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The human vomeronasal organ. Part VI: A nonchemosensory vestige in the context of major variations of the mammalian vomeronasal organ.

Kunwar P. Bhatnagar* and Timothy D. Smith

*Department of Anatomical Sciences and Neurobiology, Health Sciences Center, University of Louisville School of Medicine, Louisville, Kentucky 40292, USA;
School of Physical Therapy, Slippery Rock University, Slippery Rock, Pennsylvania, 16057, USA;
Carnegie Museum of Natural History, Pittsburgh, USA.

"The organ consists of a long narrow bag of a gland-like substance, surrounded by a cartilaginous case of the same form, located on the floor of the nasal cavity, on each side, very near the ridge on which rests the inferior border of the cartilaginous portion of the nasal septum." [1]. As translated from French by Bhatnagar and Reid, 1996:227 [2].

Abstract

A vomeronasal organ (VNO) is found in most extant amphibians, reptiles, and mammals, but is absent in extant archosaurs (birds and crocodilians). In amniotes, the VNO differs greatly from its basal form, a simple neuroepithelial patch, as it still exists in most lissamphibians, and in some taxa (e.g., primates and bats) it presents extreme variations in epithelial structure. The history of the VNO literature since Ruysch [1703] prompts the question: what is a mammalian vomeronasal organ? Situated bilaterally, in the anteroventral nasal septum, the VNO is a part of a composite epithelial tube. Like any other sense organ, it includes a patch of sensory neuroepithelium (the vomeronasal neuroepithelium, VNNE). In certain species (e.g., man, chimpanzee), a low columnar ciliated, microvillar tube is generally present which also doubles as a septal glandular duct. The ancillary vomeronasal (VN) structures are the VN nerves (axons of the neurosensory VN receptors with the interspersed paravomeronasal ganglia), the accessory olfactory bulb and projections thereof, the chondro-osseous capsule, and glands - all collectively called the vomeronasal organ complex. In order to standardize the terminology, our proposed definition of the primitive condition of the mammalian vomeronasal organ is: an epithelial patch or tube of microvillar chemosensory neuroepithelium. This neuroepithelium is generally continuous with a patch of ciliated "receptor-free epithelium"(RFE), or a bare nondescript epithelium that completes the tube around its lumen. Two broad categories of the mammalian VNO exist: chemosensory VNO or non-chemosensory vestige of the VNO.

Key words: chemosensory vomeronasal organ, human VNO, neurosensory epithelium, non-chemosensory VNO vestige, receptor-free epithelium, VN complex, VNO defined, VNO terminology.

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Introduction

After Jacobson [3] first described the mammalian vomeronasal organ (VNO), numerous reports on the structure appeared (Table 1). The most comprehensive reviews on the developmental, structural and functional aspects of the VNO cite 462 and 773 reports respectively [4, 5]. In the last 20 years the ISI Web of Science cites close to 13 reviews on the vomeronasal organ. The rationale for the present commentary concerns the human VNO, which has contributed to some inconsistencies in terminology for vomeronasal structures, as well as the varied descriptions of the mammalian VNO and its supporting elements.

The VNO is found in most extant amphibians, reptiles, and mammals. In amniotes, the VNO differs greatly from its basal tetrapod form, a simple neuroepithelial patch, as it still exists in most extant amphibians (Lissamphibia) [6, 7, 8]. Whereas extremes are seen in some amniotes (e.g., reptiles may possess or lack a VNO), mammals are char-

acterized by profound variability in the VNO and ancillary structures. Major variations of the supporting elements (e.g., cartilaginous/osseous capsule; glandular elements) and even epithelial morphology of the VNO itself are reviewed herein [see 9, 10,11,12, and references therein]. Within this context, the human VNO is one extreme variant among many where the lack of accurate structural knowledge has resulted in phenomenally diverse conclusions regarding its physiology and function.

General Structure of the VNO

In all amphibians and some reptiles, the form of the VNO is relatively simple: an epithelial sac, or even a neuroepithelial patch that partially lines a diverticulum [9]. The mammalian VNO is more complex in structure and has more supporting elements. In commonly used terminology, the mammalian VNO is understood to be an epithelial tube with two types of epithelia-medially located chemosensory epithelium (the vomeronasal neuroepithelium, VNNE), and a laterally located "receptor-free epithelium" (RFE) so named by Breipohl, Bhatnagar and Mendoza [13]. Both epithelia enclose a lumen which receives the outbound secretory products of the VNNE

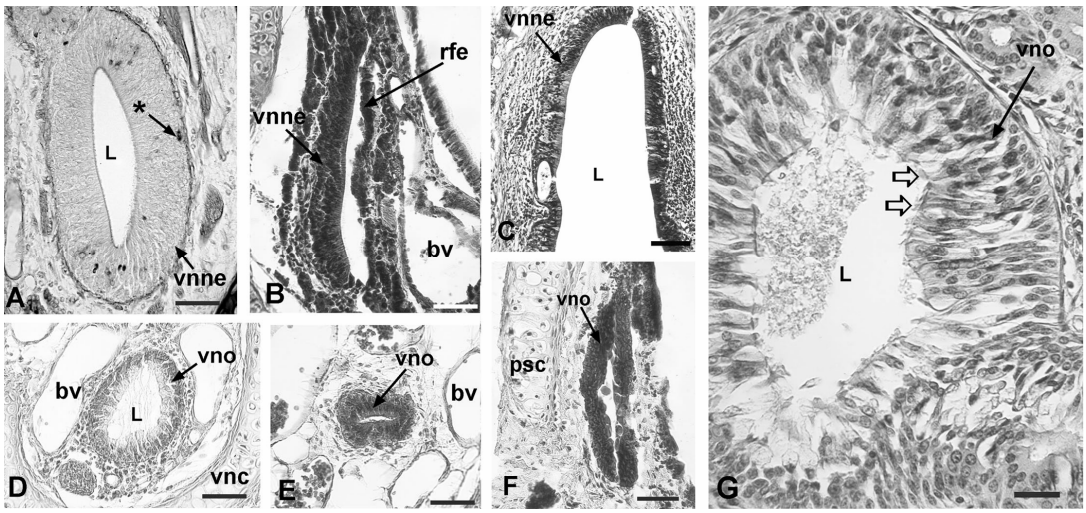

Figure 1*: Typification of the mammalian vomeronasal organ as exemplified by certain bat and primate species:*

I. VNO present - ***A****, Artibeus jamaicensis. Note the absent RFE at this level; the black (*) structures were not identifiable in the Bodian silver-stained section;* ***B****, Carollia perspicillata. Two distinct epithelia are visible despite poor preservation;* ***C****, Saguinus geoffroyi. Note the lack of a distinct RFE in this and other tamarins.*
II. VNO vestigial - ***D****, Rhinolophus lepidus;* ***E,*** *Rhinopoma microphyllum;* ***F****, Brachyphylla cavernarum;* ***G,*** *Homo sapiens.*
Abbreviations (Figures 1, 2):
bv, blood vessel; L, lumen; pc, psc, paraseptal cartilage; rfe, receptor-free epithelium; vnc, vomeronasal cartilage; vnne, vomeronasal neuroepithelium; vno, vomeronasal organ; open arrows indicate cilia. Scales: A-C, E, F, 50 µm; D, 100 µm; G, 20 µm. Gomori trichrome stain.

[11] and the "vomeronasal glands," as well as the incoming chemosensory stimuli in the form of odour elements. In mammals, as long as there is an epithelial tube (even devoid of chemoreceptors) in association with the paraseptal cartilage, it has customarily been called a VNO.

Notable exceptions to the above conception of the VNO have arisen, particularly in regard to the human and chimpanzee homologue, which loses its neuroepithelium prenatally [14, 15]. The human "VNO" has been described in parallel with the mammalian VNO for over two centuries, often without consideration of its homology (see below). In some other mammals, exceptions to the above terminology also have arisen. Most descriptions of the New World primate VNO omit mention of the RFE [10, 16, 17]. Until reported by Cooper and Bhatnagar [18], and Bhatnagar (19), there were hardly any studies on the comparative anatomy of the VNO in bats. In bats and primates, some extreme variants in the vomeronasal (VN) complex have been revealed [10, 19-22]. Extreme variations and several subtypes of the VNO are reviewed herein (Fig. 1, A–G).

It is interesting to note that the very first report on the 'organ' included the attempt to define the organ itself in question, as a "bag of gland-like substance surrounded by a cartilaginous case" [1]. Another deliberate attempt to define the VNO included the terminology used by the International Committee on Veterinary Gross Anatomical Nomenclature [23] which considers the vomeronasal duct (equivalent to the VNO itself by other definitions), vomeronasal cartilage, associated glands, vessels, nerves, and connective tissue or lamina propria to comprise the VNO. Finally, one of our own studies [24] presented a "histological definition of the vomeronasal organ" in humans and chimpanzees, characterizing these as (1) bilateral epithelial tubes; (2) superiorly displaced in the same plane as the paraseptal cartilages; (3) with a homogenous, pseudostratified columnar morphology with ciliated patches; and (4) with mucus-producing structures (goblet cells) in the epithelium itself.

It is the aim of this commentary to clarify how the mammalian VNO ought to be understood and typified, especially in light of its extreme variability across taxa, as illustrated by bats and primates. This report examines the pitfalls in the use of taxonomically specific terminology, as an epithelial tube of varying microstructure [10, 25, 26], as a neuroepithelial duct plus a complex of supporting elements [27], or in some other way. A particular matter under discussion is how one treats the receptor-free epithelium, whether part of the VNO or different from it.

The Vomeronasal Organ Compared With the Olfactory Organ

Both the VNO and the main olfactory mucosa are developed from the nasal placode. In most reptiles and mammals, the sensory patch (neuroepithelium) invaginates as an epithelial tube during early development, as the nasal placode sinks deeper and cavitates, the vomeronasal primordium separates bilaterally from the lining epithelium. In most tetrapods [15,28], this tubular structure gives rise medially to the neurosensory epithelium, and laterally to the receptor-free epithelium.

One might readily accept the concept of double nasal cavities – a large one, and a tiny one [7]. The large cavity on either side of the nasal septum harbors the olfactory organ (essentially, the olfactory epithelium) on the posterior dorsal nasal septum and most of the ethmoturbinals [29, 30]. The remainder of the undulating nasal cavity surfaces and the maxilloturbinals are covered with the ciliated respiratory epithelium. When present, the tiny second nasal cavity, a diverticulum, occurs as the small epithelial tube, the VNO. This tube has a medial neurosensory epithelium, and a lateral receptor-free epithelium, which may be ciliated, non-ciliated, microvillar, mixed, or even without any surface embellishments. The RFE is innervated by the trigeminal system, and may serve to propel glandular secretions (from the mucosal "vomeronasal" glands or those of goblet cells within the RFE itself). In other words, the RFE appears not to be directly connected with chemoreception. The main function of the RFE may be to maintain the VNO luminal surface wet and in readiness for the incoming chemosensory stimuli to react with the neuroepithelial cells.

It is enlightening to contrast the respiratory epithelium of the main nasal cavity with the RFE of the vomeronasal tube. While the RFE may operate to regulate the luminal environment of the vomeronasal tube, the respiratory epithelium may only be partially related to the function of the olfactory epithelium. Instead, respiratory epithelium is part of an adaptation for the conditioning of inspired air. This epithelium also may provide some secretions that keep the olfactory surface moist.

The Vomeronasal Neuroepithelium

The vomeronasal neuroepithelium is dissimilar as compared to the olfactory epithelium since it is (1) non-ciliated; (2) capped with morphologically distinct microvilli on its receptor cells and supporting cells; (3) lacks glandular ducts or intraepithelial glands, and (4) is highly variable in the number of receptor cells. This latter feature of variability has often been used to identify the VNO as rudimentary, poorly, moderately, or well-developed. Such terms are poor descriptors in terms of VNO function since there are no anatomical, physiological, or numerical measures for how many neuroreceptor cells may be minimally needed to react with the chemostimuli.

The Paravomeronasal Ganglion

A paravomeronasal ganglion (PVNG) is a prominent neural structure associated with the VNO, more so in bats [18, 21, 29], than in primates [*Callithrix jacchus*, 31] The neurons of the PVNG are large, ramify within the vomeronasal neuroepithelium, and intersperse within the vomeronasal nerve bundles. Whether these are aberrant ganglia [see 32, 33, 34; paraganglia 35], exteriorized intraepithelial neurons [29, 31], or elements of the nervous terminalis running together with the vomeronasal nerve, requires an extensive investigation. Presently, we are treating this tissue as related to the vomeronasal network, which has not been reported in the adult human.

The Receptor-free Epithelium

The tubular VNO of most mammals is laterally lined with a small patch of respiratory epithelium which is ciliated in most mammals. An exception has been recently observed in a bat [*Anoura* spp, 21] as well as in some primates, where the RFE is non-ciliated (e.g., *Saguinus geoffroyi*, Fig. 1C). This may indicate a variable, *albeit* questionable

role of the RFE in VNO function. There are two reasons to consider the VNNE and the RFE as components of the VNO. First, there are common developmental origins between the VNNE and the RFE. The RFE differentiates

from a homogenous embryonic VNO tube in some mammals, such as the mouse lemur [*Microcebus murinus,* 14] although it seems to become distinct soon after invagination of the VN tube in the rat [36]. Moreover, cells reactive for olfactory marker protein in mice [37], and LHRH neurons in rats [36] are observable in both RFE and VNNE in prenatal stages. Second, the RFE may actually perform a function for the VNO (e.g., in clearance of glandular secretions). There are no similar parallels between the respiratory epithelium and the RFE. The RFE is developmentally and functionally related to the VNNE, but this is not true of the relationship of the respiratory epithelium with the olfactory epithelium.

In case of an absent VNO (that is when neuroepithelium is lacking) as in man or in chimpanzee, the ciliated duct is proposed to be called a vestigial VNO (Fig. 1G), which includes only a remnant of the VNO (without neuroepithelium) and spatially separated paraseptal cartilages. Descriptions of the vestigial VNO epithelium in humans and chimpanzees [24, 38, 39] illustrate that it is not similar to RFE of mammals described to date, at least postnatally. There is greater cellular complexity in VNNE compared to the RFE [9,40].

Despite the apparent ontogenetic link and possible functional association of the RFE with vomeronasal chemoreception, we include this epithelium as part of the VNO. Presumably important functional elements of the RFE are highly variable across taxa, including presence or absence of cilia (and even presence or absence of the RFE itself). It is quite possible that the RFE functions variably or is unrelated to VNO function in some mammals. This component of the VNO deserves further scrutiny. It seems impossible to identify an RFE in some tetrapods. For instance, the VNO is a neuroepithelial recess of the nasal cavity in most amphibians [6].

Vomeronasal Capsule

Most mammals possess VNOs with a capsule surrounding the VNO tube, and its lamina propria (including nerves, glands, and blood vessels) [27, 36]. In numerous mammals, for example, ungulates, carnivores, most primates, insectivores, and bats, the capsule is cartilaginous and called as vomeronasal cartilage (VNC). In rodents, this capsule is osseous. In some bats (e.g., *Anoura*), it is chondro-osseous, lacking entirely posteriorly. Salazar and Sánchez Quinteiro [27], reported that the rodent bony capsule forms as an outgrowth of the vomer bone, and not via ossification of the vomeronasal cartilage. In other words, rodent and non-rodent vomeronasal capsules are not homologous.

The spatial displacement of the vestigial VNO away from

the paraseptal cartilages in humans and chimpanzees is an evolutionary reversal of an anciently evolved union. de Beer [41] considered the paraseptal cartilages to be homologues of the ventral margins of medial nasal walls in urodelans. The paraseptal cartilages themselves must have preceded the origin of a tubular VNO, since they are present in reptiles [41]. Only in ancestors to the mammalian lineage did a portion of the paraseptal cartilage become incorporated into the VNO complex (in amphibians the vomeronasal organ in not encapsulated by bone or cartilage [9]. This part is the "vomeronasal cartilage" (as distinguished from the *lamina transversalis anterior*, with which it is continuous). Thus, the term VNC is an inappropriate synonym for the term paraseptal cartilage.

Vomeronasal Glands

Primitively, mammals have glands that are present directly adjacent to the VNO [8, 42]. The ducts of these glands typically enter the VNO at the RFE-VNNE junctions. Posteriorly, the VNO lumen is continuous with a large gland duct that ramifies into multiple glandular ducts. The nomenclature often used for these glands, "vomeronasal glands", may obscure certain issues of homology, however. For instance, it is not clear that the glandular complex associated with the amphibian VNO is homologous with that of the mammalian VNO. In squamate reptiles, the only glandular secretions that reach the VNO are from an orbital source, the Harderian gland [8, 42].

In any case, compound glandular elements related to the VNO in mammals appear to be a subset of nasal septal glands which empties into the VNO. Such glands appear to be retained in mammalian taxa that lack a VNO. It is also noteworthy that these glands are present when the VNO is absent (e.g., pteropodid bats). Until the homology of these glands is firmly understood, the term "vomeronasal glands" should not be used.

The Human Vomeronasal Organ: a case in point

No studies have refuted the presence of a neuroepithelium in the VNO of human embryos and early fetuses, and the vomeronasal nerves are frequently described emanating from the embryonic human VNO [e.g., 12]. Gradually, as fetal development continues, only a ciliated, non-sensory epithelium remains [12]. From this point on. the human VNO is no more than a "nonchemosensory vestige." The presence of this tubular structure cannot be confused with a functional VNO such as that seen in rats, mice, and nu-

merous other mammals, including some non-human primates. It is unfortunate that the human VNO continues to be considered as functional, for instance, in the detection of pheromones in both males and females [43, 44], despite the lack of any neuronal connections to the forebrain [12,24,38,39].

The Caveat

We reiterate that postnatally, the humans lack the vomeronasal neurosensory patch and therefore its vestige – a nondescript epithelial tube – should not be equated with a functional sensory organ, a component of the accessory olfactory system of many nonhuman primates and other mammals.

Some researchers who continue to report that humans do not have a VNO [45], while others who maintain that they have seen its opening, probed it variously, and called it a special chemoreceptor organ [e.g., 46], all without the histological evidence, seem to be in a semantic standoff. Examination of serial histological sections reveals that humans lose the neurosensory patch prenatally, and a non-chemosensory vestige remains [14].

Interestingly, early human development reveals a brief association of elements of the VN complex (Figure 2). In human embryos, the VNO forms in close spatial association with the mesenchymal condensations for the paraseptal cartilages. In this association, human embryos are very similar to other mammals, including many non-human primates (Figure 2). Subsequently, the VNO and cartilage become spatially isolated from one another, and remain so throughout fetal and postnatal development (Fig. 2). Smith et al. [10] suggested this disassociation may result from the unique magnitude of downward growth of the midface in humans and other hominoids. Whether or not this explanation remains viable, this disassociation emphasizes that the VNO and its capsule do not develop as a "complex" in all mammals. Thus, the term VN complex refers to a *functional* set of structures without respect to

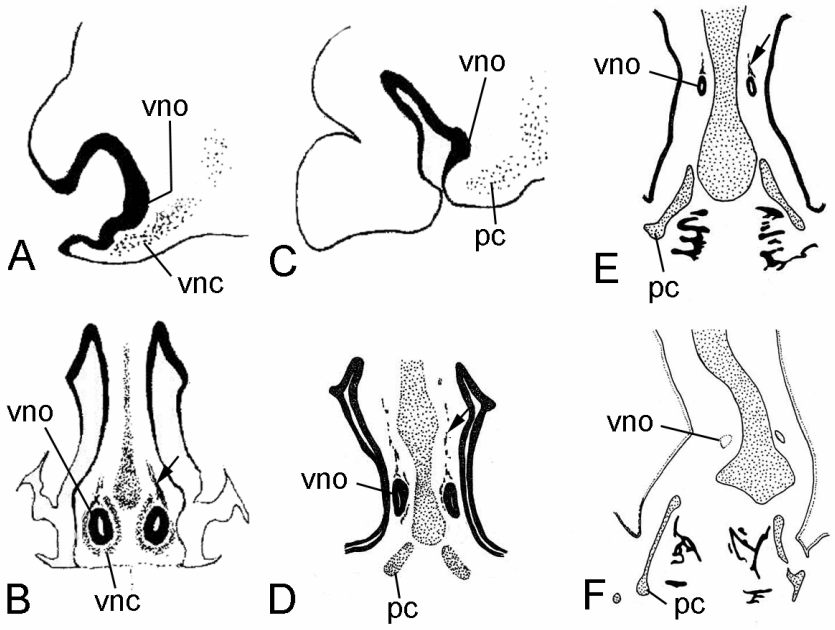

Figure 2*: Development of the human vomeronasal organ. 2 A-D. Comparison of prenatal monkeys (A , B) and humans (C, D) at similar stages of development. Line drawings after histological sections; modified after previous studies [10, 14]. Images not drawn to scale. The position of the embryonic VNO relative to the incipient vomeronasal cartilage condensation in a New World monkey (Saimiri sciureus) is shown in 2A; in a late embryonic stage, the VNO is encircled by the vomeronasal cartilage. By comparison, note the position of the VNO relative to the paraseptal cartilage condensation in an embryonic human (C, stage 17 embryo) and a late embryo (D, approximately 43 days fertilization age). Note in the late embryonic human and at later prenatal stages (E, 12- week fetus; F, 32- week feus) the VNO is spatially separated from the paraseptal cartilages. E) position of the VNO relative to the paraseptal cartilage in a fetal, perinatal, 2-year-old, and adult human.*

homology. This assertion is supported by the different derivations of the VN "capsule," considered critical for a pumping mechanism that deliver stimulus to the VNO, from nasal capsule cartilage or osseous elements of the viscerocranium [10, 27]. Indeed, some mammals have a VNO with some elements suggestive of a "pump" mechanism (e.g., venous sinuses adjacent to the RFE), which lack any osseous or cartilaginous capsule [21]. Thus the

functional arrangement of the VN complex appears to be, in part, a "mammalian" feature that evolved convergently in different higher taxa. Across tetrapods generally, stimulus delivery appears to be a common dilemma requiring multiple solutions [27,47, 48]. The fleeting spatial association of the human VNO with paraseptal cartilage reminds us of the plasticity of the stimulus delivery system to the VNO in tetrapods, and prompts us to advocate a rather restrictive definition of the VNO.

Table 1. Selected Examples of Perception and characterization of the vomeronasal organ since Ruysch [55,56].

Author	Year	Comments
Ruysch [55]	1703	Contrary to most statements, the human VNO was not discovered by Ruysch (55), since he provided no microscopic verification; Kölliker [57] described it in the human fetus and called it the *vomeronasal organ*.
Jacobson [1, 3]	1811, 1812	First report of the 'organ' in mammals described as a narrow bag of gland-like substance in animals surrounded by a cartilaginous case; Jacobson called this structure an 'organ '.
Dursy [58]	1869	refers to "J O tube"
Kölliker [57]	1877	Jacobson's organ in man (see 56)
Ritchie [59]	1944	"The organ of Jacobson consists of paired tubular bodies, vascular and richly innervated, lying enclosed in bone"
Parsons [60]	1971	neuroepithelium of amniotes (except turtles) forms in a ventro-medial pocket of the early embryo
McCartney [61]	1972	In the entire book on 'Olfaction and Odours' there is no mention of vomeronasal organ
Cooper, Bhatnagar [18]	1976	vomeronasal organ complex (in bats)
Ciges et al. [62]	1977	"two distinct epithelia exist within Jacobson's organ, a non-sensory, ciliated, pseudostratified, respiratory-like epithelium and a non-homogenous sensory epithelium."
Wysocki [4]	1979	"In some amniotes the Jacobson's organ is absent, but a vomeronasal sensory epithelium is usually present"
Evans [63]	1984	The VNO is an enclosed pouch sequestered from the nasal cavity and partially/wholly lined with a chemosensory epithelium
Garrosa et al. [36]	1992	"The vomeronasal complex includes the VNO, the underlying connective tissue, the vomeronasal glands, nerves, and numerous vessels "
Boehm, Gasser [64]	1993	"The VNO is a chemoreceptive structure… It consists of a pair of elongated, cigar-shaped tubular structures… the vno possesses a lumen lined with two types of epithelia"
Wible, Bhatnagar [22]	1996	vomeronasal epithelial tube
Poran [65]	1998	vomeronasal complex
Weiler et al. [66]	1999	the first appearance of the sensory epithelium
Smith et al. [10]	2001	chemosensory and non-chemosensory VNO
Doty [67]	2001	"tube-like structure surrounded by cartilage" (p 436); denoted as a part of the vomeronasal complex
Bhatnagar, Smith [56]	2003	historical time-line for the human VNO
Taylor, Forge [68]	2005	sensory patch
Bhatnagar and Smith	This study	patch of microvillar neurosensory epithelium that may take the form of a sac or a duct, and may or may not have an associated nonsensory epithelium

Conclusions

Recently, Wilson [49] provided a useful discussion of the benefits and pitfalls in the development and use of standardized anatomical terminology for vertebrate paleontology. His discussion applies equally well to the present topic. The use of standardized anatomical terminology has intuitive appeal in that it is based on homology [50]. Some potential drawbacks to such terminology, as articulated by Wilson [49], are that it may overly simplify complex evolutionary transformations or make premature assumptions about homology. The terminology we are promoting should be considered in the context of such concerns. Indeed, our minimalistic approach concerning a basal feature of tetrapods does exclude a complex array of supporting elements. Subsequent to its origin, it seems diverse clades evolved different means of delivering stimuli to the VNO. It is precisely the apparently diverse origins of the supporting elements that suggest that a somewhat narrow definition of this chemosensory organ may be beneficial. In strict terms, the VNO is *a patch of microvillar chemosensory epithelium that may take the form of a sac or a duct, and may or may not have an associated nonsensory epithelium, the RFE*.

Table 2. Proposed vomeronasal organ (VNO) types in mammals

VNO type	VNO characterization	VNO features in the literature
A. Chemosensory	Highly-developed, well-developed (vampire bats, *Artibeus* (Fig. 1A: Jamaican fruit bat), *Carollia* (Fig. 1B: short- tailed fruit bat), present in *Miniopterus* (long-fingered bat), *Saguinus* (Fig. 1C: Geoffroy's tamarin), rats and mice.	The following structures must be identifiable: well-developed ~~(vampire~~ microvillar neuroepithelium, RFE, and other ancillary VNO structures
B. Nonchemosensory (Vestigial)	Rudimentary in *Rhinopoma* (Fig. 1E: mouse-tailed bat), *Hipposideros* (Indian leaf-nosed bat), *Brachyphylla* (Fig. 1F: lesser Antillean fruit bat), chimpanzee, *Homo* (Fig. 1G: human), *Rhinolophus* (Fig. 1D: horse-shoe bat)	None of the structures given in '**A**'are present; only a ciliated microvillar epithelial tube is present superior to the paraseptal cartilage.

Consistent with our minimal definition of this chemosensory organ, we propose two broad categories of VNO that may be broadly considered concerning mammals: chemosensory VNO or non-chemosensory vestige of the VNO (Table 2). Even with these categories in mind, VNO evolution among mammals appears to be an intricate story [see, e.g., 9]. The human vestigial VNO is hardly an unusual case among mammals, but it is for humans that some authors continue to purport a functional VNO [43, 44, 51, 52] without adequate evidence [see 24, 26, 38, 53]. In our terminology, the non-chemosensory vestige may be regarded as a case of evolutionary loss of the vomeronasal system, that is, with respect to its pheromonal and/or other proposed functions [54].

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Correspondence:

Kunwar P. Bhatnagar
7000 Creekton Dr., Louisville. KY 40241
USA

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