You read the words in a newspaper to find out what is going on in the world; the dog and cat read the semiochemical messages left in the environment by other animals in order to gather information. Just as words on a paper are a message intended to be received at a later time, animals apply pheromones to surfaces to communicate a message to be received at a later time.

**PHEROMONES DEFINED**

Pheromones are “a substance secreted by the outside by an individual and received by a second individual of the same species in which it releases a specific reaction.” Substances carrying a chemical message are termed “semiochemicals”, derived from the Greek word “seminon” which means a sign. Pheromones are semiochemicals which exert an effect on animals of the same species. Allelomones are substances which are produced by one species that influence members of another species. Pheromone signaling substances are contained in bodily fluids such as urine, sweat, specialized exocrine glands and mucous secretions of genitals. Our understanding of the physiological, behavioral and molecular aspects of pheromones is based on research in many species from insects and mammals. The chemical diversity of pheromones ranges from small volatile molecules, sulfated steroids to large families of proteins. These compounds as classified as pheromones based upon their binding to specific receptor and subsequent influence on behavior; not based on similarity of molecular structure. Pheromones are detected within in the vomeronasal organ and molecules bind to specific receptors which mediate an effect within the limbic system. The major effects of pheromones may be further classified as: priming and releasing effects. For example, sows in estrus respond to $3\alpha$-androstenol and $5\alpha$-androstenone, two steroid pheromones which is found in the saliva of boars, by exhibiting immobility, a rigid, motionless pose that reflects the degree of the sow’s reproductive readiness. This is an example of a releasing effect since a specific behavior is triggered. Releasing pheromones are less common and most of the clinically relevant pheromones we will consider are primer pheromones. Primer pheromones induce delayed effects which are modulated through the activation of the neuroendocrine system including the amygdala which is the fear and emotional control center for the brain. A pheromone primer blend causes a change in the signal receiver’s physiology that may not manifest itself as an immediate behavioral response. An example of a primer pheromone is the dog appeasing pheromone, represented by the commercially available product Adaptil®, which may induce a feeling of wellbeing and a bias toward a perception of a sense of safety and comfort.
Examples of natural pheromones and behavioral effects:

<table>
<thead>
<tr>
<th>Species</th>
<th>Molecular structure</th>
<th>Source</th>
<th>Behavioral effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silkworm moth</td>
<td>Bombykol ((10E,12Z)-hexadeca-10,12-dien-1-ol)</td>
<td>Produced by the female</td>
<td>Released to attract mates. Used commercially to ‘confuse’ males and disrupt reproduction</td>
</tr>
<tr>
<td>Sow</td>
<td>3α-androstenol and 5α-androstenone</td>
<td>Boar saliva</td>
<td>Rigid immobility stance by sow indicating sexual receptivity</td>
</tr>
<tr>
<td>Male elephants in musth.</td>
<td>frontalin (1,5-dimethyl-6,8-dioxabicyclo[3.2.1]octane)</td>
<td>temporal gland secretions, urine, and breath</td>
<td>Subadult males display avoidance. Receptive females are attracted and display mating related behaviors.</td>
</tr>
<tr>
<td>Female Asian</td>
<td>(Z)-7-dodecen-L-yl acetate</td>
<td>Urine</td>
<td>Signal readiness to mate</td>
</tr>
<tr>
<td>Atlantic lobster</td>
<td>Structure not specified</td>
<td>Released during molting</td>
<td>Signal readiness to mate. May only mate while molting. Initiates courtship dance with their claws held closed.</td>
</tr>
</tbody>
</table>

CHEMOSENSORY SYSTEMS AND THE DETECTION OF PHEROMONES

Pheromones are typically thought of as being received by the vomeronasal system. The vomeronasal organ (VNO) is a paired tubular structure which is located just above the hard palate near the inter-nasal septum. The VNO connects to the nasal cavity and, in some species such as the dog and cat, also to the mouth by an incisive duct. In ruminants and horses, the “Flehmen response” is accomplished by closing the nostrils, curling the lip away and inhaling deeply to draw air into the passageway of the VNO. Cats display a characteristic response called a ‘gape’ and dogs ‘tongue’ to gather pheromones into the passageways. Generally air flow in the respiratory passages does not come in contact with the specialized epithelium; instead the molecules are sucked into the lumen in response to a pumplike action of the surrounding vascular tissue. Specialized receptor neurons line lumen of the VNO and the information is relayed by the afferent neurons to the olfactory bulb, amygdala and ventromedial hypothalamus. In addition to the familiar pathways of the VNO, specialized chemosensory receptors also occur in the olfactory system. All of these receptors trigger the cascade of molecular and electrical events which ultimately influence the social behavior of the recipient animal.

PREVENTATIVE AND TREATMENT APPLICATIONS FOR PROBLEM BEHAVIORS IN CATS WITH FELIWAY

Pheromones may be useful preventatively or as treatment for specific behavior problems. Five feline facial pheromones have been identified in cats. These facial pheromones are identified as F1-F5. The F3 fraction is the pheromone which is deposited by the cat when facial marking and chin rubbing on objects or people. This creates a familiar, comforting scent of “self” in the environment.3,4
Applications for Feliway®
Kitten separated from littermates
Settling into a new home
Stress reduction
New experiences (first car ride, first grooming or first exposure to noises)
Veterinary visits
Carrier transportation
Urine marking
Intercat aggression
Territorial scratching
Loss of appetite due to stress

Feliway® spray applied onto previously marked areas has been shown to reduce
urine marking in 74–91% of households, and in eliminate urine marking in 33%–52% of
households.5,6,7,8,9 In a recent meta-analysis, there was significant reduction or improvement in
urine marking by at least 90% using fluoxetine, clomipramine or feliway.9

In a placebo controlled trial synthetic F3 pheromone was shown to promote grooming behaviors
and increased interest in food for hospitalized cats.10 The cats in this study were admitted for
evaluation of signs of lower urinary tract disease. Further, the 24-hour food consumption for cats
was significantly higher for cats that were offered a Feliway and a carrier for hiding was placed
in the cage and treated with Feliway compared to those only given Feliway.10

Another placebo controlled trial evaluated the effects of F3 analog alone, or in combination
with acepromazine as a premedication prior to catheterization. F3 analog was found to have
additional calming effects on cats when combined with acepromazine, and to a lesser degree cats
that were not given acepromazine. A synthetic analog FFP may make cats calmer but does not
reduce struggling for catheterization. The cats in the Feliway and acepromazine treatment group
also appeared more relaxed in the cage based on head postures and position within the cage.11

PREVENTATIVE AND TREATMENT APPLICATIONS FOR PROBLEM BEHAVIORS
IN CATS WITH ADAPTIL

Canine appeasing pheromones are released by the mother while nursing her puppies. The
pheromone enhances bond formation while comforting and reassuring the puppies. Adaptil® is a
synthetic analog of this canine appeasing pheromone which has similar effects on adult dogs.
Synthetic analogues of this pheromone have been clinically available as D.A.P.® and are now
available under the name Adaptil®. This appeasing pheromone analog has been effective in
helping puppies adapt to new homes, reducing fear and anxiety in puppy classes, the veterinary
clinic, shelter, car travel and improving long term socialization, and in improving separation
anxiety and noise phobias in conjunction with behavior therapy.12, 13,14,15,16,17,18,19

A randomized placebo controlled clinical study published in 2008 examined the effects of DAP
collars worn by puppies enrolled in socialization classes. The study found that compared to
placebo, puppies exposed to the pheromone exhibited significantly lower degree of fear and
anxiety, more positive interactions during play and a better response to training. Follow up at
1,3,6 and 12 months revealed the puppies were better socialized and adapted favorably to unfamiliar situations.20

**Applications for ADAPTIL®**
- Puppy separated from littermates
- Settling into a new home
- New experiences (first car ride, first grooming or first exposure to noises)
- Noise related fears and phobias
- Travel related anxiety
- Night time waking

**LEADER DOG STUDIES**

A double-blind placebo-controlled D.A.P.® collar study included 62 seven-week-old future guide dogs at Leader Dogs for the Blind in Rochester, Michigan.21 Collars were worn by puppies during the socialization period (7–19 weeks) and their response assessed by surveys completed by puppy raisers at 19 weeks, 3, 6 and 12 months. When compared to placebo, more D.A.P.® subjects achieved “perfect” response to the following: approach by unfamiliar dog at 12 m ($p = 0.038$); sudden or loud noises: 12m ($p = 0.064$), C ($p = 0.028$); and first exposure to new situations (veterinarian, car, elevator) at 19w ($p = 0.022$), 6m ($p = 0.046$) and C ($p = 0.011$). More placebo-subjects scored “perfect” response to unfamiliar objects on sidewalk at 19w ($p = 0.029$), and bathing at 12m ($p = 0.020$) and C ($p = 0.044$). On LD survey at 3m & 6m, more D.A.P.® subjects achieved perfect response to movement at 3m ($p = 0.0081$) and 6m ($p = 0.090$); children 6m ($p = 0.048$), animals 3m ($p = 0.060$) and noises 3m ($p = 0.072$) while there was not evidence placebo-subjects did better. When applied during the socialization period, D.A.P.® was useful in reducing anxiety and fear in puppies during and even beyond the treatment period.

A D.A.P diffuser study was conducted at Leader Dogs for the Blind assessing the benefits for canine appeasing pheromones for enhancement of graduation success for guide dogs assigned to recipients. Thirty-nine student/dog teams participated in this double blind placebo-controlled. D.A.P. or placebo diffuser was plugged in each dormitory room and each dog was in their room at night and during rest periods (~10–13 hours/day). D.A.P. diffuser group graduation rate was 17/17 (100%) compared to the placebo group graduation rate of 17/21 (80.9%) with 4 placebo dogs failing due to behavior related causes. The graduation rate difference between the treatment groups did not reach statistical significance ($p = 0.11$) (Fisher exact test), however, all 4 of the dogs failing due to behavior were from the placebo group ($p = 0.11$). The D.A.P. group had a 19.1% higher graduation rate indicating D.A.P. improved these highly trained dogs’ graduation success during final stage of training to become working guide dog.22

**COMMERCIAL PHEROMONOTHERAPY**

In natural circumstances, relatively minuscule amounts of pheromones are released and the resulting influence on behavior occurs in ordinary contexts. The advent of commercial pheromones provides opportunities to influence behavior solely by exposure to a synthetic
analog pheromone product. In natural exposures, the pheromone may also be associated with the sights, sounds and presence of the sender to deliver a complex multidimensional message. For example, boar pheromone is produced in the saliva while the boar also sniffs, noses, attempts to mount and sings a “courting song” series of soft guttural grunts. The result is the boar’s multisensory message to solicit the sow’s reproductive attention. A lactating female dog produces her blend of appeasing pheromones from the intermammary sulcus which provides a motherly comforting and reassuring influence for her offspring. Maternal relationships are also enhanced by licking, suckling and auditory signals. Collectively this message communicates the maternal commitment and comforts the puppies. Commercial pheromones are synthetic analogues of naturally occurring molecular blends derived from natural examples. Samples are collected from an individual and ideally an animal which displays superior semicommunication related behaviors when interacting. These samples must be carefully and accurately obtained, then analyzed by gas chromatography and mass spectroscopy. Based on analysis of the chromatogram the product is artificially synthesized. Biological screening plus clinical trials are necessary for confirmation of efficacy of the end product. The product concentration will necessarily be much higher than naturally occurring pheromones. Natural always sounds better. While the allure of new products which proclaim a natural formulation rather than a synthetic analogue seem intriguing, one must wonder how many dogs must be housed from which to derive a natural formulation. A clear understanding of the complexities involved in harvesting natural pheromones illuminates the absurdity of such claims.

Further, understanding the derivation and the natural applications of pheromones help elucidate the appropriate applications and possible misapplications. If a cat is extremely terrified and simultaneously detects a semiochemical message conveying comfort and tranquility, one can imagine this may be more confusing or disconcerting to the feline psyche. Pheromone products are best applied to influence a behavioral response as they are not intended to completely control a specific response. A complete understanding of motivation of pet misbehaviors is essential to consider intervention strategies. For example, a client requests help to alleviate her dog’s barking it is important to understand the dog’s motivation for barking. A fearful or anxious dog may bark less when comforted by appeasing pheromones. A dog that barks freely and continuously due to habit or experience may not have any anxiety while barking; therefore anxiety reduction is not going to alleviate barking. Many clients resort to startling techniques for barking since the dog may stop barking when startled. Clearly this approach does not alleviate anxiety though the barking may temporarily cease until the dog habituates to the startle technique.

REFERENCES

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