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Odor-guided behavior in mammals

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Introduction

Most organisms depend upon chemical cues for their survival. Indeed, chemosensation exists in all animal phyla and is among the most universal of the senses. However it is within the chordates – in particular the vertebrates – that chemically-sensitive systems have achieved their greatest complexity, culminating in neural circuitry encompassing not only the general integument, but numerous specialized receptor regions as well. In mammals – the subject of this article – odorants stimulate several intranasal chemosensory structures, including olfactory receptors (CN I), free nerve endings from the trigeminal nerve (CN V), and specialized epithelial receptors from the vomeronasal organ of Jacobson and the septal organ of Masera[25]. Thus, the focus of this paper is on 'nasal chemoreception', rather than on 'olfaction' per se, as in most instances the relative contributions of these various systems are not known.*

The present article has two primary goals: first, to review a number of ways in which odors guide important behaviors of mammals in their day-to-day activities; and second, to examine the complex relationships between odor-guided behaviors and organismal factors such as endocrine state and prior experience. The 'primer' influences of chemicals upon such phenomena as estrus synchrony, pregnancy blockage, and acceleration of puberty are not discussed, and the reader is referred to recent reviews on this topic[4,72,135]. Instead, emphasis is placed upon the 'signaling' or 'cueing' aspects of olfactory stimuli. A dominant theme in this review is that odors provide a complex matrix or pattern of the world to which the organism learns to respond, conceptually similar to the visual matrix provided by various intensities and wavelengths of light. Thus, few mammalian odor-guided behaviors are pre-programmed to correspond to specific odorants, just as few visually-guided behaviors are preprogrammed to correspond to particular intensities or wavelengths of light[18].

Organizationally, the paper is divided into three major sections. In the first, the relative merits of chemical communication are discussed, and a brief description of the roles of volatile and nonvolatile chemicals in nasal chemoreception is presented. In the second, the differential development of the intranasal chemosensory systems and associated odor-guided behaviors is examined. In the third, examples of adult odor-guided behaviors are explored in detail. Because most research on odor communication has been done using rodents, the review emphasizes this group, although data from lagomorphs, carnivores, and ungulates are also presented. The reader is referred elsewhere for detailed accounts on humans and other primates[57,58,60,69,70,76,145,181].

Olfaction and social behavior – general considerations

A) Advantages of chemical communication

Given the importance of social relations to group survival and the ubiquity of chemosensation within the animal kingdom, it is not surprising that olfaction has come to play a critical and often unparalleled role in mammalian sensory communication. However, one must not lose sight of the fact that redundancy and complexity exist in the repertoire of behaviors and physiological events that make up the communicative process. For example, every major class of intraspecific and interspecific information communicable via odors (table) has visual and auditory analogs. Since a primary function of these senses is to provide information about the environment, stimuli sampled by each sense are often fused into complex higher-order mental constructs[85,136]. Thus, many apparent sensory redundancies are interactive and nonorthogonal, and caution is warranted in assuming that any one sense provides a totally unique contribution to the organism's umwelt.

In light of such sensory redundancy, what advantages might chemosignals have over visual and auditory signals in the communication of conspecific or heterospecific information? Aside from potential benefits derived from the close anatomical association between some of the nasal chemosensory systems and brain regions related to arousal, feeding, and endocrine activity, several rather straight-forward advantages seem apparent.

First, it is obvious that odors can be used in situations where visual or auditory signals are absent or difficult to discern (e.g., at night or in dark burrows or near loud sound sources). Thus, as discussed later in this paper, odors are of considerable significance in the nesting situation, where they provide cues for the infant to locate the nipple when the mother is asleep and the infant's eyes are not yet functional. In the latter case, considerable infor-

Types of messages likely conveyed by mammals by means of olfaction (Most categories from Mykytowycz[152])

Age appraisal
Alarm
Attention-seeking
Defense
Distress-signalling
Encouraging approach
Frustration
Gender appraisal
Greeting
Gregariousness
Group membership appraisal
Identification with home range
Individual appraisal
Pain indication
Preditor
Prey
Reproductive stage indication
Social status appraisal
Species membership
Gender appraisal
Submission
Territory marking
Trail marking
Warning

mation can be gained about the social environment, including the smell of the nest, of the mother, and of the species.

Second, odors can be easily distributed in both space and time, making them uniquely suited to provide information about 'territoriality' or space occupancy. Thus, the distribution, intensity, and qualitative aspects of scent marks presumably provide a conspecific with key information about the resident(s) of an area, such as their stamina, physical condition, physical size, reproductive state(s), mobility, energy level(s), motivational tendencies, group constituency, and group size. The temporal aspects of odor signals allow for the sending of 'time-coded' messages, such as the length of time since a given area has been visited or occupied, or specific information about reproductive state [e.g. in the Norway rat *(Rattus norvegicus)*, the attractive components of estrous urine dissipate within 24 h[126]].

Third, relative to other sorts of sensory signaling, odors can remain in the environment for rather long periods of time without jeopardizing the immediate safety of the signaling individual. If an animal emitted a continuous noise or visual signal in a manner analagous to leaving a long-lasting odor, not only would an inordinate amount of energy be expended, but predators would have a field day (literally) in locating him. This long-lasting property of odors allows a dominant male, for example, to make his odor more or less continuously present in the social environment – a presence that may have endocrinological, as well as sociological, implications[173,204].

A forth advantage of conveying information via an odorous signal is that the sender and receiver need not be in close proximity for the communication to take place. This permits a resident to communicate to an intruder or rival that a given space is occupied, or that he or she is reproductively active, even though they are outside the range of hearing or sight. Such communication minimizes the physical harm, expenditure of energy, and exposure to predation which can result from direct physical encounters or inappropriately directed mating advances.

B) Volatile versus non-volatile semiochemicals

Until recently it was assumed (in land vertebrates) that nasal chemoreception differed from oral chemoreception in requiring volatile chemicals for stimulation; i.e., a stimulus source whose molecules are present in the air-phase and capable of diffusing or being sniffed into the nose. However, it is now apparent that non-volatiles are a major source of semiochemicals, capable of entering the vomeronasal organ of many species via the external nares or the oral cavity (e.g., through the the nasopalatine duct or by tongue transfer to the external nares)[209]. Nonvolatile components of urine likely contain at least some of the chemicals normally involved in (a) sexual recognition in guinea pigs, (b) acceleration of puberty in female mice by male conspecific urine, (c) urine-induced reflex ovulation in anovulatory rats, (d) synchronization of estrus in mice by male urine, and (e) blockage of pregnancy in mice by strange male odor[23,106,109,135].

That the vomeronasal organ is mainly responsive to nonvolatile stimuli is suggested by findings that (a) flehmen (a sexually-dimorphic lip-curling behavior associated with vomeronasal activity in many ungulates) occurs only rarely after sniffing female urine, but quite frequently after direct contact with such urine[111] and (b) urine labeled with fluorescent dye does not reach the vomeronasal organ unless such direct contact is allowed[211]. Assuming that the main olfactory system is primarily responsive to volatile stimuli, it appears likely that volatile and nonvolatile semiochemicals may serve quite distinct functions, differentially activating the olfactory and vomeronasal systems, respectively. Anatomically, these two systems have quite different central brain projections – those of the olfactory system include the olfactory tubercles, the prepyriform cortex, the enthorhinal area, and the anterior part of the corticomedial amyglada, whereas those of the vomeronasal system include the accessory olfactory bulb, the medial and posteriomedial sections of the cortical nuclei of the amygdala, and numerous other brain regions intimately associated with sexual behavior[184,185]. As suggested by Nyby[155], several discrepancies in the olfactory communication literature are likely explained by procedural factors which determine the degree to which volatile and nonvolatile components of the 'odor' source are available to the subjects.

Intranasal chemosensory systems and odor-guided behaviors in the developing organism

A) Anatomical considerations

The available data suggest that the various intranasal chemosensory systems do not develop at the same rate and, thus, may serve differential functions in early life.** For example, in the late prenatal and early postnatal stages of development the rat's main olfactory bulb is small and undifferentiated, whereas its trigeminal system and accessory olfactory bulbs are functional, with the

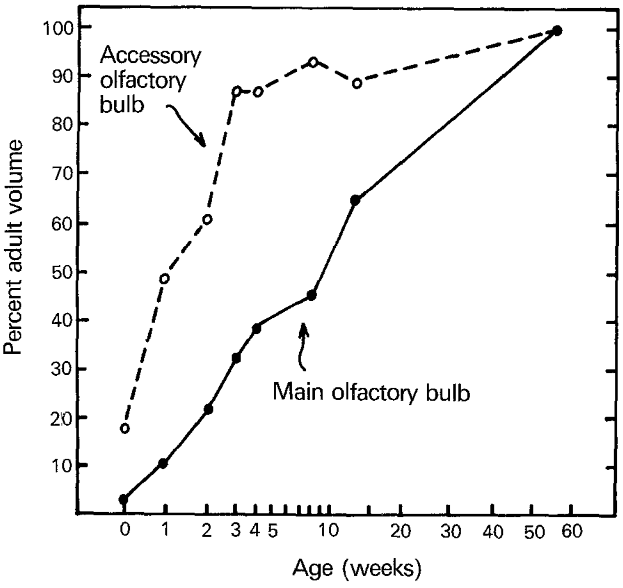

Figure 1. Postnatal volumetric growth of the main and accessory olfactory bulbs in the rat. From Alberts[1] with permission. Values are medians based on data reported by Smith[192] using the 1-year-old rat values as the 'adult' volume.

latter having the internal organization and structure of the adult bulbs[1,162,192]. By one week of age the rat's accessory bulb has reached about one-half of its adult size, whereas the main olfactory bulb has attained only about 11% of its adult volume[1] (fig. 1). Thymidine-H^3 studies reveal that mitral and granule cells of the accessory olfactory bulb proliferate and migrate to their final destination sooner than their counterparts in the main olfactory system[5,6,7,78] (figs 2 and 3). Although most mitral cells appear functional on morphologic grounds during the first week of life, few granule cells appear functional until the second week, during which time a dramatic increase in the number of short axon interneurons occurs[134].

Electrophysiological and behavioral studies support the notion that the main olfactory system of many rodents is in rapid transition during the first few weeks of life. In rats, mitral cells exhibit spontaneous electrical activity within 12 h postpartum, whereas spontaneous bulbar EEG responses are first noted at 3 days of age[140,141,183]. As indicated by Alberts[1], a striking correspondence is present between the development of tonic olfactory bulb electrical activity and the development of approach behavior to home nest materials in rats across the first few weeks of life (fig. 4). Since the development of the visual EEG did not show a similar relation, this correspondence is probably not due to a general increase in nervous system activity or behavior. Interestingly, sniffing behavior, although present at three days of age, becomes prominent after 11 days of age – the same time when most of the pups approach the nest odors.

Comparative studies suggest that marked species differences exist among rodents in the age at which the adult level of structural organization of the main olfactory bulb is attained. Thus, postnatal olfactory bulb maturation in the precocial spiny mouse *(Acomys cahirinus)* is much more rapid than that in the Norway rat[33]. As noted by Leon, Coopersmith, Ulibarri, Porter and Powers[119], the adult level of bulbar organization is present on postpartum day 1 in spiny mice, by day 14 in Norway rats, and by day 21 in Mongolian gerbils *(Meriones unguiculatus)*. Interestingly, these are the times when reliable approach to conspecific maternal odors is observed in each of these species[122,164,167,212].

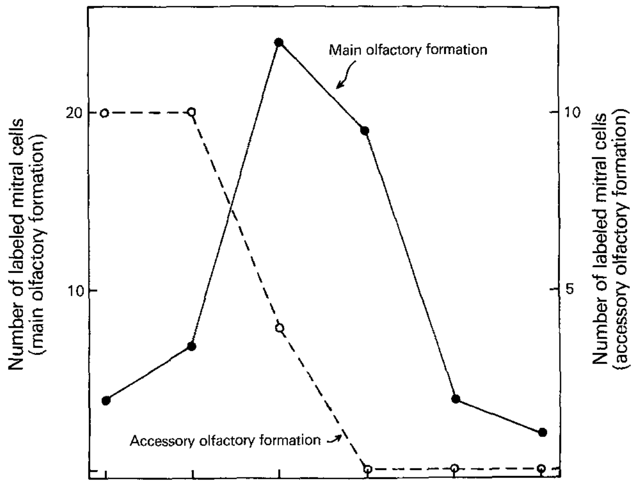

Figure 2. Proliferation during gestation of mitral cells in the main olfactory formation (solid line) and accessory olfactory formation (broken line) of the housemouse. From Alberts[1] with permission. Figure previously adapted by Alberts, with permission, from Hinds[97].

Although the morphological data imply that the main olfactory system of Norway rats is not well developed at birth, there is recent evidence that a histologically distinct group of glomeruli (separated from the accessory and main olfactory bulb glomerular layers by cell bodies and undifferentiated regions of neuropil) is metabolically active at that time[90]. Despite the fact that the function of

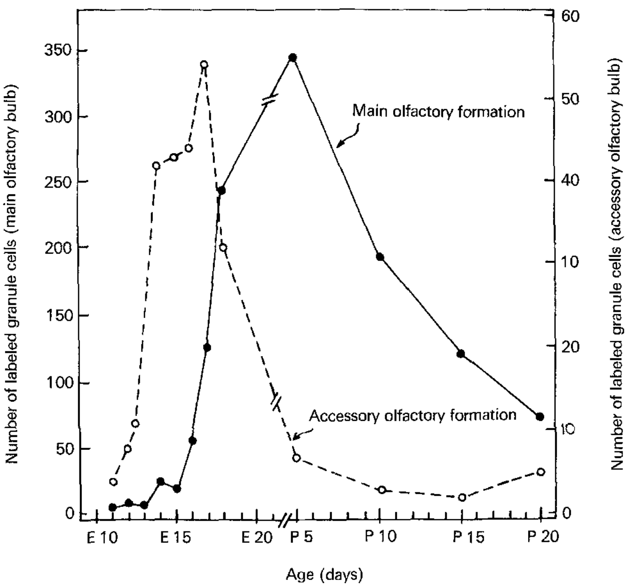

Figure 3. Proliferation of granule cells in the main olfactory formation (solid line) and accessory olfactory formation (broken line) of the housemouse. Age denoted as embryonic (E) and postnatal (P) days. From Alberts[1] with permission. Figure previously adapted by Alberts, with permission, from Hinds[97].

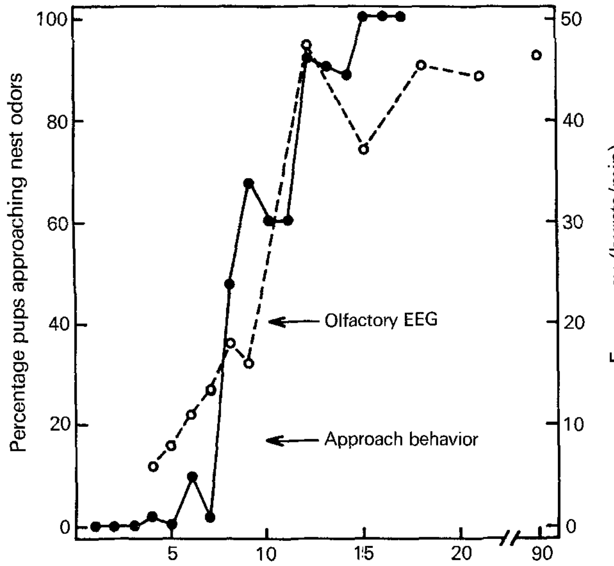

Figure 4. Relationship of olfactory bulb EEG development to nest odor approach behavior in the young rat. From Alberts[1] with permission. EEG data from Salas et al.[183] and the development of approach behavior from Gregory and Pfaff[89].

this region is not understood, it is conceivable that it is responsible, in part, for some of the odor-guided behaviors of the neonatal rat discussed later in this review.

B) Odor-guided behaviors in utero

It is not known if odor-guided behaviors occur in utero. However, as indicated above, several chemosensory systems are functional at that time. Interestingly, there is now behavioral evidence that odorants are detected prenatally and that intrauterine exposures to odorous chemicals can modify odor-guided behaviors in later life. Thus, fetal rats (Gestation Day 20) that received in utero injections of apple juice and lithium chloride show postpartum evidence of having developed a conditioned aversion to the odor of apple juice[193].

C) Odor-guided behaviors in the nursing environment

Despite the underdevelopment of the main olfactory system of the young rat relative to that of the adult, odors within the nesting environment play a key role in such phenomena as nipple location and nursing, orientation to the nest, and attraction to social cohorts. Furthermore, as emphasized below, odors within the nesting environment can greatly alter later social preferences through imprinting and associative learning.

1. Suckling and olfactory function

Evidence for the importance of olfactory cues in rat nursing behavior comes from the demonstration that (a) disruption of afferent olfactory input eliminates or greatly impairs the suckling behaviors of infant rats, (b) washing the dam's nipples eliminates the ability of pups to locate and attach to them, and (c) applying an extract of the aforementioned wash reinstates suckling behavior[1,99,188,199]. Interestingly, painting the nipples with either the parturient mother's saliva or amniotic fluid can induce newborn rats to attach to and suckle washed nipples[200]. Evidence that such responses may be largely learned comes from the finding that rat pups exposed prenatally and immediately after birth to citral attach to washed nipples of an anesthetized parturient dam when they are scented with citral, but not to unscented and unwashed nipples that elicit suckling in control subjects[161].

Odors also play a key role in the suckling behaviors of mammals other than rats. For example, kittens form specific nipple-position preferences during the first few days of life which are likely dependent upon maternal odors, and zinc sulfate-induced anosmia leads to disturbances in suckling and in nipple location in rabbits[176].

2. Attraction to maternal odors

A number of mammals emit odors during lactation which influence the behaviors of their nurslings. For example, rat pups briefly inhibit movement in the presence of odors from their mother during the first postpartum week, and reliably approach odors from their mother during the first few weeks of life[121,122,154]. The proportion of individuals approaching their own mother's odor increases dramatically at 12–14 days postpartum, and a marked preference is exhibited at least through postpartum day 27. By day 41, this preference ceases[122].

In a series of fascinating studies, Leon and associates have shown that one source of the mother's attractant comes from anal excrement. The odorous material is synthesized (probably from cholic acid) in the cecum (a specialized pocket of the gastrointestinal tract at the junction of the large and small intestines) by bacterial processes, and can be suppressed by antibiotics[121,122,146]. Although this material (called cecotrophe by Leon; see critique of this terminology by Moltz and Lee[146]) is apparently manufactured by both male and female rats, it is released in larger quantities to the external environment by lactating females, and is normally dependent upon systemic elevations of prolactin. Restricting the diet of the rat dam greatly decreases the amount of cecotrophe defecated. Rat pups acquire their preference for the odor through association with the maternal odor during the first two postpartum weeks – a preference which depends upon the mother's diet. Exposure of pups to maternal odors in the absence of the mother is sufficent to induce subsequent attraction[120].

Although maternal odors are attractive to pups of a number of rodent species, including gerbils, hamsters, housemice and spiny mice[27,84,164,189], several workers have been unable to observe the cecotrophe-specific phenomenon described by Lyon et al. in either rats of the same strain or those of a different one[45,82]. For example, Galef and Muskus[82] report that 21-day old Long-Evans rat pups find (a) the body odors emitted by adult virgin females of their strain attractive, (b) the odor of the anal excreta of such females attractive, (c) the anal excreta of virgins as attractive as those of lactating females, and (d) the odor of the lactating rat itself more attractive than that of the anal excreta. The basis of the difference between the findings of these investigators requires further exploration.

3. Induction of odor preferences and aversions

Aside from serving as cues for orientation and suckling, odors in the nesting environment can induce olfactory preferences which influence later social behaviors. Thus, Mainardi demonstrated that adult estrous female house mice *(Mus musculus domesticus)*, normally reared by both parents since weaning, preferred odors from males of the same strain to those from *Mus musculus bactrianus*. Estrous *Mus musculus domesticus* females, reared only by their mothers in the absence of adult males, showed no sexual preferences and were attracted indifferently to *M. m. bactrianus* and *M. m. domesticus* male odors, suggesting that the females 'imprint' on the odor of their fathers[132]. A similar phenomenon was found in a study of bedding preferences of infant rats by Brown, who noted that female rats reared with both their dam and sire (but not ones reared with the dam alone) strongly preferred the odor of male bedding over that of clean shavings[32]. A number of studies suggest that such 'imprinting-like' processes are not confined to biologically-relevant odorants, and that they reflect a generalized susceptibility of the organism to odor preference or aversion induction[42,54,56,79,120,133,165,166]. For example, Porter and Etscorn[166] briefly separated newborn spiny mice *(Acomys cahirinus)* from their dam and placed them in the presence of either ground cinnamon or cumin odor for one hour. In two-choice preference tests administered 24 h later, the mice evidenced a preference for bedding odorized with the odor of exposure. In subsequent work, these authors demonstrated a 'primacy' effect in inducing the odor preference; namely, mice exposed to one of these odors on the day of birth and to another odor on day 2 evidenced a preference for the first odor on subsequent tests, analagous to comparable visual studies of avian imprinting. However, this primacy effect could be eliminated by increasing the exposure time to the second odor[165]. That such exposure may induce changes in subsequent neurological responsiveness is suggested in a recent study by Coopersmith and Leon[47]. In this work, rats pups exposed to peppermint odor for 18 days postpartum evidenced increased bulbar uptake of radio-labeled 2-deoxy-D-glucose in response to exposure to peppermint odor on the 19th day of age, as compared to controls who did not receive the previous 18 days of peppermint odor exposure.

In a paradigm similar to that used by Porter and Etscorn[166], Alberts and May[3] demonstrated that daily 4-h exposures of rat pups to a perfumed foster dam for two weeks resulted in a subsequent huddling preference for a perfumed inanimate furry cylinder (relative to an identical, but nonperfumed, furry cylinder). In addition, these authors showed that equal amounts of 'mere exposure' to the odor (induced by placing the litters in small containers containing perfume odor) induced a similar preference. However, when rat pups were exposed every other day to an odor placed on a lactating mother and on the intervening days to a different odor in a 'mere exposure' situation, a stronger preference for the odor paired with the lactating dam was observed. Subsequent experiments suggested that this greater preference was not due to the reinforcing properties of milk ingestion, but rather to temperature influences. Thus, a preference equivalent to that observed in the foster mother situation could be induced in a 'mere exposure' condition when the odor was placed on a warm glass cylinder wrapped with linen cloth having a surface temperature of 35 °C.

Aside from being capable of forming odor-related preferences early in life, neonatal rats are also capable of forming conditioned aversions, as was noted in the in utero situation. For example, two-day old pups injected with lithium chloride in the presence of lemon scent evidence a pronounced aversion to lemon odor when tested 6 days later[179]. However, when the LiCl injection follows the odor exposure by 15 min, only pups four days of age and older develop the aversion, suggesting the physiological mechanisms underlying the phenomenon undergo considerable development during the first week of life[180].

The studies of this section clearly demonstrate the important role of early experience with odors in determining later filial and social preferences, and suggest that both preferences and aversions to odors can be induced at an early age. However, before acccurate assessments of the periods of optimal induction can be established, the intensity of the induction and test odorants should be controlled. Thus, in the case of odor preferences, it is conceivable that the animal forms an attachment to the most intense odor in the induction situation. For example, the tendency of female mice to 'imprint' on their fathers' odors in the Mainardi[132] study may simply reflect the fact that the male odor was the most salient odor in their social environment. Similarly, in the work by Alberts and May[3], it is conceivable that the increased temperature of the surrogate object resulted in a larger amount of odor released from it, and that temperature, per se, was not the major factor producing the observed preference enhancement. Alternatively, it is conceivable that the pup's olfactory system was simply more responsive in a higher temperature environment. Potential support for this notion comes from the finding that the electro-olfactogram (a summated surface potential recorded from the olfactory mucosa which, in humans, is correlated with perceived intensity) is larger when stimulated with higher temperature airstreams[159].

Odor-guided behaviors in the adult organism

As can be inferred from the table, odors guide or influence nearly every major class of mammalian behavior imaginable. In this section, examples of odor-guided behaviors related to the broad behavioral classes of mate selection, sexual behavior, foraging, and territorial formation and maintenance are presented. Specifically, studies of individual recognition and preferences, gender identification, estrus detection, species recognition, copulation, feeding site selection, agonistic behavior, and the communication of alarm are examined in detail. The important influences of prior experience and endocrine state upon the behaviors under study are emphasized to underscore the flexibility of the underlying mechanisms involved. No attempt has been made to be inclusive, and the focus on adult organisms reflects, in some instances, the fact that only adult subjects have been tested, not that younger ones cannot similarly perform or respond.

A) Individual recognition and preferences

Individual recognition is a prerequisite for complex social behavior. For this reason, it is not surprising that most mammals can distinguish amongst one another on the basis of odors, and that naso-nasal, naso-genital, naso-anal, and naso-glandular sniffing accounts for much of the time spent in conspecific social encounters[187]. Individual discrimination has been demonstrated in rodents (e.g., house mice, rats, gerbils, hamsters, wood mice, and guinea pigs[26,36,48,92,107,178], carnivores (e.g., dogs and wolves[30], lagomorphs (e.g., the European rabbit[152]), ungulates (e.g., pigs and blacktailed deer[143,144]) and numerous non-human primates (e.g., ringtailed lemurs and marmosets)[76,145].

There is now evidence that individuals prefer the odors of certain conspecifics to those of others, and that such preferences reflect general social and mating preferences. For example, male lemmings prefer the odors of unmated receptive females to those of receptive females with whom they have just copulated, and preferrentially mate with the unmated females[104]. Likewise, estrous female lemmings prefer the odor of males which, in later social tests, prove to be dominant over most of their like-sexed counterparts. In subsequent mating tests, these males are preferred as mates[102]. That this phenomenon may be rather general is suggested by Doty and Dunbar's[66] finding of a relatively high correlation between (a) the relative amounts of time spent by Beagles investigating odors from conspecifics whose sexual phenotypes were varied by endocrine system manipulations and (b) social preference data previously collected by LeBœuf[115] for Beagles under analogous gonadal and hormonal conditions.

Given the basic importance of individual recognition in animal societies, one might expect mammals to be capable of remembering, by odor, large numbers of individuals for reasonably long periods of time. Although data are lacking in most forms, there are rodent data which suggest this to be the case. Thus, house mice can discriminate between as many as 18 individual mice over a distance of up to 20 cm[108] and guinea pigs can remember, for at least seven days, urine odors of individual females presented to them for only two minutes apiece[19].

B) Gender identification

As in the case of individual recognition, all mammals that have been tested can distinguish between conspecific males and females using intranasal chemosensory cues. For example, Landauer et al.[113] demonstrated that sexually experienced male hamsters spend more time investigating the odors originating from ear glands of females and gonadectomized males than those from intact males, and Bowers and Alexander[26] found male and female C57BL house mice can discriminate between chemosignals from male and female conspecifics when tested in a Y-maze.

The importance of social experience in influencing a behavior based upon gender identification is illustrated in the pioneering research of Nyby et al.[156–158]. These investigators found that male house mice *(Mus musculus)* that have briefly encountered a female mouse after weaning subsequently emit ultrasonic vocalizations to chemosignals from female mice, their urine, or their bedding. Males that have never encountered a female at that time rarely elicit ultrasonic vocalizations to such stimuli. Although it was initially believed that the active urinary components were eliminated by hypophysectomy, recent research has discovered that males whose first social encounter was with a hypophysectomized female elicit such ultrasounds to urine from hypophysectomized females[131]. Thus, the nature of the initial information exchange is highly specific.

An exploration of the relative roles of the olfactory and vomeronasal systems in eliciting such vocalizations reveals complex relationships between these two systems and social experience. Thus, Wysocki et al.[210] found that (a) either olfactory bulbectomy or removal of the paired vomeronasal organs results in marked deficits in the pattern of vocalizations in males elicited by female chemosignals and (b) removal of the vomeronasal organ prior to adult heterosexual experience virtually eliminates the males' vocalization to female chemosignals, whereas such removal after such experience greatly attenuates, but does not eliminate, such vocalization. These results were not due to decreased testosterone titer, and mice without vomeronasal organs were unimpaired in their ability to detect food odors.

C) Detection of estrus

In many species, the period of reproductive readiness of the female is signaled by changes in body odor. With few notable exceptions (e.g., guinea pigs, hamsters, and possibly rhesus monkeys[17,51,88,112]), female urine and vaginal secretions take on an attractive character for conspecific males around the time of ovulation – an attractiveness which largely depends upon the male's hormonal state and previous sexual experience.

In rats *(Rattus norvegicus)* and probably lemmings *(Lemmus sibiricus* and *Dicrostonyx groenlandicus)*, the general rule that has emerged is that gonadally-intact sexually experienced males evidence a behavioral preference for estrous over diestrous female odor, whereas both sexually experienced castrates and sexually inexperienced noncastrates do not[37,103,126,194].*** Mounting without intromission is sufficient 'sexual experience' to produce the preference[194], although there is some evidence that injecting nonsexually experienced immature rats with high levels of testosterone can also induce it[38]. Castration appears to have no marked influence upon the ability of sexually-inexperienced males to discriminate between estrous and diestrous female rat odors[34], nor upon their absolute detection threshold for estrous female urine[40]. Sexually-experienced males find bladder urine from estrous females to be equally attractive to externally-voided estrous urine, suggesting the attractants are not added by glands along the urethral tract or near the vaginal orifice (e.g., the preputial glands), but filter from the blood into the urine via the kidney[126]. The preference for estrous over diestrous urine odor is not seen if the estrous urine is over 24 h old, demonstrating the attractive signal dissipates rapidly after its production and is probably time-coded to accurately reflect the female's reproductive state[126].

Studies in dogs have revealed findings similar to those noted above. Thus, sexually-experienced adult male Beagles investigate estrous urine and vaginal secretion odors more than diestrous urine and vaginal secretion odors[13,14,66,73,74] (fig. 5). In studies where males are allowed

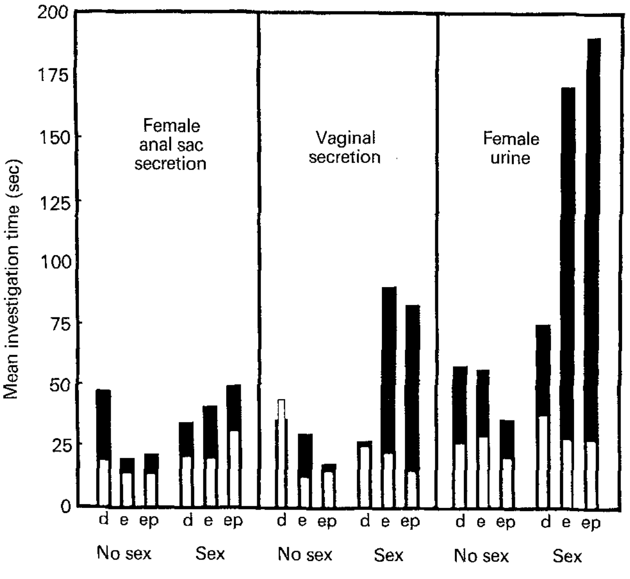

Figure 5. Mean investigation times of three sexually experienced (sex) and three sexually inexperienced (no sex) male beagles for odors of females. Dark bars represent mean time spent investigating the female odor during six 2.5 min trials in 2-choice test box. White bars represent mean time spent investigating juxtaposed distilled water stimulus. d = diestrus (i.e., no hormone given); e = prior estrogen injection given to female odor donor; ep = prior estrogen and progesterone injections given to female odor donor. From Doty and Dunbar[66] with permission.

to 'visit' and sniff females isolated in wire-mesh cages, males visit estrous females for longer periods than nonestrous ones and urinate more frequently against their cages[73].**** This preference occurs before the time of the pubertal increase in circulating testosterone, but can be induced at an earlier age in castrates by injections of testosterone[15].

D) Copulatory behavior

In addition to the detection of estrus, olfactory cues can influence behaviors associated with copulation, per se. As in the case of odor preferences, complex relations between factors such as sexual experience, species, and rearing condition are present. For example, removal of the olfactory bulbs or deinnervation of the olfactory epithelium has little influence upon the copulatory behavior of sexually-experienced male rats; however, such manipulations greatly decrease copulatory behavior in sexually-inexperienced ones socially isolated after the time of puberty – influences which cannot be reversed by exogenous testosterone[114,206]. Although the limited data suggest little or no influence of removal of the olfactory bulbs on the copulatory behaviors of male dogs[93], rabbits[29], or rhesus monkeys[87], bulbectomized cats copulate more often, sooner, and maintain longer intromissions than nonbulbectomized ones[10].

In the early 1970's several investigators reported that the male copulatory behavior of hamsters and house mice was eliminated by removal of the olfactory bulbs[65,151,177]. Furthermore, the male-like mounting behavior of female hamsters masculinized by neonatal androgen injections were similarly eliminated by bulbectomy[65]. Although this phenomenon occurred in male hamsters made anosmic by lavaging the nasal cavity with procaine hydrochloride[64], it was seen in only some subjects after a similar lavage with zinc sulfate[169,170].

Because olfactory bulbectomy and intranasal procaine lavage eliminate not only sensory input from the olfactory receptors, but input from the vomeronasal organ and the other intranasal chemosensory systems as well, the discrepancy between the results obtained from these procedures and those from intranasal zinc sulfate treatment may have been due to the elimination of only some of the intranasal chemosensory inputs by the latter technique. This hypothesis was supported by a series of hamster studies which demonstrated that the zinc sulfate procedure spared destruction of the receptors within the vomeronasal organ[169,170]. Thus, the vomeronasal system alone provided enough sensory input for some individuals to maintain copulatory ability. However, removal of its input in addition to that from the main olfactory system eliminated copulatory behavior in all animals. Interestingly, anosmic male hamsters with functioning vomeronasal organs are not attracted towards conspecific vaginal secretions presented on the wall of a plastic test chamber. However, when such secretions are rubbed on an anesthetized castrate male hamster, marked nasal investigatory behaviors ensues once direct contact with the secretion occurs[170].

Little is known about the influences of chemosensory input upon female copulatory behavior. Removal of the olfactory bulbs of adult female rats facilitates lordosis, darting, and ear wiggling. However, removal of the bulbs at 2 days of age has no influence upon these measures in adulthood[125]. Unlike the rat, the duration of lordosis in the female hamster is not markedly influenced by olfactory bulbectomy[41], although bulbectomy depresses their ultrasound production and flank marking. Recent work suggests that removal of the vomeronasal organ of hamsters may decrease their responsiveness to manual induction of lordosis[129].

E) Species recognition and selection

As with individual recognition and gender identification, species recognition is a key component of evolutionary progression. Numerous studies suggest that odors can serve as a primary medium for such recognition in mammals[56,62] and that olfactory preferences for conspecifics are formed early in the life history of the animal. Analogous to color dimorphisms in avian forms, specialized endocrine-dependent scent glands are often excellent indicators of taxonomic relationships within a given genus, and likely serve in intraspecific mate selection[56,68].

In perhaps the first empirical demonstration of conspecific odor preferences, Godfrey[86] evaluated, in a Y-maze, the approach behaviors of male bank voles (genus *Clethrionomys*) to estrous odors of various *Clethrionomys* species and subspecies. Males of a given kind approached the odor of the female of their own kind in preference to an alternative. In some instances, males would approach females from their own localities in preference to females from other localities. Although hybrids were usually discriminated against, the hybrids did not show a differential preference for hybrid and parental types.

Subsequent laboratory studies have demonstrated analagous conspecific odor preferences in other rodents which, in some cases, are modulated by endocine state. For example, estrous (but not diestrous) female deer mice *(Peromyscus maniculatus bairdii)* spend more time with the whole-body odors of conspecific males than with those from the white-footed mouse *(Peromyscus leucopus noveboracensis)* when tested in a two-choice olfactorium[61]. However, when conspecific urine odor alone is paired against air in the olfactorium (rather than against the heterospecific odor), both estrous and diestrous females spend more time with the conspecific odor, suggesting that the test paradigm or the specific odors tested may influence the results[62]. In a similar laboratory study, Nevo, Bodmer and Heth[153] found that estrous, but not diestrous, chromosomal forms ($2n = 52$, $2n = 58$) of the speciating fossorial mole rat *(Splax ehrenbergi)* preferred the odor of the homochromosomal form.

Field studies collaborate such relations. For example, Daly et al.[49,50] found clear relations between the reproductive condition of both sexes of several rodent species and their tendencies to enter traps containing homospecific or heterospecific odors. Thus, *Peromyscus maniculatus gambelii* in reproductive condition preferred traps baited with conspecific odors over neutral traps, whereas those not in reproductive condition preferred the neutral traps. Similar results were seen by these authors in Kangaroo rats *(Dipodomys agilis* and *D. merriami)* and in pocket mice

(Perognathus fallax). Summerlin and Wolf[198] reported an analagous pattern of trap preferences in cotton rats *(Sigmodon hispidus)*, although a statistical analysis of their data by Daly et al.[49], suggested the phenomenon was present only in females.

Taken together, these results suggest complex relations between sexual experience, gonadal state, and conspecific odor preferences exist in a wide variety of rodent forms, as might be expected if odors serve a similar role in rodents as that served by visual and auditory stimuli in many avian species[56].

F) Communication of stress and alarm

It is well documented that social behavior changes as a function of crowding in a variety of mammals, and that changes in the adrenal/pituitary axis occur in animals under such 'stressful' situations[43,44]. Interestingly, a number of experiments support the popular belief that some animals can detect the odors of 'stress', 'alarm', or 'fear', and that they behave differently in the presence of odors of conspecifics who have recently been the recipient of stress-producing events (e.g., electric foot shock). Whether such odors mediate some of the stress-related physiological changes which occur in crowded natural populations is not known, but is a likely possibility.

Mice and rats are 'more active' in the presence of odors from stressed conspecifics compared to odors from non-stressed conspecifics[127,174]. Furthermore, presenting odor from stressed rats can disrupt an ongoing operant task[203]. Likely related to this phenomenon is that of decreased running speed in rats passing over a sector of a runway earlier traversed by a rat who was 'frustrated' by nonreward in a previous trial in the runway[124,147,205].

Although the exact sources of these odors have not been determined, it is known that they occur in air passed over either urine or the whole body and that, in the latter case, the odor is released within 30 seconds of a footshock[128]. Furthermore, Stevens et al.[195,197] showed that rat blood and muscle homogenates (but not brain homogenate) from stressed rats produced 'fright' responses in other rats. Both intact and castrate male mice exhibit a pronounced aversion to the urine odors of castrates that have been subjected to prolonged series of stressful electrical shocks, indicating the odorant is not dependent upon intact gonads and is perceived by both gonadally-normal and castrated males[182].

G) Feeding site selection and food marking

Most mammals are attracted to food sources by odor, and olfactory cues have come to play a key role in preditor-prey relations. Some forms, such as deer mice, are so good at locating buried seeds by odor that they have been known to remove all of the seeds planted in commercial forest reseeding operations[101].

Aside from directly attracting an animal to a food source, odors also mediate foraging activities indirectly by providing odor trails or signs related to optimal feeding areas. Thus, laboratory studies suggest that rats prefer feeding sites which have been previously visited by other conspecifics. For example, rat pups prefer to explore and feed in sectors of laboratory test arenas containing olfactory cues previously deposited by adult females[91]. Experience with odors largely determines the olfactory cues which guide such feeding site selection, since (a) pups reared normally with the dam preferred to eat at a feeding site at which either an anesthetized conspecific or conspecific excreta were present relative to a clean site, (b) pups deprived of contact with conspecifics during maturation failed to show such a preference, (c) contact with conspecifics for 4 days before testing was sufficient experience to induce the preference, and (d) exposure of pups to an artificial odor (peppermint) rendered that odor capable of subsequently influencing feeding site preferences[79].

Recent studies by Galef and Widmore[83] and Galef[80] demonstrate that both dietary choices and simulated foraging behaviors of rats can be influenced by food odors emanating from other rats. An 'observer' rat caged for 15 min with a 'demonstrator' rat previously fed a saliently-odored diet subsequently ate, in a two-choice situation, more of the 'demonstrator' diet than a different odorized diet. This phenomenon occured even when the demonstrator rat was anesthetized and separated from the observer by a wire mesh partition. Observers rendered anosmic by intranasal zinc sulfate lavage did not show the phenomenon, demonstrating its dependence upon chemosensory cues. In a simulated 3-arm maze foraging environment, rats taught the locations at which each of several foods were present utilized odor cues from a demonstrator rat in their foraging strategies.

To what extent conspecific odors influence foraging behaviors in the wild is not known. However, several studies suggest that conspecific odors are deposited on food or food reminants in the natural habitat. Thus, Henry[95,96] has shown that wild red foxes *(Vulpes vulpes)* urine mark inedible food remnants (e.g., bones, ungulate remains and scats), as well as burrow entrances of prey such as squirrels and hares, and suggests that such marking behavior may serve to make their scavenging more efficient. Although it is conceivable that food remnant or heterospecific odors simply elicit nonspecific marking behaviors or serve as a focal point for conspecific interaction (analagous to sandbathing sites in certain desert rodents), it is of interest that the European wild rabbit *(Oryctolagus cuniculus)* eats fewer carrots which have been scented with male urine than carrots which were not urine scented or those scented with female urine[21]. Thus, it is conceivable that marking of food sources by dominant males may serve to inhibit their ingestion by subordinant conspecifics, possibly an example of 'food envy' phenomena described by Ewer[77].

H) Agonistic behaviors

Although several sensory systems are involved in the mediation of intraspecific aggression in mammals, olfaction plays a central role in a number of forms. For example, many species engage in odor-depositing displays during aggressive encounters, including numerous ungulates, lagomorphs, rodents, carnivores, and primates[20,24,76,150,160,163,186]. Since the mediation of agonistic behavior by olfactory stimuli has been extensively studied in the house mouse *(Mus musculus)*, this species will serve as the primary example of an odor-guided intraspecific agonistic behavior in this section. As will be shortly noted, prior experience with the odor determines the nature and degree of the house mouse's reaction to it. Evidence for odor-mediated aggressive behaviors in house mice comes from a number of sources. First, as in many rodents, an increase in investigatory sniffing often occurs before aggressive encounters[11,12,123]. Second, blind mice behave similarly to normal ones in initiating aggressive behavior towards strange males[202]. Third, aggressive behaviors increase in an established group of male mice following introduction of odor from a group of strange mice[175]. Fourth, stable groups of pairs of male mice evidence increased aggression after being placed in cages containing sawdust soiled by excreta of strange males[8], a situation which results in an increase in adrenocortical activity[9]. Fifth, bilateral ablation of the olfactory bulbs of fighter mice eliminates their aggressive behavior, even after they have had extensive fight training before bulbectomy[52,175]. Sixth, the frequency of attacks directed at a male house mouse by trained fighter mice can be reduced by masking the mouse's natural scent with perfume[116,175] or by swabbing him with urine from a female[46]. Finally, castrated mice are only infrequently attacked by territory-occupying male conspecifics; however, application of an unfamiliar male conspecific's urine to the fur of such castrates results in frequent attacks[130,148].

While the specific compounds in male mouse urine responsible for eliciting attack behavior are not known, the 'strangeness' of the odor appears critical. Thus, Kimelman and Lubow[110] demonstrated that a male mouse's aggressive behavior directed towards a 'stranger' was markedly attenuated if the mouse had been preexposed to the odorous bedding from the stranger's home cage for 1 h daily for 10 consecutive days before testing. These results are in agreement with the conclusions of Mackintosh and Grant's[130] early study of mouse agonistic behavior: "The experiments indicate that mouse urine contains a substance or substances giving olfactory information to other members of the species as to the familiarity or unfamiliarity of the mouse in question and so affects the behaviour which will be shown towards it." (p. 586).

I) Spacing behavior

While it is generally believed that odors do not serve as strict barriers to movement by conspecifics, there is evidence that they do discourage such movement to some degree, and least in animals who have encountered like-sexed conspecifics. For example, urine from a male house mouse not only elicits attack behavior, but, when spread in a testing arena, tends to discourage exploration of the 'marked' area by group-housed males[105]. However, castration of the group-housed males eliminates the avoidance behavior, and testosterone replacement restores it, demonstrating the importance of endocrine state in its mediation. This testosterone related response is rather specific, since it does not generalize to alarm odors from stressed castrate mice[182].

In wolves and presumably other wide ranging animals, urine odors serve to define home ranges and territories. As noted by Peters and Mech[163], "At their usual rate of travel, 8 kilometers per hour (Mech, 1970), wolves encounter and produce an olfactory sign about every 2 minutes, including an RLU (raised-leg urination) every 3 minutes. Even if they strike out cross-country to pursue prey or to take a shortcut, they leave sign frequently, although the RLU rate is depressed. This means that the entire territory is studded with olfactory 'hotspots,' and wherever a wolf is it can tell whether or not it is in its own territory. The concentration of scent marks around junctions further ensures that any traveling wolf will detect a mark in a short time no matter what route it uses. Each pack can also quickly detect when it reaches another pack's territory, and the nomadic lone wolves probably know just where they are in relation to the various packs' territories – on the border of two packs, in the center of a territory, and so on" (p. 143). In addition to the well-established relation between RLUs and dominance, breeding, and territorial defense, these authors cite a number of instances where RLU odors appear to cause aversion on the part of neighboring wolf packs. In general, the scent marking is done primarily by the dominant males of the pack.

Summary and conclusions

The odor-guided behaviors selected for presentation in this paper encompass the major areas of animal behavior, and illustrate the important principal that complex relations exist between odor-guided behaviors, hormonal state, and experiential factors. Clearly, experiences with odors at several life stages results in profound influences upon later behaviors, including those related to eating, mating, fighting, and nesting. Interestingly, only brief social encounters are needed in rats to induce such phenomena as ultrasonic calling to conspecific estrous females or their odors, preferences for estrous over nonestrous odors, and the short-term modification of feeding behaviors. Although the mechanisms behind these intriguing phenomena are poorly understood, it is noteworthy that rats can learn relatively complex concepts on the basis of odors, rivaling even the ability of our own species to learn analogous tasks by visual cues[190].

Despite the fact that close relationships can be demonstrated between odor-guided behaviors and variables such as endocrine state and sexual experience, caution is warranted in assuming that simple causal relations exist between such variables. In normally cycling women, for example, the correlation between olfactory sensitivity and plasma levels of estradiol during the menstrual cycle is relatively high; however, attenuation of the cyclical estradiol fluctuations by oral contraceptives does not eliminate the olfactory fluctuations, suggesting the relation is not causal[59,67,71]. In house mice, social experience can override hormonal factors in their odor-guided urine marking and submissive behaviors[139]. Thus, even though androgen titer usually correlates with such measures, a mouse made subordinant in a social encounter will not exhibit scent marking even when its circulating testosterone is maintained at a high level by a silastic implant. Further reason for caution comes from studies that suggest olfactory input influences the endocrine systems of sexually experienced and sexually inexperienced animals in different ways. For example, in sexually experienced male rats, anosmia decreases testosterone and estradiol levels and increases corticosterone levels, whereas in sexually inexperienced ones it has no significant influence on the levels of these steroids[53]. Taken together, such observations suggest the the causal bases of a number of the odor-guided behaviors described in this paper are complex.

A fascinating and somewhat poorly understood phenomenon illustrated by many of the studies reviewed in this paper is the marked plasticity of the mammalian olfactory system, both in terms of its susceptibility to learning (or imprinting) and in terms of the range of chemicals to which it responds. Indeed, the rat's olfactory system is clearly capable of detecting substances to which it has never been exposed during the course of its evolution or during its ontogeny. For example, the detection thresholds of rats for three homologous perfluorocarbons – perfluoromethylcyclohexane, perfluorodimethylcyclohexane, and perfluorodecalin – are low and within the range of organic odorants used in olfactory threshold research[138]. This plasticity, along with the fact that many of the so-called 'natural' odors to which infant mammals are exposed are dependent upon dietary factors[16,189], suggests that the classical 'pheromone' concept does not apply to such odor-guided behaviors[18]. Furthermore, while the propensity to detect and respond to some odorants is likely dependent upon rather specific genetic mechanisms, this does not appear to be true for the majority of substances. Unfortunately, it is difficult to determine behaviorally the underlying basis for differences in olfactory ability, even in light of a large element of heritability. For example, differences in sensitivity may arise from factors as diverse as subtle differences in olfactory neural transduction mechanisms, the composition of nasal mucus, and variations in nasal architecture which influence the number of molecules reaching the olfactory receptors.

Given the complexities involved in the production of biochemical signals in mammals, it is perhaps not surprising, in retrospect, that experience plays a large role in determining the 'meaning' of odors. Thus, ecological opportunists (e.g., many rodents) which populate diverse habitats might be expected to emit odors which reflect, to some degree, the nature of their current ecological circumstances. Under such conditions, natural selection would be brought to bear on those individuals who discern information about the ultimate 'quality' of the habitat and its conspecific inhabitants and who act accordingly in regards to mate selection and reproductive activities. It would be of interest to establish, using Galef et al.'s 'observer rat/demonstrator rat' paradigm[83], whether rats can discern the health of the demonstrator rat and, if so, whether they evidence a preference for foods eaten by healthy demonstrators over those eaten by unhealthy ones. In light of Huck and Bank's[102] finding that female lemmings prefer the odors of males who, unbeknownst to them, are dominant in subsequent male-male social encounters, it is conceivable that complex relations exist between health, diet selection, and mating – relationships of considerable evolutionary significance.

A problem which relates to the interpretation of the results of a number of the studies reviewed in this paper and which has plagued olfactory research for years is that of stimulus characterization and control. Just as tones can be high or low pitched, pure or complex, 'bright' or 'dull', and strong or weak, odors can likewise be salient on a number of analogous dimensions. Unfortunately, in the case of odors, few physical correlates of such dimensions have been isolated. At a basic level, intensity depends upon the number of molecules reaching a given set of receptor sites. However, it also depends upon intrinsic aspects of each stimulant, as well as inherent properties of the transduction process (e.g., the number and types of receptor sites and fibers destined to be recruited). In attempts to understand which stimuli are most salient in the natural situation for influencing odor-guided behaviors, much more attention to such factors must be made. Indeed, it is still an open question as to what degree evolution has developed inborn mechanisms for detecting specific biologically-relevant chemicals.

It has been the modus operandi of many studies of chemical communication to biochemically categorize components of scent glands and other scent sources and to search for a few single compounds that elicit, at least to some degree, the behavior in question. Unfortunately, many compounds likely work in unison, and statistical procedures to systematically deal with the various potential combinations of chemicals have rarely been brought to bear on these issues. Given the large experiential component to odor communication, more close work between developmental psychobiologists and chemists would appear to be in order. As noted by Bronson[28], the major stimulus attribute for eliciting scent marking in mammals appears to be novelty. While such a characterization is useful, other salient stimuli are also presumably effective in such processes, suggesting that stimulus saliency, rather than novelty per se, may be the attribute of import. Assuming this to be true, then it may be fruitful to focus initially on those components of conspecific odors which make them most salient before addressing their activity in the final behavioral bioassay.

Sparked by the important recent advances in the understanding of basic aspects of vomeronasal organ function[22,137,210,211], future research efforts will undoubtedly lead, within the next decade, to a much better understanding of the relative roles of all of the intranasal chemosensory systems in mediating mammalian social behavior. Of particular interest will be to what degree learning influences the behaviors mediated by each of these systems. Although the picture is far from clear, it appears that the vomeronasal organ is the key determinant of many of the so-called primer effects described in the chemosensory literature, including the strange-male odor-induced blockage of pregnancy, the acceleration of maturation, and the synchronization of estrus. Odor-guided behaviors, such as those reviewed in this paper, appear to be largely dependent upon the olfactory system proper, although the specific roles of the septal organ, of the vomeronasal organ, of the intranasal trigeminal free nerve endings, and of the allusive nervus terminalis have yet to be elucidated.

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* The term 'olfaction' is used in the text to refer to general intranasal chemoreception, unless otherwise qualified. Behaviors dependent upon chemical stimulation of one or more of the intranasal sensory systems are referred to as 'odor-guided behaviors'. Chemicals which can activate such systems are termed 'odorants' or 'odors'. The traditional distinction between 'odor' as the psychological sensation, and 'odorant' as the stimulus source, is not made.

** Little is known about the development or function of the septal organ of Masera or of the nervus terminalis in mammals, so these systems are not discussed further in this section.

*** Brown[31] reported data at variance with these conclusions; namely, that while his sexually-experienced male rats preferred female odors, odors from estrous and diestrous females were equally preferred. Although Brown suggests that this discrepancy may be due to the fact that his rats had been paired with only sexually-receptive females, Nyby[155] points out that his study was the only one where direct contact with the urine was allowed, making it possible that non-volatile substances (and, by inference, the vomeronasal input) may have been the reason for this result.

**** Interestingly, the addition of male urine to estrous female urine diminishes its attractiveness by a factor far greater than a simple dilution effect. Thus, a male urinating in response to a female mark could, at least theoretically, decrease the likelihood of other males being attracted to the female's urine mark[75].

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Chemistry of odor stimuli

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Summary. The present state of the molecular basis of olfaction is shown. With the aid of various examples the regioselectivity of odor sensation is proven. The main part of the experimentation concerns the stereocontrolled process of odor release.

Key words. Olfaction; odorants; structure-activity relationships; stereospecificity.

Odorant recognition process

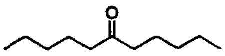
Since Ottoson's decisive experiments[59] olfaction is considered to be a bimolecular process involving the interaction of an airborne molecule with a complementary site of a receptor system which takes place at the interfaces of peripheral nerve cells located within the mucous layer of the olfactory epithelium. The induced intramolecular results in the formation of a reversible non-covalent complex giving rise to cell-depolarization, triggering the receptor potential in the sensory neurons. Membrane proteines can serve as olfactory receptors in mammals[36]. There is strong evidence, that cyclic AMP function as a second messenger in olfactory transduction[60]. The generated impulse discharge encodes the strong reponse and signal a pattern to the brain's olfactory center which already provides all information about the molecular properties of the ligand and in particular about the biochemical nature of the neuro-active complex. The resulting output signal is analyzed in the brain and then confronted with stored-up recognition patterns. The final outcome of this still incompletely understood cascade of biochemical and neurophysiological reactions, which can be as brief as 300–400 ms[33] is the ability to perceive and describe both the quality and strength of an odor. Even so the process of information is not yet finished. Olfactory neural signals can pass from the olfactory bulb to other parts of the central nervous system. It is through these further connections that the olfactory process affect overall brain functioning including learning and memory, sexual behavior and emotional regulation in men.

Molecular criteria for olfactory compounds

The physical and chemical properties required of a suitable stimulant molecule are determined by the location, molecular architecture and physiological medium of the chemoreceptor. It is evident that sensory activity is exclusively associated with volatile molecules. The highest molecular weight found so far for an odorant is 294[18]. Chemical reactivity of a ligand has little if any direct connection with olfactory activity since odorant molecules are uncharged and not associated with metabolic biochemical transformation. Nevertheless, several molecular requirements must be met. Thus it is evident that odorous molecules always contain both a strong hydrophobic and a relatively weak polar region. The latter, usually termed the 'osmophore'[69], is associated with a functional group such as carbonyl, hydroxyl, occasionally an ether or a limited variety of heteroatomic homologues. However, the presence of a functional group is not a *conditio sine qua non* for receptor interaction. Even alkanes can have distinctive odors.

Regioselectivity in molecular olfaction

Although changes in sensory activity associated with small and gradual changes in molecular structure have been intriguing scientists active in a number of disciplines for at least 30 years, no major breakthrough has been made so far in the quantitative or qualitative correlation of these changes[7]. All we know today is that the olfactory character of an organic compound is somehow a function of the spatial arrangement of the molecule, and that it is further influenced by its electronic and hydrophobic properties. Here the immediate molecular environment of the osmophoric group appears to play an important role, as impressively demonstrated by v. Braun and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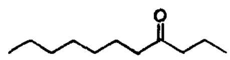
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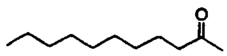
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