: After exposure to the secretions, their cycles shifted toward the normal cycle-length of 29.5±3 days (Cutler et al., 1986).

Two further studies focused upon effects of female axillary secretions. Stern and McClintock (1998) reported that women with normal menstrual cycles exposed to underarm secretions from women in their follicular phase (the days following menses but several days prior to ovulation), shortened the length of the recipient's menstrual-cycle. Exposing the same women to secretions collected near the time of

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NEWS

Heron Island Meeting

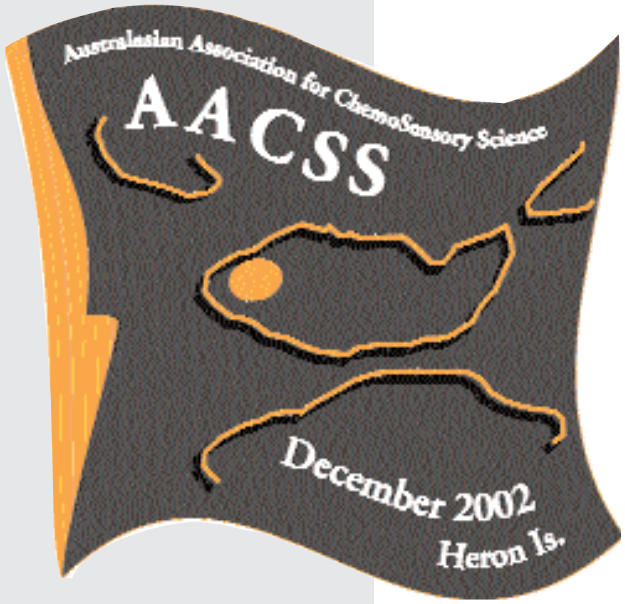
96 people have gathered at Heron Island in December 2002 for the Fifth Annual Scientific Meeting of the Australasian Association for ChemoSensory Science.

There are 61 active conference participants giving 59 papers in 12 oral and poster sessions. The plenary lecture will be given by Prof. Sophie Dove, of University of Queensland's Marine Biology Research Centre, which has a permanent research station at the island. She will introduce the chemical senses community to the fine science being done at the Barrier Reef, and her special interest in photosensitivity and proteins.

This is the largest regional gathering in 30 years of ChemoSensory experts. Participants are coming from Japan, Sweden, France, the Netherlands, Germany, UK, USA, Australia, New Zealand and Bermuda!

The Meeting's abstracts will be published in the next issue of *ChemoSense*.

Sponsors include Goodman Fielder and Carlton United Brewery.



Human Pheromones:

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ovulation of the donors, lengthened the recipient's menstrual-cycle. In a study by Shinohara et al. (2001) , exposing women to underarm secretions, obtained from other women, changed the frequency of pulsing of luteinizing hormone (LH). Studies that have sought to provide a measure of primer pheromone activity by looking for a change in the length of the menstrual cycle have received criticism for statistical and/or methodological errors (Doty, 1981; Wilson, 1987, 1992; Weller and Weller, 1993). Other criticisms have been fueled by the intra- and inter-subject variability found in normal, consecutive menstrual cycles (Strassmann, 1999; Schank, 2000).

New evidence for a primer effect in females comes from the authors' laboratory (Preti et al., in press). Extracts of underarm sweat from males were wiped under the nose of normally cycling women in the early to mid-follicular phase of their menstrual cycle, three times during six hours. Plasma LH was monitored every 10 min. Relative to measures in a six-hour control phase, the sweat extract significantly advanced the upcoming LH pulse. In natural situations, periodic, close contact with a male may modulate the female's menstrual cycle by affecting the hypothalamic LHRH pulse generator.

2. Releasers. Excepting the thousands of web pages devoted to the topic (a *Google* search, using "human AND pheromone" at the time of this contribution revealed 21,402 hits), there is no good biomedical evidence for human releaser pheromones. Cutler et al., (1998) would have us believe differently (see critique by Wysocki and Preti, 1998). Although many products are being sold with human sex attraction as the goal (many contain pig pheromones androstenone or androstenol), the advice most appropriate to the consumer is *caveat emptor*.

3. Signalers. In humans, there is good evidence that mothers can recognize their children by smell alone (Kaitz et al., 1987). Furthermore, newborns can recognize a lactating female (Makin and Porter, 1989) and soon come to recognize their own mother by smell (Winberg and Porter, 1998). Actually, the odors associated with the breast of a lactating mother approximate a releaser pheromone in humans: Infants were attracted to the breast odors of their mother and moved in the direction of the odors (Varendi and Porter, 2001).

Information about MHC can be extracted from odor cues (Yamazaki et al., 1998-99; Singh, 2001). Indeed, there is evidence accumulating to suggest that, among humans, MHC odors may influence the choice of ones mate (Eklund et al, 2000; Jacob et al., 2002). Here too, these MHC-associated odors may become more

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releaser-like than signaler, but much more research needs to be performed before this happens.

4. Modulators. When some people experience a fearful film their odor differs from what it is when viewing comic sequences (Chen and Haviland-Jones, 1999, 2000; Ackerl et al., 2002). Other people can discriminate these odors. How this generalizes to other emotional states and whether the emotional state of others is modified by these chemical signals remain to be determined.

In related work, it was recently noted that females became significantly less tense and more relaxed when they were exposed to an extract of underarm sweat from males (Preti et al., in press). These females were the same as those described above in the discussion of primer pheromones. The hospital setting in which the females were tested was by no means optimal for noting shifts in affect. Perhaps under natural settings additional effects would be noted.

D. Candidate Human Pheromones: Chemistry and Structures

Preti et al. (in press) presented evidence that primer and modulator pheromones reside in the human axillae. Studies of axillary chemistry have demonstrated that a complex mixture of volatile and non-volatile compounds can be found there (Preti et al. 1987; Zeng et al., 1991; 1992, 1996). Despite what is advertised on various web-sites and suggested in certain peer-reviewed publications (Grosser et al., 2000; Savic et al., 2001; Sobel et al., 1999), there are no bioassay-guided studies that reduce the complex mixture of axillary compounds to one or more compounds with pheromonal function.

The authors have suggested above that pheromonal information may be conveyed by odorants. Unfortunately, myriad potential candidates are present (Preti et al., in press). Compounds present in the human axillae that have been most commonly assumed to be human pheromones are the volatile steroids androstenone, androstenol and 4, 16-androstadienone. The concentration and biogenesis of these compounds have been extensively studied (Gower and Ruparelia, 1993 and references cited therein; Rennie et al., 1991), and they have been shown to have primer (Shinohara et al., 2000) and modulator (Jacob and McClintock, 2000; Wilson et al., under review) pheromone activity when used at concentrations 1,000-fold above endogenous level. One preliminary study reported no effects when androstadienone was used at sub-threshold levels that approximated physiological levels (Lundstrom and Olsson 2002).

The odorants that characterize the axillae have been demonstrated to be C6-C11 saturated, branched, and unsaturated acids. In terms of relative abundance, these acids, in particular (*E*)-3-methyl-2-hexenoic (*E*-3M2H), are present in men in far greater quantities than are the volatile steroids noted above (~ 700:1; Zeng et al., 1991; 1996). In women, the straight-chain acids are present in greater relative abundance than is E-3M2H (Zeng et al., 1996). For people who can smell them (there are specific anosmias to both), E-3M2H and androstenone have low olfactory thresholds (Wysocki and Beauchamp 1984; Baydar et al., 1992; Wysocki et al., 1993).

The characteristic axillary odor is formed from the interactions between odorless, water soluble, precursor molecules, found in apocrine gland secretions (Zeng et al., 1992; 1996; 1996a), with cutaneous, axillary microorganisms (Labows et al., 1982). These precursors are Apocrine Secretion Odor-Binding proteins: ASOB1, (apparent molecular weight 45 kDa) and ASOB2 (apparent molecular weight 26 kDa). These proteins carry 3M2H to the skin surface. The polypeptide chain of ASOB2 is identical to apolipoprotein D (apoD), a known member of the lipocalin proteins (Zeng et al 1996a). Hence, a ligand for apocrine apoD (ASOB2) is 3M2H.

The chemistry of axillary odor production suggests a similarity between human axillary secretions and non-human mammalian odor sources where lipocalins carry chemical signals used in pheromonal communication. In pigs (Spinelli et al., 2002) and hamsters (Singer et al., 1989), volatile molecules appear to be bound to lipocalin proteins that transport them and are in part responsible for some of the activity. Hence, both the chemistry of axillary secretions and their effects upon other people appear to be analogous to other mammalian primer pheromone systems. However, despite the interesting comparisons and analogies, only bioassay-guided isolation of components from the complex axillary secretion will identify which of the many compounds are pheromones.

E. Sensors in the Nose

Excluding marine mammals and old world primates, the general plan of the mammalian nose contains five possible neural routes for afferent information to enter the brain. These include 1) the olfactory epithelium with its ciliated receptor cells and associated olfactory nerves; 2) the vomeronasal organ with its microvilli-studded receptor cells and vomeronasal nerves; 3) the trigeminal nerve, which conveys information about chemical irritancy; 4) the septal organ and its associated receptor cells, which are anatomically and

Messages? continued

physiologically distinct from receptor cells found in the olfactory epithelium proper (Graziadei, 1977; Marshall and Maruniak, 1986); and 5) the terminal nerve (nervus terminalis), which contains LHRH-positive neurons (Wirsig-Wiechmann, 2001).

F. Which System Is Devoted to Pheromone Reception?

Given what is known about trigeminal afferents (Alimohammadi and Silver, 2002), it is safe to conclude that most likely it is not involved in the reception of pheromones. Chemosensitive afferents of this system appear to convey information about chemical irritation (chemesthesis).

Very little information is available about function of the terminal nerve; however, it appears not to be responsible for pheromonal detection in male hamsters (Wirsig and Leonard, 1987; Wirsig-Wiechmann, 1993). Function of the terminal nerve in other species, including humans, remains untested.

No direct evaluations of septal organ function in pheromonal reception have been published; however, in male hamsters, elimination of both olfactory epithelial and septal organ receptors (leaving an intact vomeronasal organ) eliminates up-regulation of fos expression (a measure of neuronal activation) in the brain in response to female pheromones (Swann et al., 2001). Interestingly, eliminating the vomeronasal organ did not affect fos expression. The males in these experiments had had sexual experience with females prior to the experiment. Such experience by male hamsters blunts, if not eliminates, the effect of removing the vomeronasal organ (VNO) on both fos expression in the brain and sexual behavior (Fewell and Meredith, 2002).

Although we cannot rule out participation of the septal organ, the more likely route of entry of chemosensory information in sexually experienced male hamsters lacking a VNO, i.e., VNX, is via olfaction. As Mike Meredith's laboratory has shown repeatedly, when it comes to sex and pheromones in male hamsters, experience is a great teacher. In sexually inexperienced males, the VNO appears crucial for the reception of pheromones from the female; however, with experience, the olfactory system assumes additional control and information, via either the VNO or olfactory epithelium, can support sexual behavior. Thus, we must conclude that both systems appear to support reception of pheromones; however, after experience, the apparent pheromonal effects via olfaction may be learned responses to non-pheromonal odors associated with female hamsters. Pheromonal learning of this type was demonstrated some time ago (Nyby et al., 1978). The basis for such learning apparently resides within the vomeronasal system: stimulation of this system is inherently rewarding (Beauchamp et al., 1985); hence, odorants associated with stimulation of the vomeronasal system can themselves become pheromone-like by being paired with the true pheromone.

There is excellent evidence that the VNO contains receptors for pheromones (Leinders-Zufall et al., 2000; Zufall et al., 2002) and that these receptors do indeed function as pheromone receptors (Del Punta et al., 2002). The preponderance of such reports has erroneously led many, from reporters to biomedical researchers, to conclude that the VNO is the pheromone receptor organ, to the exclusion of other afferent inputs to the brain. There are three false corollaries that follow from this assumption. False corollary 1: Substances that stimulate the VNO must therefore be pheromones. This conclusion has been refuted by demonstrating that VNO receptors respond to *off-the shelf chemicals* (Tucker, 1971; Muller 1971; Sam et al., 2001). False corollary 2: If the VNO is used by an animal, it must be processing pheromonal information. Excellent refutations can be found in the work by Halpern and co-workers who show that the VNO is used by snakes to track the chemical trail of their prey (Martinez-Marcos et al., 2002). False collary 3: To be a pheromone a compound must function through the vomeronasal system. There are reports showing that the VNO is not necessary for an animal to exhibit a response to a pheromone. The sow's response to the boar pheromone, androstenone, is an excellent example (Dorries et al., 1997). Others include courtship vocalizations in mice (Sipos et al., 1995), perhaps maternal behavior of ewes (Levy et al., 1995; c.f., Booth and Katz 2000), and socio-sexual behaviors in the lesser mouse lemur, a prosimian primate (Aujard, 1997).

G. Human Pheromones and the VNO?

Table 1. Comparative Summary of Biomedical Evidence for a Functional Vomeronasal System in Mice (Representing Non-Primate, Non-Marine Mammals) and Humans.

OBSERVATION	MOUSE	HUMAN	
		FETUS	ADULT
VNO	+	+	+
Sensory cells	+	+	-
Receptor genes	+	?	-*
Receptor transduction	+	?	-**
Nerves to brain	+	+	-
Brain region (AOB)***	+	?	-

Key: + = good evidence for presence; - = good evidence for absence; ? = not known.

* One V1R1L gene is expressed in the olfactory epithelium (Rodriguez et al., 2000).

** TRP2, which directs construction of a Ca++ channel in the membrane of receptor cells in the VNO, is a pseudogene in humans.

*** AOB = accessory olfactory bulb; the first relay and integration site within the central nervous system to process afferent information from the VNO.

Human Pheromones:

Oxymoron, Marketing, Maya, or Meaningful Messages? continued

Another false conclusion follows from the last false corollary above, viz., organisms that lack a functional VNO cannot use a pheromonal communication system because they lack pheromone receptors. There is good evidence that humans lack a functional VNO (reviewed by Wysocki and Preti, 2000; Meredith, 2001), at least in the way we understand function from studies in non-primates, e.g., mice (see Table 1).

However, as noted above, there is also a body of literature supporting the view that humans respond to pheromones. If humans do not have a functional VNO, then what system supports the receptor end of a pheromonal communication system? We suggest that olfaction per se is capable of extracting pheromonal information from odorants, if it is present. This may even occur at a subconscious level (Jacob and McClintock, 2000; Wilson et al., submitted). Whether human pheromonal communication is inconsequential or is as important as the Hindu concept of Maya (the power that deludes) remains to be determined.

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Upcoming Events

7-11 December 2002
Australasian Association for ChemoSensory Science (AACSS)
Fifth Annual Scientific Meeting Heron Island, Queensland, Australia
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18 - 20 January 2003
Progress and Directions in Olfactory Development
Tucon, Arizona, USA
www.neurobio.arizona.edu/olfactory_development

6-10 April 2003
Australian Water Association Ozwater Convention and Exhibition "Innovations in Water"
Burswood, Perth, Western Australia
www.awaozwater.net

9-13 April 2003
AChemS XXV
Sarasota, Florida, USA
www.achems.org/index.html

20-24 July, 2003
The Pangborn Sensory Science Symposium
"A Sensory Revolution"
Boston, MA, USA
Deadline for papers: 31 January 2003
www.Pangborn2003.com

10 - 15 August 2003
39th IUPAC Congress and 86th Conference of the Canadian Society for Chemistry
Ottawa, Canada
www.iupac2003.org

24-27 August 2003
"2003 Foods For Life", 36th AIFST Convention and 2nd World Symposium of Dairy Products in Human Health and Nutrition plus DIAA Dairy Science World Series Conference
Melbourne, Australia
www.2003foodsforlife.com

5-9 July, 2004
XIII International Symposium on Olfaction and Taste (ISOT) / JASTS
Kyoto, Japan
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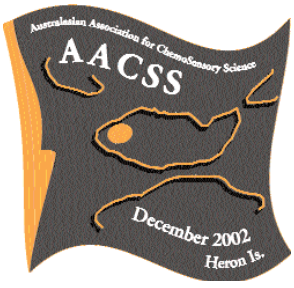

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More information is available through the Smartlink website: www.smartlink.net.au or from Linda Moscrop, Smartlink Program Manager on (08) 8302 0172 or linda.moscrop@unisa.edu.au.

NEWS

Postdoctoral Associate for Sensory Neurobiology Group

to study cellular/molecular signaling in taste buds (e.g., Chaudhari et al, 2000, Nat.Neurosci. 3:113; Caicedo & Roper, 2001, Science 291:1557; Caicedo et al, 2002, J. Physiol in press). Seeking dedicated, enthusiastic PhD, MD, or DVM to join a team investigating transduction mechanisms and cellular microphysiology in gustatory receptor cells. Experience in calcium imaging, patch-clamp, or closely-related field required. See http://chroma.med.miami.edu/physiol/faculty_pages/sroper.htm

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Send CV and names of references to Dr. S. Roper, Physiol/Biophysics (R430), U Miami Medical School, 1600 NW 10th Ave., Miami, FL 33136 USA roper@miami.edu ■

NEWS

Chardonnay Kills Harmful Food Bacteria

For millennia people have made wine and valued its contribution to the enjoyment of food. As most wine drinkers know, wine often preceeds the meal: a glass or two is quaffed before the arrival of the food. Why do we drink wine before and during a meal? Is there a purpose other than inebriation? Recent research suggests that wine protects the eater from food poisoning.

An Oregon State University food scientist, Mark Draeschel, has found that wine, particularly white wine, has antibacterial properties that kill E. coli, salmonella and other bacteria that commonly contaminate food and make people sick. The work is scheduled to appear in Journal of Food Technology.

Using a model stomach (plastic bag) and sterile baby food of known composition, he added various combinations of bacteria from cultures, synthetic gastric fluid, red wine (pinot noir), white wine (chardonnay) or grape juice. He then simulated the heat and movements of the digestive process. Bacterial levels were monitored at five-minute intervals.

Chardonnay had a marked bactericidal effect. Pinot noir, which had a higher alcohol content, nevertheless had a smaller effect. The acidity of the white wine was higher and this might have been crucial (7 gm/L versus 5.5 gm/L). Even without the help of gastric fluid both wines killed all bacteria within an hour. Chardonnay killed salmonella in 14 min and E. coli in 44 min. Pinot noir took 30 min and 60 min respectively.

This evidence suggests that wine confers an advantage on human survival against malevolent food microbes that are common in food. Any process that renders food safer to consume would earn a strong place in human food practices. Wine has certainly featured prominently throughout recorded human history, in association with food and feasting.

This research suggests there may have been survival value in doing so, particularly as food poisoning can be lethal. About 76 million events of illness and 5000 deaths are attributed to food poisoning annually in the USA. This new evidence suggests a smaller proportion of these would occur after wine consumption.

The findings have yet to be corroborated from evidence derived from within the human body. Meanwhile Oregon State University has applied for a patent on the use of wine as a surface disinfectant. Wine consumers can now decide which is the better use for a particular wine: drink it or wipe down the kitchen bench with it.

Source: Food Online November 13, 2002.
www.foodonline.com

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E-MAIL from Harbin, China

By Marilyn Styles
(Sensory Person in the Frozen North)

What have I done? Well may you ask! I have returned for another year in China! That question keeps recurring in my brain as I contemplate my flight on China Eastern Airlines from Beijing to Harbin, my new home. That is the airline that had 3 crashes before I left China in July...killing EVERYONE on board. Scary.

I am about to be introduced to the students who are marching in the quadrangle under the supervision of soldiers. There is a stronger communist presence here than Beijing. Last night I was treated to dinner with the college principal and the Communist Party Sectretary for the Hei Long Jiang Province.

It's October 14th and it's begun to snow: OMINOUS!

They tell me the snow is about 8 days early. Eight Days! Can they predict it that closely? Brrrr! I went to look at the city of Harbin on Sunday. There are some nice parts. No bikes - the winter months are too dangerous to ride, so local travel will be on foot, bus and snowmobile from here on.

I started my classes today, reviewing the English news on the Sydney Morning Herald sight on the internet: the Bali bombs. My students shared the shock we have all felt so acutely.

Well, it turns out, that after 36 days in freezing Harbin I'm off to sunny Beijing again. We had an assembly at school Friday afternoon and the students were told that I am going. In no time they were all crying and sobbing. It is the Chinese way to take emotions to excess. The principal was crying so much he couldn't go on. The teaching assistant was crying. So what did I do? Oh horror of horrors. I made multiple gurgling sounds which was a mixture of tears and irrepressible giggles. The net result, luckily, was very acceptable wet-faced convulsions. Phew! - now I know what saving face means. China is full of surprises.

Anyway, I had a lovely meal and karaoke Friday night. Its 6.30pm, Saturday, now. I've seen the frozen park of Harbin, had a snow fight, have seen the Japanese torture chambers, the keys to the cells and the gas masks. I've had lunch and karaoke (again), back to school, more tears and kisses saying goodbye to the students. Then off to have dinner (at 4.30pm) with the admin staff and the head of the school and the secretary of the Communist party and for a treat, guess what? Yes, karaoke! If I hear "Eldelweiss", "Only you" or that song from "Titanic", about love going on and on, again before I leave Harbin, I will suggest that the people of Harbin have discovered a new torture chamber: the karaoke restaurant!

I'll e-mail again if I don't crash on the way back to Beijing.

NEWS

ChemoSensory Retirements

Two prominent Australian scientists officially retired recently, but will work on and continue to contribute to their fields.

Donald Barnett, Deputy Director of the Centre for ChemoSensory Research, a Conjoint Associate Professor of Chemistry, and **Peter Barry**, Professor of Physiology and Pharmacology in the Faculty of Medicine, retired recently from their positions at the University of New South Wales.

The next day they were back in the lab with renewed vigour. Both have enjoyed long and productive careers in science, have taught and influenced many young minds and have contributed to the published literature. In the past decade or so, they have taken an interest in the chemical senses.

Don has applied his interest in molecular recognition and capture as performed by antibodies, to the development of chemical sensing materials and the electronic nose. A spin-off company and an active program on e-noses are among the on-going outcomes of Don's dedication to his work (see *ChemoSense*, 2002, **4**(3), 8-10).

Peter has adapted his interest in membrane biophysics and channel properties to understanding the mammalian olfactory receptor cell. His collaborators recently held a three-hour seminar to review his scientific contributions. Notable among the accolades was his high output in the best journals in the field and citation rates that would make sailor blush, as it were. His computer programs for the teaching of membrane physiology are now used in dozens of universities around the world.

We look forward to more of their fine work and wish the Barnett and Barry families the best of everything in the years ahead.

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