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Current research in canine and feline pheromones

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Everyone who has observed dogs or cats, if only once, has been impressed by how important olfactory communication is in these species. Carnivora are known as the order that has developed the greatest variety of glands secreting chemical signals. Among all the molecules secreted by these glands, some seem to transmit highly specific information between animals of the same species—the pheromones. In 1959, Karlson, Luscher, and Butenand created this word by combining the Greek verbs *pherein* (to carry) and *horman* (to stimulate). Initially, this kind of chemical communication was supposed to exist only in invertebrates. At that time, more attention was paid to the pheromones of insects, and a few products to fight against some pests have been developed. Many ethologists thought that this really strict and biologic way to communicate should not be considered in mammals because of the complexity and plasticity of their social behaviors [1].

The description of the ''ram effect,'' which is the activation of ovulation in the ewes by the ram's skin secretions, has shown that pheromones could exist in mammals [2]. The first pheromone to be analyzed was the boar's pheromone, which is produced by the submaxillary glands. The main component of this pheromone is 5 α-androsterone, a steroid with 19 carbons, which has a urine odor [3]. This pheromone induces an immobility response in the sow when she is in estrus. Synthetic analogues of this pheromone have been developed to detect estrus in sows before artificial insemination.

For the last 10 years, the functions of some pheromones in dogs and cats have been elucidated, and synthetic analogues of some of these are beginning to be used as a therapeutic approach in behavioral medicine [4,5].

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Marking behaviors seem to be more and more interesting parameters for the evaluation of the behavior of our patients.

It seems to be important for veterinarians to be able to identify scent marking during the behavioral examination and to take care of the activity of the glands that produce these secretions.

Olfactory communication in carnivores in general, particularly in dogs, has been the subject of a number of studies over the years. Among the substances produced, pheromones have an important place. The complexity and great number of substances produced led many authors to consider the chemical analysis of these messages to be impossible or at least unpredictable.

Many recent studies as well as the development of synthetic analogues of pheromones have improved our knowledge. An important point has been to determine the difference between pheromones and odors. Pheromones are not simple smells. The perception of the odors is a spontaneous phenomenon. During respiration, part of the inhaled air (up to 30% in some species [4]) is deviated to the olfactory mucus. In that way, animals perceive the odors when breathing. The perception of the pheromones does not work in the same way. The vomeronasal organ (VNO) is not easily accessible during normal respiration. To be stimulated, it has to be opened, and the pheromones can then go to receptors on the membranes of the nervous cells of this organ. The pheromones may have particular olfactory characteristics, but they do not act only as an olfactory stimulus. The odor of the pheromones can be a stimulus that induces the opening of the VNO.

Perception of pheromones

The perception of pheromones is not completely understood. The best-known hypothetic is that there is a stimulation of the VNO. The VNO is a part of the accessory olfactory tract (Fig. 1). There are two VNOs situated on each side of the nasal septum in a small fossa. Each VNO is about 4 cm long in the dog (Figs. 1 and 2) [7,8]. Three nerves innervate the VNO. The nasopalatine nerve (part of the trigeminal nerve), which includes fibers of the parasympathetic and sympathic nervous system, may control both the vascular activity and secretion of mucus by the glands. There is also a functional relation between the nasopalatine nerve and some mechanoreceptors included in the nonnervous part of the VNO. The vomeronasal nerve is dedicated to the transmission of stimulation initiated by the pheromone. This nerve is connected to the accessory olfactory bulb and then to the amygdala through the limbic system (in the medial nucleus and the cortical posteromedial nucleus). In contrast to the main olfactory tract, there is no connection between the VNO and the neocortex even through the thalamus [9]. The connections between the sensory cells and the glomeruli in the accessory olfactory bulb and in the main olfactory bulb are absolutely different. In the main olfactory system, there is a rich variety of odor

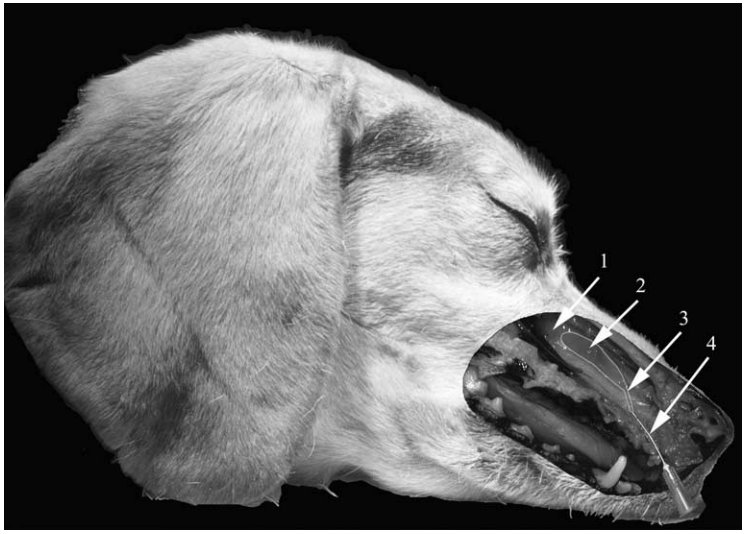


Fig. 1. Photographic montage of the dissection of the vomeronasal organ in a dog. Right canine and a part of the incisive bone are removed. 1 = nasal septum; 2 = body of the vomeronasal organ (outlined); 3 = vomeronasal duct; 4 = incisive duct (needle).

receptors. Each kind of sensory cell (meaning cells carrying the receptors for one specific odor) is connected with only one glomerulus; it enhances the precision and sensitivity of detection. In the accessory olfactory bulb, each sensory cell is connected with several glomeruli, which, in that manner, receive the information from cells carrying several types of receptors, enabling a complex coding with a limited variety of receptors [10,11].

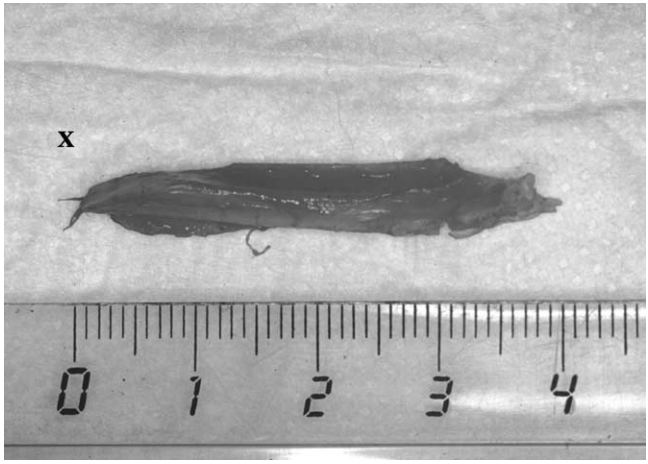


Fig. 2. Vomeronasal organ (with cartilage) of a dog. X = cranial extremity.

The third nerve, the nervus terminalis, which has no precisely known function, travels from the nose to the brain and includes gonadotropin-releasing hormone LHRH cells.

The VNO is wrapped up in the vomeronasal cartilage (Figs. 2 and 3) to form a tube closed at its caudal end. There are many elastic fibers and smooth muscular fibers that show motor activity during the suction of the pheromones [11–14]. The lumen of this organ is surrounded by two kinds of epithelium: the medial one, which is thick and includes nervous cells, and the lateral one, which is thin and consists of a respiratory mucous membrane (Figs. 3 and 4). The axons of the nervous cells of the medial epithelium merge together to create the vomeronasal nerve. On the lateral side are

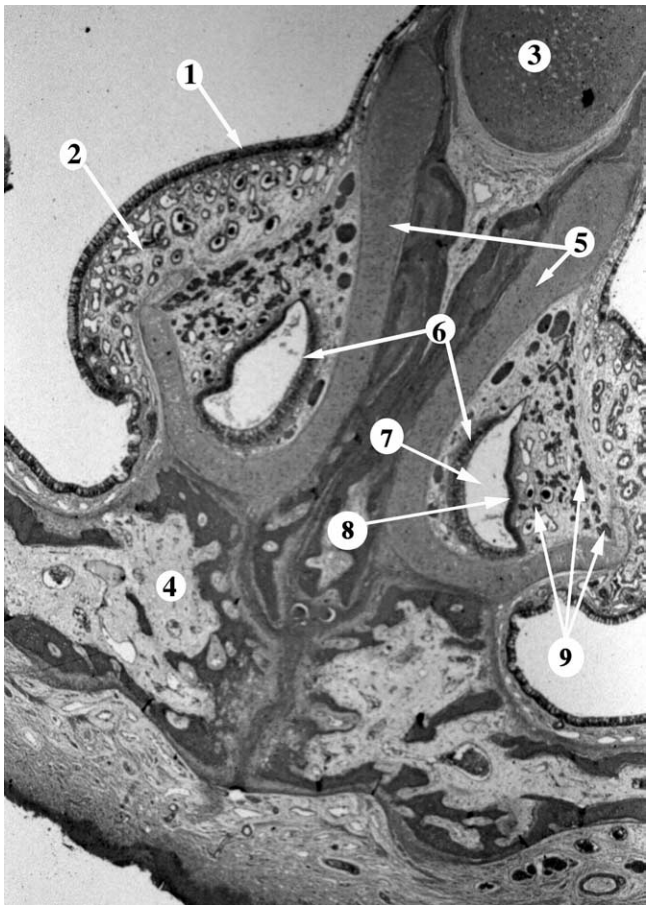


Fig. 3. Cross section through the nose in a kitten (original magnification × 25). 1 = respiratory mucosa; 2 = conjunctive chorion; 3 = nasal septum bone; 4 = vomer bone; 5 = vomeronasal cartilage (U-shaped conformation); 6 = medial (receptor) epithelium; 7 = crescent-shaped lumen of the vomeronasal organ; 8 = lateral (respiratory) epithelium; 9 = vomeronasal glands.

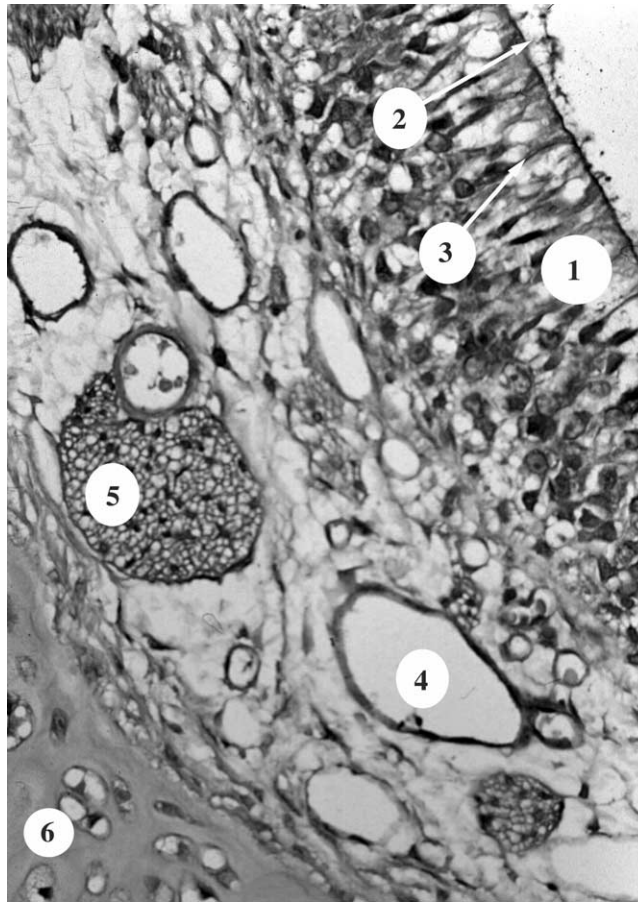


Fig. 4. Cross section of the vomeronasal organ in a kitten (original magnification × 400). Details of Fig. 3. 1 = receptor epithelium; 2 = microvilli; 3 = sensorial cell; 4 = capillary blood vessel; 5 = fascicle of the vomeronasal nerve; 6 = vomeronasal cartilage.

many blood vessels and mucus-producing glands that are important during the suction of the pheromones. The components of the mucus are those usually observed in respiratory mucus and, in addition, some specific lipocaline proteins that may be pheromone-binding proteins (PBPs). These proteins, weighing around 20 kd, show a high affinity for hydrophobic molecules like fatty acids [15–17].

In many species of mammals, the suction of the pheromones by the VNO follows a behavior described as flehmen. This behavior is specific to some mammals, including the cat. Flehmen consists of raising the upper lip with the mouth half-open and, in cats and dogs, movements of the tongue. The movement of the upper lip is achieved by contraction of the muscle levator

labii maxillaris [12,13]. During this contraction, the accessory head of this muscle, which attaches on the incisive papilla, opens the incisive ducts that communicate with the vomeronasal duct and then the VNO. In the dog, the occurrence of flehmen remains controversial [3]. We do not observe any real flehmen in this species, but the analogous behavior may be tonguing, in which the dog pants, raises the upper lip, creases the nose, and rapidly flicks the tongue against the incisive papilla during exploration of feces, urine, or proestral blood. The role of flehmen has sometimes been limited to detection of sexual pheromones, but it is also known that castrated subjects carry it out and that this behavior appears in circumstances having nothing to do with sexual activity [3–5]. This is most noticeable in cats when a subject is located close to a urine mark or even in close proximity to a facial mark [6,18].

The mechanism of flehmen induces aspiration of the pheromone into the VNO, where it is mixed with the mucus. This suction occurs because of vasoconstriction in the wall of the VNO. This increases the diameter of the lumen of the organ and thus creates the fall in pressure necessary for the suction. The components of the pheromone are mixed with the mucus, which consists primarily of hydrophobic molecules. The components of the pheromone bind with the pheromone binding proteins (PBPs) and so can stimulate the receptors located on the membrane of the sensorial cells [5,14,16].

After the suction period, the washout of the VNO begins. The blood pressure increases, and the diameter of the VNO's lumen decreases, expelling the mucus, including the PBP-pheromone complexes. Because of the opening of the VNO into the incisive channel and then into the mouth, the expelled mucus is not visible in carnivores. Conversely, this expulsion is easily observed in the stallion just after the flehmen to the urine of a mare in estrus.

What the response of the brain is after the stimulation of the VNO's receptors by the pheromones is not really known. A number of hypothesis related to sexual pheromones have been proposed. In the doe and the ewe, the pheromones produced by the postcornual gland (sebaceous glands from the skin between the horns in Artiodactyles) of males may induce a peak of LH in females that is responsible for the ovulation [3]. The action of the other types of pheromones has not been demonstrated, but the use of new techniques like positronic cameras and radiolabeled pheromones should be of great help to explore these phenomena.

Even if we do not precisely know the whole mechanism, it is possible to summarize the action of the pheromones by dividing these biologic mediators into two groups [19]:

- Primers: pheromones that induce some major modifications of the physiology in the receiving individual
- Releasers: pheromones that induce an immediate modification of the behavior of the receiving individual

Structures secreting pheromones: the main known pheromones

Carnivora are identified as the mammalian species that have the most developed and varied types of pheromone-secreting glands. Different types of glands present in the skin and in certain mucous membranes are involved in producing pheromones. The histologic structure of these glands does not reflect a functional specificity, except for the anal sacs, which are often mentioned and seem to be the most typical pheromone-secreting structures in carnivores [3,6,20–22].

If we try to explore the pheromone-secreting glands from the nose to the tail of dogs and cats, we encounter six major sources of pheromones.

The facial area

The area of the cheek and perioral glands brings together a whole set of secreting structures spread throughout the chin, lips, vibrissae, and cheeks. These glands exist in both dogs and cats. The dog has one more gland, however, the ear gland, which consists of some ceruminous glands of the ear duct as well as some sebaceous glands from the external ear.

In the cat, five different facial pheromones named F1 to F5 have been isolated from the sebaceous secretions of the cheeks (Table 1). At the present time, we know the function of only three of them (F2, F3, and F4). These pheromones are involved together in territorial marking behavior (in its widest meaning) in cats and in complex social exchanges that can easily be observed.

The cat seems to mark some points around his preferred pathways in his territory by rubbing his face on them (Fig. 5). In so doing, he deposits the pheromone F3, which may appease him and helps in organizing the

Table 1
Chemical components of the facial secretions in the cat

Secretion	Components	Function
F1	Oleic acid, caproic acid, trimethylamine 5-aminovaleric acid, n-butyric acid, α-methylbutyric acid	Unknown
F2	Oleic acid, palmitic acid, propionic acid, p-hydroxyphenylacetic acid	Sexual facial marking in tomcats
F3	Oleic acid, azelaic acid, pimelic acid, palmitic acid	Facial marking on items, antagonist of urine marking and scratching
F4	5β-cholestan acid 3β-ol, oleic acid, pimelic acid, n-butyric acid	Allomarking, antagonist of territorial or irritative aggression
F5	Palmitic acid, isobutyric acid, 5-aminovaleric acid, n-butyric acid, α-methylbutyric acid, trimethylamine, azelaic acid, p-hydroxyphenylacetic acid	Unknown

Data from MacDonald DW. The carnivores: order Carnivora. In: Brown RE, MacDonald DW, editors. Social odours in mammals. Oxford: Clarendon Press; 1985. p. 619–22.

Fig. 5. Facial rubbing of a cat. This part of the ethogram of the cat is well known to all cat owners. The cat rubs its head against an object from the side of the chin to the base of the ear. Cats of both sexes show this behavior, and frequency of rubbing depends on the individual. The facial secretions combined with urinary secretions inform male cats about the sexual receptivity of female cats, but rubbing is not a behavior implicated only in reproduction. Rubbing seems to have a visual communication function associated with the placing of facial pheromones. In fact, cats seem to perform this marking behavior when a known individual approaches. Facial secretions are divided into five fractions, with each of them having a specific action. The F4 fraction of facial pheromones has a relational function—allomarking. The F3 fraction of facial pheromones represents spatial orientation and emotional stabilization functions. These marks seem to be involved in the cat's geographic orientation; they are placed on objects that form the boundary between a passage and a territorial zone.

environment by classifying it into ''known objects'' and ''unknown objects'' [3–5]. During sexual behavior, when detecting and attracting females in estrus, the male cat rubs his face on some points around the place where he is with the female cat and deposits the F2 pheromone. This pheromone seems to improve the efficacy of the sexual display [4,5,18]. In tomcats, the development of the cheek glands is dramatic, and we observe an extreme reduction of this gland in neutered male cats [23]. The social function of another facial pheromone is also known in the cat—the F4 pheromone, called the allomarking pheromone. The allomarking behavior is observed between cats who live together or between a cat and a dog or a cat and a human being when the cat is socialized with these other species. This pheromone decreases the probability of aggressive behavior between the cat and a marked individual [4,5,24–26]. In this species, it has been proven clearly that the sebaceous glands synthesize a protein that is known to be the main feline allergen for human beings—Fel-d-1 [23,27]. This protein is a dimer whose structure is similar to PBP, and it has a high affinity for hydrophobic small molecules like the fatty acids that are components of the pheromones [15,17,23,27]. This protein could be secreted to bind and

protect the pheromones and so enhance their probability of being detected. According to some experimental data, Fel-d-1 seems to be a persistent substance, because it is possible to find the protein even 3 weeks after a cat has marked a place [21,27].

In the dog, the facial complex seems to be involved, especially in social relationships (Fig. 6) [3,20,26,48]. Some information has recently been acquired about the chemical structure of these secretions. The secretions of the ear gland seem to be related to the social status of the dog. Some secretions seem to be secreted only by dogs that show assertive behaviors (eg, eating before the others, taking other dogs' food because they show a submissive attitude, exhibiting sexual behaviors in front of others). Just after submission, a dog generally approaches the winner of the fight and smells the opening of his ear with small movements of the tongue and the lips [18,26].

The pedal complex

This area consists of the pedal glands of the four legs. These are diffuse structures present both in the plantar pads and in the skin of the interdigital region. The presence of glands in the plantar pad is not as clear in the dog as in the cat. The cat shows many sweat glands in the plantar pads, which secrete the sweat emitted, for example, during fear reactions [3,6,18]. The histologic structure seems to be really different in the dog, and the pedal area is perhaps limited to the interdigital area.

In both cats and dogs, this complex is involved in marking territory and in producing alarm pheromones [3,4,6,18,20,26,28]. During territory marking, the pedal secretions are associated with a scratching behavior, which creates a persistent visual signal [3,4,6,18,26,28]. In the cat, the scratching

Fig. 6. Main pheromone-secreting glands in the dog. 1 = labial glands; 2 = auricular glands; 3 = perianal glands; 4 = vulvar or preputial glands; 5 = interdigitous glands.

marks are generally made on vertical places, and this behavior is considered as unacceptable by many owners (Fig. 7) [3,18]. In the dog, the scratches are on the ground and are commonly remarked with urine by the male dogs [18,28].

Some alarm marks seem to be emitted by the pedal center. Even if there are no precise data about these secretions, it is easy to observe that the sweat secreted by fearful cats enhances avoidance behaviors in the cats who encounter these marks. It is possible that this kind of pheromone is involved in the fear elicited by the veterinary clinic in dogs and cats. The alarm pheromones secreted by the previous animals could create the fear reactions that are commonly observed by the veterinarian [18].

Fig. 7. A cat is scratching a vertical object. This object is covered by a special resin containing a synthetic pheromone that enables scratching. Scratching usually occurs near a place associated with a precise activity (eg, litter, bowl) and in the pathway of a human being or other animal.

The perianal complex

This area consists of the supracaudal glands, the circumanal glands, and the anal sacs. The supracaudal glands are well developed in the cat. They consist of a high concentration of sebaceous glands located at the dorsal aspect of the root of the tail [3], sometimes extending distally on both sides of the tail. Each gland is visible, with the size varying between 0.85 mm × 0.5 mm in female cats and 1.84 mm × 1 mm in tomcats. In each organ, we may identify tubular apocrine glands that lie between large sebaceous glands comprising cistern-like cavities running into ducts [3]. This structure is well known to veterinarians because of the inflammations that can occur, particularly in tomcats, but we do not precisely know their function, except that it seems to be related to the identification of the male by the female in estrus. Neutered male cats show reduced supracaudal glands.

In the dog, the supracaudal glands are less developed. In the hunting wild dog *Lycaon pictus* and in the domestic dog, these glands seem to be undeveloped in some individuals [3]. These glands are associated with the sebaceous disorders that can occur in some dogs. These glands generally form an elliptic patch of large sebaceous glands on the dorsal surface of the tail 5 to 40 mm below the base and are more developed in male dogs than in female dogs. In male red foxes, it has been reported that there was an increase in the sebaceous activity in this gland during spermatogenesis [29]. Extrapolating from that, we can suppose that this secretion could be involved in the stimulation of the bitch during sexual display. Conversely, the supracaudal glands seem to be active throughout the year and thus could be involved not only in sexual behavior but in social communication (see Fig. 6).

The circumanal glands include the sebaceous and modified sweat glands that are disseminated all around the anus. These glands seem to be more developed in the dog than in the cat. The circumanal glands of male dogs are the more developed, and their size increases with age. In old male dogs, the diameter of the circumanal area is 3 to 4 cm and there are more glands on the upper part of it. These secretions seem to be important for the social life of the dogs, and it seems that the special color of the hairs around this area plays an important role in improving the efficacy of the chemical signal (see Fig. 6). During estrus, these glands produce trimethylamine-rich secretions in bitches [30].

In cats, these glands are well developed only on the skin below the tail. As has been described in many Felidae (eg, lions), the secretions of the circumanal glands of cats differ from the canids' secretions in that they lack trimethylamine [1].

The anal sacs are found in both dogs and cats, and their physiology is really important in understanding some critical points about chemical communication.

Dogs show two symmetric sacs that open by a small ostium at the limit between the anus and skin. The wall of this sac is stratified and keratinized

epithelium with several apocrine glands. These particular glands are modified sweat glands and sebaceous glands. Some of them excrete their secretions into the sac and some into the duct of the sac, which is 4 to 5 mm wide [3,6,31]. The secretions change in color from cream to brown and often contain large flocculent globules. Anal sacs are fermentation chambers where aerobic and anaerobic bacteria metabolize the original secretions of the glands to produce aliphatic acids and amines (eg, putrescine, cadaverine, methylamine trimethylamine). These sacs are surrounded by smooth muscular fibers that make possible the strong expulsion of these secretions in marking behavior and especially in alarm marking during fear-induced reactions; spraying of these secretions over 0.5 to 1.2 m has been observed by some authors [31]. In bitches, the composition of the secretions varies during ovarian activity. During estrus, these secretions seem to be highly attractive to male dogs, and their concentration of C2 through C5 aliphatic acids, acetone, and trimethylamine increases [3,30]. Variations of the bacterial flora are common in the anal sacs [30–32]. The consequence is a modification of the composition of the chemical signals, which may result in behavioral problems in groups of dogs, such as aggression toward the dog with an anal sac infection. This point is critical for the veterinary behaviorist, and it is absolutely necessary to examine the anal sacs of dogs when there are some social behavioral problems between dogs that live together [18].

In the cat, the same anal sacs exist but their opening is into the rectum; thus, their secretions participate in the communication in the feces. The walls of their anal sacs contain more sebaceous glands than in dogs, and, correspondingly, they produce lipid-rich secretions [3]. These glands secrete large amounts of Fel-d-1 protein, which could be important in binding the pheromones so as to maintain them in the environment [33].

The genital complex

This area includes sebaceous glands of the prepuce or the vulva and urethral or genital mucous glands together.

In the dog, this complex is intensely explored during each social contact (see Fig. 6) [34]. These secretions participate in both social and sexual behaviors. In bitches, during estrus, a secretion of methyldihydroxybenzoate seems to be highly attractive to male dogs and enhances sexual excitement [3,18,20,35]. It is interesting to note that this component is commonly used as a preservative in many human cosmetic products. It could be involved in some sexual behavior shown by some dogs toward their owners.

In the cat, these glands are not so well studied and there is a lot to be learned about their functions.

The mammary complex

This complex has been discovered in recent years. Some authors described olfactory interactions between mothers and babies in primates

and especially in human beings, but there was no proof that there was any pheromone secreted in this area. The first pheromone isolated in this area was in the sow [36]. Shortly thereafter, we isolated the same kind of pheromones in bitches, mares, cows, ewes, queens, and does. Because these pheromones seem to have an appeasing action on the babies and adults, we proposed calling them appeasines. These pheromones are secreted by the sebaceous glands of the sulcus between the two mammary chains [18,26].

The appeasines of the bitch or the queen have the same chemical structure as those of the other species; three fatty acids could be considered as the "mammal appeasing message": oleic acid, palmitic acid, and linoleic acid. They are always associated in the same ratio. The other components could be considered as the species-specific message, which always begins with myristic acid (in a varying ratio). The specific message of the bitch is in the following order: myristic acid, lauric acid, pentadecanoic acid, and stearic acid [36]. In the queen, the specific message is similar but the pentadecanoic acid is lacking and thus the ratios of each component are different. As in the anal sacs, the association between the secreting glands and the saprophytic bacteria is critical. The glands produce fatty acids that are not too volatile. It seems that the temperature of the skin rises as the result of an increase in blood circulation but that it is not sufficient to vaporize the acids. The chromatographic analysis of the sebum shows that there is a balance between acid and methyl-esters. Both have the same efficacy according to the pheromonal message, but they do not have the same volatility [36]. The methyl-esters are much more volatile; all of them are liquid at 20°C when many acids are solid.

These pheromones are not secreted immediately after the birth of the litter. The secretion appears 3 to 4 days after parturition and persists 2 to 5 days after the weaning of the puppies or kittens (4 months of age for puppies and 6–12 weeks for kittens) [18,36].

Urine and feces

The importance of urine and fecal marking is well known in both dogs and cats. Both are a complex source of pheromones. In both urine and feces, the chemical components of the pheromones are produced by both glands, which emit their secretions in the lumen of the urinary tract or in the anal duct, and also by saprophytic bacteria, which metabolize some components of urine or feces [3,20,26,29].

Urine marking is certainly the most well-known marking behavior in the cat. It is considered the main behavioral problem of cat owners. The posture of the cat during urine marking is typical (Fig. 8). The cat stands up and sprays small amounts of urine on vertical surfaces. The spots of urine on the marked surface and the attitude of the cat are visual signals specifying that there has been an emission of pheromones. It is easily visible, because the cat that detects such signals exhibits a flehmen [18]. Several situations can

Fig. 8. Urinary marking in the cat is characterized by distinct behavioral patterns. After selecting a vertical support, the cat sniffs it, kneads the ground and turns its back to the support. With the tail held vertically, the cat sprays a horizontal jet of urine. The two most common types of urine marking are sexual and reactional urine marking. Sexual urine marking occurs by male cats when they are sexually excited (by the presence of a female in heat). Urine marks are left on exits to the outside (doors and windows). Female marking is related to the onset of estrus. Sexual urine marking often comes together with vocalizations. Reactional urine marking is often caused by a change in the cat's environment (eg, new piece of furniture, moving to a new house, a visitor or new occupants).

enhance urine marking in cats. Spraying as sexual activity is well known in tomcats but also exists in female cats during estrus. Some components of the sexual pheromones in the tomcat are aromatic and are provided by the seminal secretions [18,21,37]. After neutering, these aromatic components disappear and the occurrence of this kind of urine marking decreases. Urine marking is also used in situations of territorial modifications (arrival of an unknown individual or modification of the physical environment [eg, introduction of a new piece of furniture]). Facial marking with F3 is an antagonist of this urine marking [4,25]. Fecal marking is less common in cats than in dogs. The significance of this marking is not well known, and it seems that this behavior could be related to alarm marking [18].

In dogs, urine marking is also recognized easily because it is a visible marking. This behavior can be observed in both female and male dogs even if it is more frequent in male dogs (Fig. 9). The movements of the rear limb are pronounced in dominant male dogs when they mark in front of conspecifics [3,18,26,38]. In the absence of conspecifics and especially when there is no challenger, this marking is really rare. Urine marking can be associated with scratching the ground, especially when there are female dogs in estrus or if there is a situation of severe hierarchic challenge [18,26,28]. In the situation of hierarchic disorders between dogs and owners, urine

Fig. 9. Dog's posture of urinary marking. This behavioral pattern involves a complex association of messages. Visual cues inform others dogs in a wide range of the presence of olfactory information in this precise area. The urine-marking behavior of the dog can be completed by laying of podal pheromones on the ground by scratching the ground with its legs. This behavior is significantly more frequent in male dogs [20,28]. Performance of this marking seems to bear a relation to certain situations of competition between male dogs as well as to the intrusion of individuals not belonging to the pack [20,26,28].

marking increases and sometimes becomes the main complaint of the owners [18]. Fecal marking is also well developed in the domestic dog as in many Canids (eg, fox, coyote) and Mustelidae (eg, badger). The feces are laid on high surfaces like stones, stumps, or furniture. Generally, only a small amount of feces is associated with the secretions of the anal sacs and glands of the anal duct. This marking is common in females too, especially during metestrus [18,26].

Because we understand the mechanisms that control the emission of pheromones better and better, it is possible to use them as therapeutic measures.

Pheromonotherapy

We proposed this word to describe the use of pheromones to treat behavioral disorders [5]. Because our pets are living in a world full of smells, this particular clinical approach seems interesting and is considered acceptable and pleasant by owners. The limits of this approach are related to the precision of this communication. The right pheromone has to be chosen and emitted at the right time and on the right place so as to obtain the expected results. It means that the propedeutic approach to behavioral disorders also has to be precise.

The precise mechanism of action of most pheromones is still unknown, but they induce some modifications in both the limbic system and the

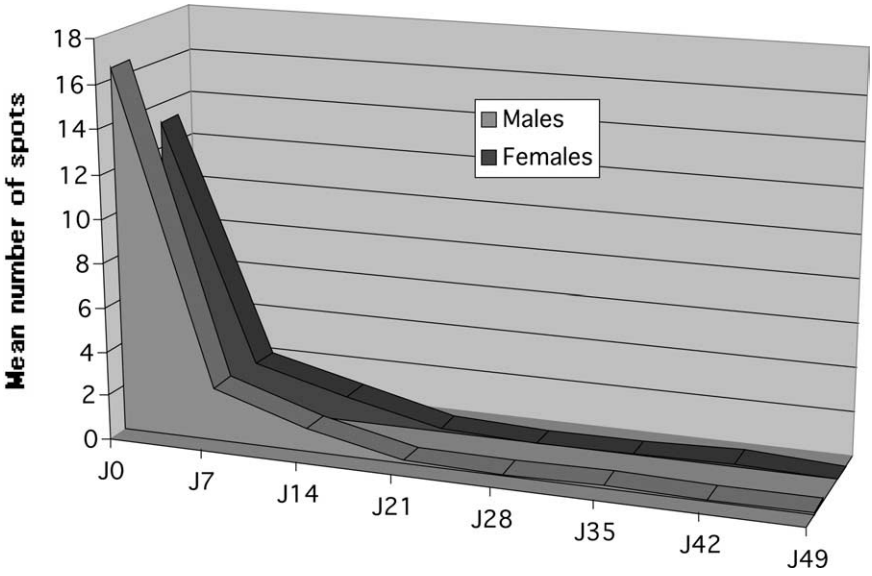


Fig. 10. Usefulness of F3 in the treatment of urine marking in the cat [5]. The studied population (1–6.5 years old) is composed of 30 male (29 neutered) and 31 female (22 spayed) cats. These cats are treated for reactional and sexual type urine marking that had been evolving for between 1.5 and 3 months. The treatment consists spraying F3 once a day on the urine marks and on salient objects and locations in the house. This treatment is continued for 28 days, and the cats are followed up to day 49 so as to monitor any relapse.

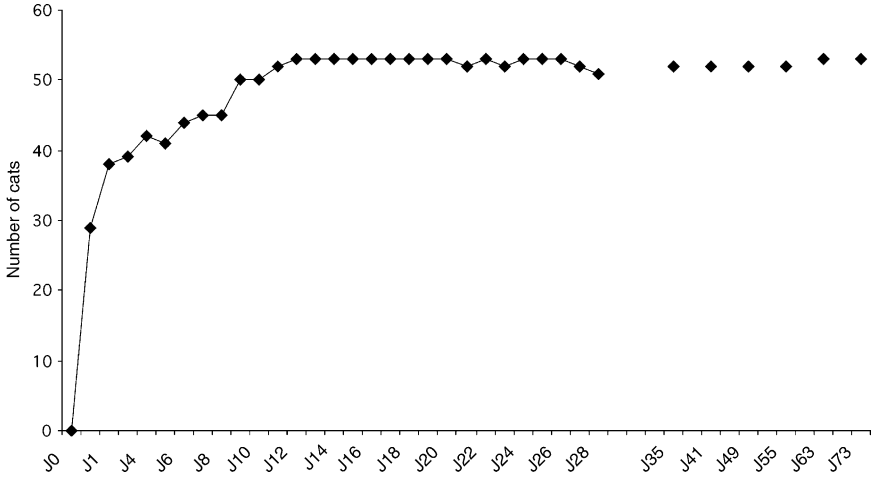


Fig. 11. Usefulness of F3 to decrease excessive scratching. Fifty-three cats are included in this trial. F3 is sprayed daily for 28 days on every scratch mark. All cats are followed up for 7 weeks so as to monitor any relapse.

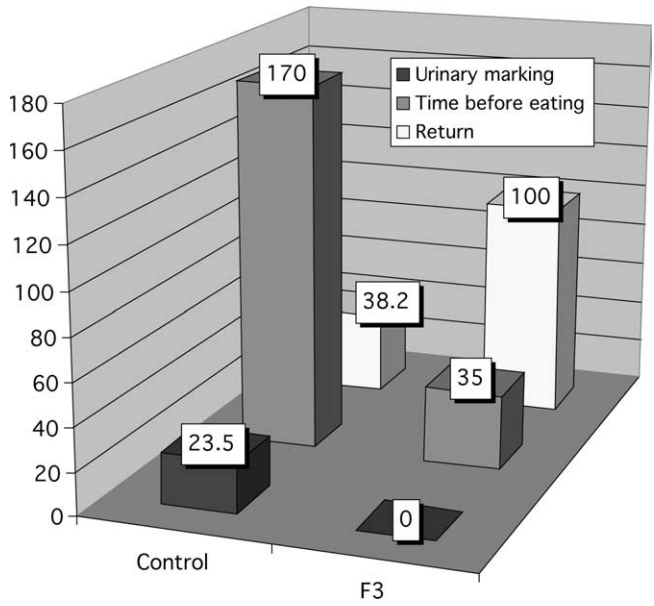


Fig. 12. Usefulness of F3 in preventing behavioral problems in cats during holidays [39]. This is a controlled, randomized, and double-blind clinical trial. The studied population includes 68 cats without any behavioral problem at home. When arriving at the holiday home, the owners had to spray the main pieces of furniture and walls before introducing the cat. Three parameters were studied: occurrence of urine spraying, time elapsing before eating for the first time in the new surroundings, and number of cats coming back to the new home after a walk outside (return).

hypothalamus. In that way, the emotional status and the way the animal reacts are altered during the behavioral modification program. According to the type of pheromone prescribed, behavioral patterns can be induced (eg, facial marking in the cat, scanning the environment) or can inhibit some unacceptable or uncomfortable behavior (eg, urine marking, fear reactions). With this approach, the synthetic analogue of pheromone is used as a kind of psychotrope, the transmitted messages of which are specific.

Pheromonotherapy has some specific technical problems. In natural conditions, the pheromones are not expelled alone. The emitting animal shows a particular posture or mimicry (eg, the posture for urine marking in cats or dogs), sometimes shows a part of its body that is usually hidden (eg, the anal area), modifies the marked substrate (eg, scratches on the ground in dogs or on vertical surfaces in cats), and also expels some individual odors and the odor of the pheromone itself. The function of all these messages is to induce the opening of the VNO, which is usually closed as mentioned previously. We call these signals emphasizing signals because they emphasize the emission of the pheromone and improve the probability of the receiving animal detecting the expelled pheromone. Of course, it is difficult to produce

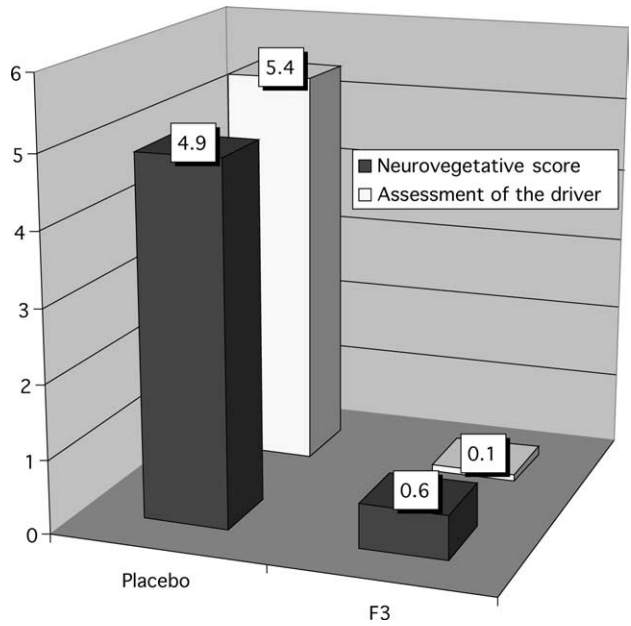


Fig. 13. Effect of F3 on manifestations of stress in cats during transport [40]. The studied population includes 32 male (30 neutered) and 26 female (21 spayed) cats from 1 to 7 years old. This is a controlled, randomized, and double-blind study. Each cat stays in a crate during the travel period (100–500 km). The crate is treated with F3 or controlled spray 10 minutes before the cat enters the crate. The neurovegetative score is the number of defecation, vomiting, and spoiling episodes occurring during travel. The assessment of the driver is a score based on a scale of seven degrees ranging from 0 (comfortable travel) to 6 (continual annoying manifestations that do not end when the driver stops the car).

emphasizing signals except by using the odor of the pheromone. This means that we diffuse more pheromone than the necessary natural amount to make sure that there is a really high probability for the treated animal to smell the odor of the synthetic analogue and thus to open his VNO.

Another particularity of the use of pheromones in behavioral therapy is the need to inform the owner of the particularities of pheromones so as to help him or her use the product under the right conditions.

Prescribed and used in the right way, pheromones show a great effect and can help the practitioner solve many problems in a totally safe way. The pheromones are only messengers that do not penetrate into the organism. Reception of pheromones creates an input and sets off internal and physiologic reactions. Therefore, there is no toxicity or side effects. This property of pheromones is particularly helpful in old or ill animals and allows associations with psychotropes.

The first pheromone of Carnivores that we have been able to synthesize is the F3 facial pheromone of the cat [4,5]. This pheromone shows interesting efficacy in inhibiting urine marking (Fig. 10) [39,41–51] and scratching

(Fig. 11) [4,52]. The observation of the behavior of F3 (Feliway)-treated cats shows not only a decrease in the unacceptable marking behaviors but an improvement in feeding, scanning, and playing (Fig. 12) [4,5,39,44,46,48]. It emphasizes that the positive effects of F3 in treating spraying are not only linked to the antagonism between facial and urine marking but are related to a decrease in anxiety. This anxiolytic effect becomes really evident when we observe the results of the clinical trials evaluating the effects of F3 in treating transport-related disorders in cats (Fig. 13) [40], in calming cats before intravenous catheterization [53], or in preventing stress-induced anorexia in hospitalized cats [54]. In these cases, F3 shows a great emotional stabilization function.

The other synthetic facial pheromone used in the cat is the F4 fraction (Felifriend). The use of this facial fraction makes intra- or interspecific interactions easy (Figs. 14 and 15). When an unknown animal is treated with

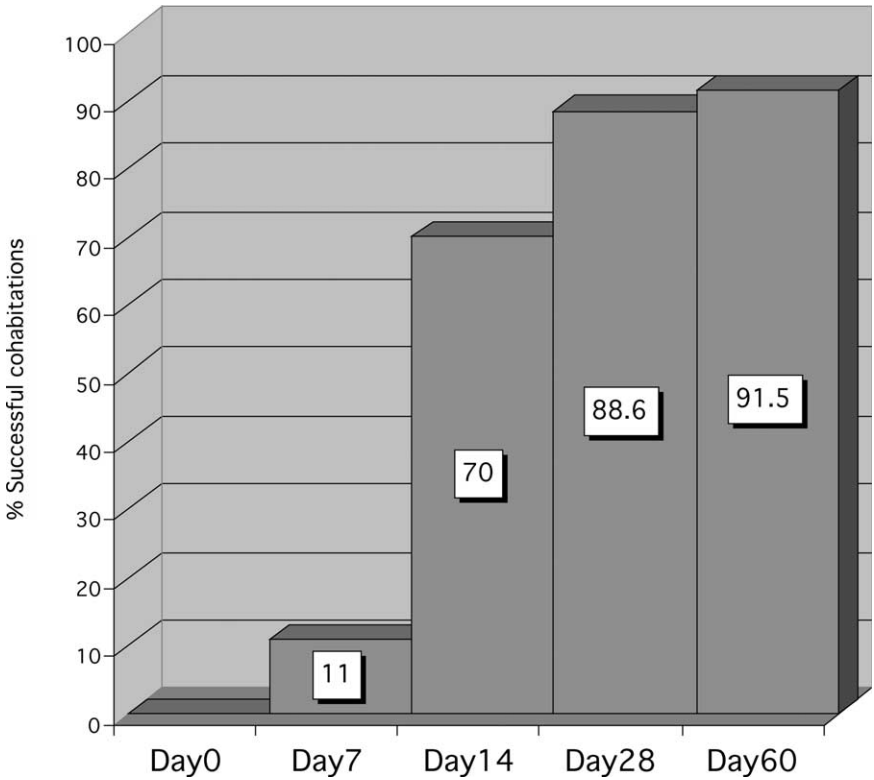


Fig. 14. Effect of F4 for prevention of intraspecific aggression in poorly socialized cats [24]. This trial is designed to assess the efficacy of the F4 pheromonal fraction to get a cat that had never accepted any specific in its home to welcome an unfamiliar cat. Seventy cats (35 pairs, 6 months to 7 years old) are used in this monocentric pilot study. Treatment consists in daily application of F4 on both sides of the head and flanks of the 35 pairs of cats for 28 days. The cohabitation is considered successful as soon as the owners see allomarking between the 2 cats.

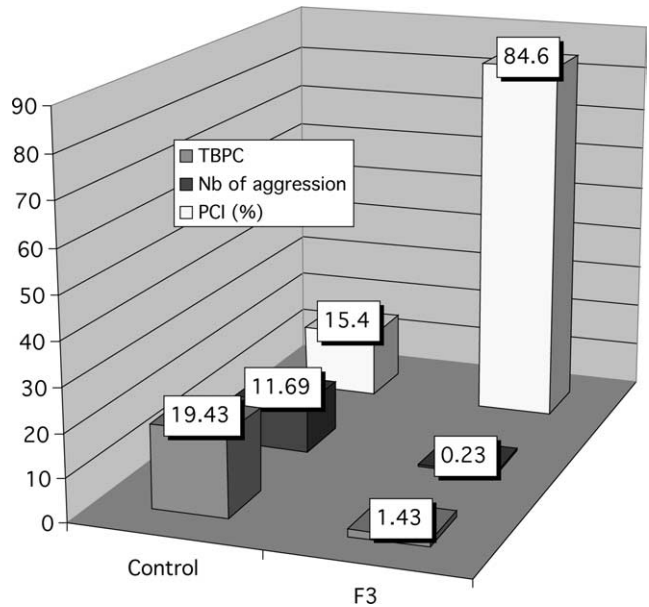
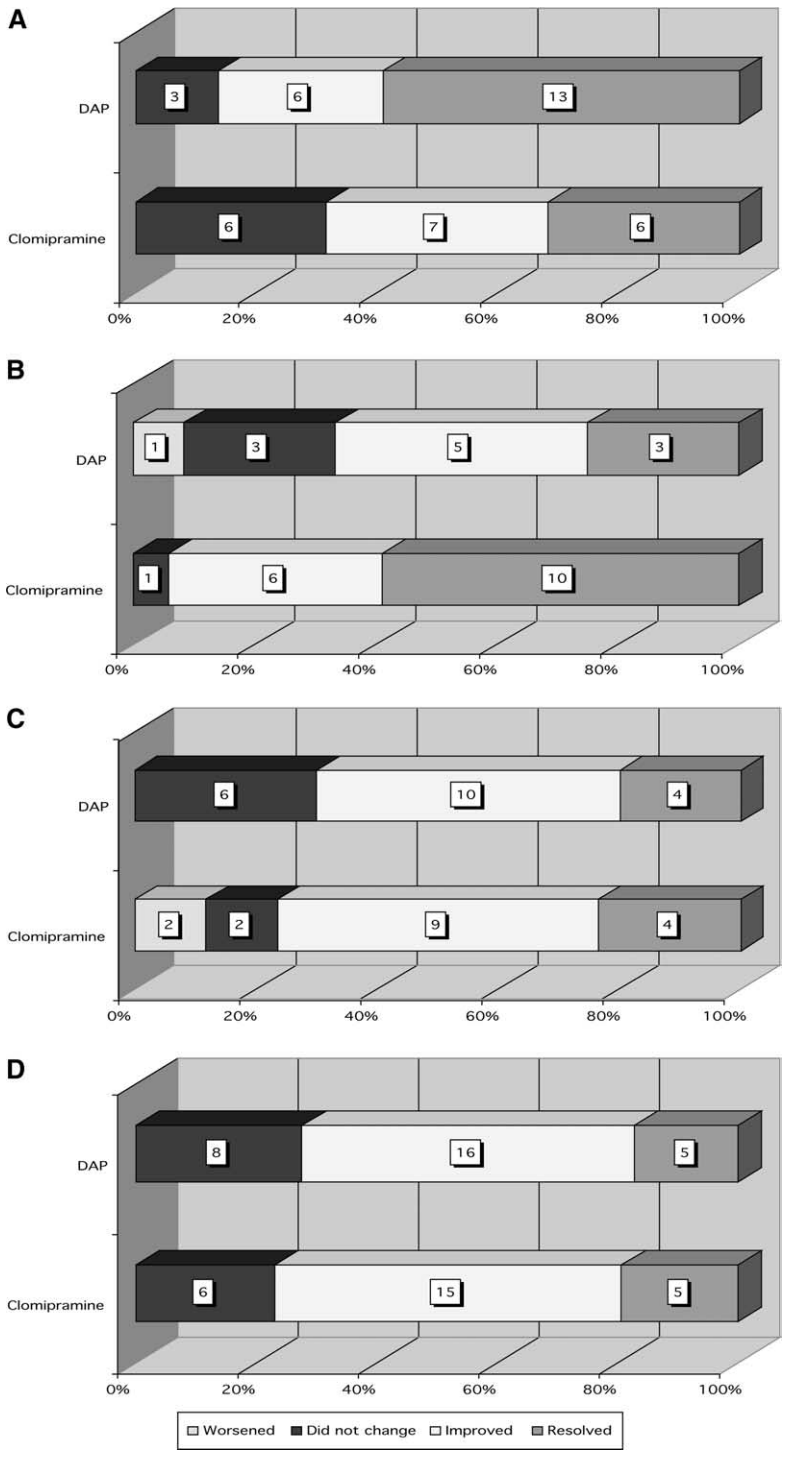


Fig. 15. Effect of F4 to enable handling of cats with phobia of the veterinarian during the consultation [25]. This is a monocentric, randomized, and single-blind clinical trial. The studied population includes 26 cats (6 months to 7 years old) that systematically demonstrate aggressive behavior directed against veterinarians. F4 solution is applied on the hands and arms of the veterinarian 5 minutes before opening the cat's traveling crate. For the first 2 minutes after the opening of the crate, the veterinarian has to stand still, leaning on the opposite side of the examination table on which the crate has been set and presenting his hands to the cat. Once the first stage has elapsed, the investigator can slowly put forward his hands toward the cat and gradually come into contact with it. Three parameters are recorded: the time before the first peaceful contact (TBPC), the number of aggressions, and the point at which the cat is the peaceful contact initiator (PCI).

the F4 fraction, the cat is misled about the correct status of the protagonist and should consider it as a familiar. Therefore, the probability of peaceful contact increases with the use of this allomarking pheromone; it helps the resident cat to accept a newcomer [24], and it reduces the risk of aggression caused by handling [25,55]. The success of the treatment is determined by

Fig. 16. Main comparative results of the use of clomipramine and dog-appeasing pheromone in the treatment of separation anxiety [56]. Fifty-seven dogs are included in this multicentric double-blind clinical trial. The inclusion is based on the presence of disturbances (excessive barking, howling, destructive behavior, and/or house soiling) and the presence of signs of hyperattachment. The pheromone treatment group receives a plug-in diffuser delivering pheromone and placebo capsules. The clomipramine group receives clomipramine capsules (1–2 mg/kg twice a day) and a placebo plug-in diffuser. The same behavioral modification program is employed in the two groups. The comparison of efficacy is assessed by an evaluation by the owner at day 28 based on (A) destruction, (B) soiling, (C) vocalization, and (D) global assessment by the owner.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3
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Clomipramine
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Clomipramine
6
15
5
0%
20%
40%
60%
80%
100%
Worsened
Did not change
Improved
Resolved

the willingness of the cat to mark unfamiliar people or animals spontaneously (this spontaneous renewal of facial rubbing is also the sign of a treatment success with F3).

In the dog, pheromonotherapy is based on the use of dog-appeasing pheromone (DAP), which is a pheromonal analogue of the appeasing pheromone secreted by nursing bitches. This appeasine shows great efficacy in a wide range of fear-inducing situations. Preliminary results of a clinical trial have shown that DAP delivered via a plug-in diffuser can be used to treat signs of separation anxiety (eg, destruction, vocalization, house soiling) (Fig. 16). A preliminary study performed in the United Kingdom confirmed the use of DAP in the treatment of firework phobias [50]. Updated trials attempt to assess the efficacy of DAP on dogs suffering from deprivation syndrome.

Summary

Pheromonotherapy seems to be a new therapeutic approach allowing practitioners to tackle the treatment of behavioral disorders in a natural, specific, and safe way. Although the efficacy of pheromones has been assessed in some specific behavioral problems, it seems that their range of action could cover the wide field of reduction of stress. Therefore, the use of pheromones should not be reduced to treatment of behavioral disorders (potentially associated with psychotropes or a behavioral modification program) but should be included in a strategy of improving the welfare of pets in veterinary structures (during examination and hospitalization) and in breeding networks (separation from the mother and transport).

Moreover, further studies may allow the veterinary practitioner to use pheromone analogues in the field of diagnostics to determine the behavioral status of a pet (eg, anxious or not, dominant or not). Pheromonotherapy is at its beginning, and the use of pheromones in various fields of medicine is heartening.

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