Structure of the principal olfactory tract

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Although the purpose and importance of the sense of smell in human beings has not been totally clarified, it is one of the principal information channels in macrosmatic animals. It was the first long-distance information system to have appeared in phylogenetic evolution. The objective of this article is to deepen the knowledge of the pathways that join the olfactory epithelium with the cortical olfaction areas, to better understand olfactory dysfunction in human beings. Differential staining and marking techniques were applied to histologic sections obtained from 155 animals of different species, to study the different connections existing among olfactory tract components. Our study of the connections between the olfactory mucosa and the principal olfactory bulb deserves special mention. The distribution of second neuron connections of the olfactory tract with the central nervous system is quite complex and diffuse. This indicates an interrelation between the sense of smell and a multitude of functions. These connections seem to be of different quantitative importance according to species, but qualitatively they exist in both human beings and other macrosmatic animals. (Otolaryngol Head Neck Surg 2000;122:129-38.)

Sense of smell is a fundamental part of the information system in macrosmatic animals and was the first long-distance information system to have appeared in phylogenetic evolution. It enables animals to detect enemies, to search for food by tracking, and to carry out normal breeding. Pheromones play a transcendental role in the conservation of the species.[1]

The use and importance of smell in human beings is subject to debate. The implications of this sense (very important and well studied in different animals of various phylogenetic scales) are not perfectly quantified in human beings. It is known that in mammals olfactory stimuli condition responses that control food search and identification, dietary preferences, mate selection (even—as Bakker et al[2] demonstrated experimentally—orientation toward heterosexuality or homosexuality), reproduction, protection of the young, prey detection, and alarm against predators. The relationship with alarm is well defined by Orlandi et al,[3] who showed that electric stimulation of the olfactory epithelium sets off an increase of plasmatic cortisol, rising to 100% at 20 minutes, with a decrease to normal threshold levels 1 hour after stimulus. This increase is not generic, but specific, because it is not produced by electric stimulation of nasal fossa zones covered with respiratory epithelium.

As can be seen in the Results section, the distribution of the second neuron connections in the olfactory pathway to the central nervous system is quite complex and diffuse. This indicates an interrelationship between smell and a multitude of functions. These connections seem to be of different quantitative importance according to species, but qualitatively they exist in both human beings and other macrosmatic animals.

The olfactory sensorial area in human beings, as in other microsmatic animals, occupies only a small zone within the nasal fossa. In contrast, the olfactory system is extensive in macrosmatic animals. In human beings, the olfactory mucus—the true peripheral organ of smell—covers the fossa roof (ethmoid lamina cribrosa), the space next to the external wall corresponding to the dorsal segment of the superior horn, and the most cranial zone of the nasal septum, which forms a dihedral angle with the fossa roof.

The structure of the olfactory apparatus is described schematically in this article because this knowledge is essential to understand human olfactory dysfunctions. The quality and intensity of olfactory perceptions depend on the anatomic situation of the nasal epithelium and the state of the central and peripheral olfactory system. Complementary data on olfactory epithelium and bulb connections are also presented.

METHODS AND MATERIAL

The structure of the principal olfactory pathway has been studied in the Department of Otorhinolaryngology of the

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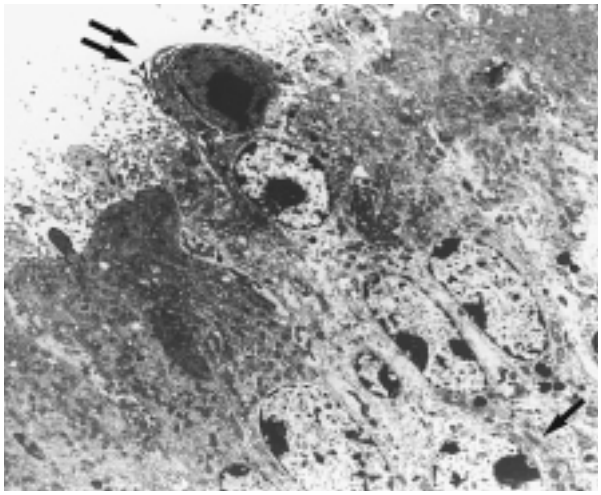

Fig 1. Neuron receptors are in a constant cycle of renovation; the youngest *(arrow)* are found deeper, and the oldest *(double arrow)*, and closest to renovation, are found nearest the epithelial surface (3.5 × 1.600).

University of Valladolid. Between 1983 and 1995 a total of 155 animals were used: 29 hamsters *(Cricetus auratus),* 96 Wistar-Lewis rats, 22 giant albino rabbits, and 8 cats. The structure of the epithelium and the lamina propria of the olfactory mucosa, the olfactory bulb structure, the connections between the receptor neurons and the bulb mitral cells, and the general composition of the principal olfactory pathway have been studied in these animals. The results of these investigations were published partially in various media between 1985 and 1996.[4-8] All of the animals used were treated according to the international principles of the care of animals.

To delimit the extension of olfactory mucosa in the different animals, we performed macroscopic dissection of the nasal and anterior cranial fossa, histologic study of the olfactory mucosa limits, and injection of horseradish peroxidase (HRP) with test of anterograde axonal transport to the peripheral receptor neurons.

HRP bulb injection was performed by drill craniotomy, microdissection, and product injection with a Hamilton microsyringe. The animal was euthanized 24 hours later by intracardiac perfusion of glutaraldehyde, and HRP diffusion in the olfactory epithelium was tested by optic microscopy.

For the nasal mucosa study by optic microscopy, tinctures with hematoxylin and eosin, argentic, toluidine blue, and Masson's trichrome stains were used. These preparations yielded good basic images of the epithelium and the lamina propria.

The olfactory epithelium was studied by electron microscopy, with special interest in the external surface and receptor neurons.

The olfactory epithelium-bulb connections were studied by anterograde (bulb-epithelium) and retrograde (epithelium-bulb) traces with HRP. The anterograde trace was performed with microinjection of the olfactory bulb through craniotomy as described earlier. For the retrograde trace, the muzzle was incised, and the great nasal bone was articulated, which allowed us to view the entire nasal fossa from above; HRP was deposited selectively in the specified site with a microneedle, which remained in the olfactory mucosa. The surgical approach was then repaired, and the animal was euthanized 24 hours later by perfusion of intracardiac fixative. The bulb was then extracted for histologic study.

Basic histologic studies were performed on the 4 fundamental cellular elements of the olfactory bulb: periglomerular, tufted, mitral, and granular cells. Other bulb cell types, named for the author who described them or for their shapes and relationships, are all grouped together as what we call short axon cells[9]; these were not included in this article. Afferent and efferent central connections of the mitral cell were reported on the basis of review of already published and generally accepted accounts.

RESULTS

Olfactory Epithelium Distribution and Histologic Nature

Distribution of the olfactory mucosa is relatively similar in the various mammals studied. It extends over practically the entire nasal septum and the surface of its extensive turbinal formations.

Three types of cells are classically recognized in olfactory epithelium: olfactory neurosensory cells (or receptor neurons), sustentacular cells (or support cells), and basal cells (or germinative cells). The excretory conduits of Bowman's glands run among these toward the surface from the lamina propria.

The principal cell is the olfactory neurosensory cell because it is the receptor sensory neuron. An authentic bipolar neuron, it emits 2 prolongations. One is the apical dendrite, which extends toward the exterior and appears in the nasal fossa lumen as a bundle forming the olfactory vesicle. Some ciliary structures or olfactory cilia rich in sensory terminations or olfactory buttons extend from the vesicle. The other prolongation is the axon, which extends downward, penetrating the basal membrane and the lamina propria. It then joins with other axons in bigger and bigger bundles to form part of an olfactory nerve.

The 20 to 30 olfactory nerves penetrate the cribriform plate of the ethmoid through its openings and are distributed over the first bulb layer. The relation of the olfactory nerves with the meninges is complex. The pia mater forms a conjunctive sheath around each olfactory nerve, constituting its neurilemma. The arachnoids are fixed in the surroundings of the cribrum, but the subarachnoidal space is prolonged under this lamina

around the nerves up to their origin. The dura mater is divided at the level of the cribrum openings into 2 sheets: 1 blends with the periosteum, and 1 descends to the nasal fossa around the olfactory nerves and forms an individualized sheath of the pia mater covered by the subarachnoidal tissue.

The body of the olfactory neurosensory cell is located in the middle of the epithelium because the most external zone is occupied by the body of the sustentacular cells. The nucleus lies in the innermost part of the cell. Because these receptor neurons are in a constant cycle of replacement, the youngest are found deeper, closer to the basal cells from which they come. In contrast, the oldest and closest to replacement are found nearest the epithelium surface[10]; their elimination can sometimes be seen through the epithelium surface of the now useless neuron (Fig 1).

The neurosensory cells are interspersed with the sustentacular cells, deeper than the former and perpendicular to the epithelium surface. The cell is shaped like a bottle or flask. Its widest zone is mainly occupied by a clear nucleus 4 to 5 μm in diameter, having scant zones of dense chromatin; there are sometimes 1 or 2 nucleoli. Neurosensory cells are aligned under the nuclei of the sustentacular cells but do not form as clear a file as the sustentacular cells do. Above the nucleus, the cytoplasm contains the Golgi apparatus and abundant ribosomes and polyribosomes, both free and attached to the granular endoplasmic reticulum cisterna.

The dendrite is a tubular protoplasmic prolongation 20 to 30 μm long, with a diameter of 0.6 to 1.5 μm. It comes out from the cell body, opening its way through the sustentacular cells to reach the epithelial surface. There it forms the olfactory vesicle, which is a prolongation in the shape of a drumstick or club some 3 μm long and 2 μm wide, which spreads perpendicularly to the surface.

Olfactory cilia emerge from the entire border of the olfactory vesicle in all directions (Fig 2). Their length is difficult to specify (about 3 μm). They have a thicker basal section, approximately 250 μm wide, which gradually becomes thinner distally until it measures about 100 μm. Its structure is typical of all flora and fauna cilia, having 2 central tubules and 9 pairs of peripheral double tubules.

In the dendrite stalks there are numerous neurotubules, mitochondria, lysosomes, and granular endoplasmic reticuli. The axons, which are much finer than the dendrites, penetrate deeply toward the cell down to the basal membrane. They contain abundant mitochondria in the most proximal segment and pronounced neutrotubules throughout their pathway. In their trajectory between the basal cells and the basal feet of the sustentacular cells, they unite various axons in bundles to penetrate the basal membrane together. In the lamina propria these axon groups are surrounded by Schwann cells and gradually form fascicules of more elements by mixing with surrounding groups.

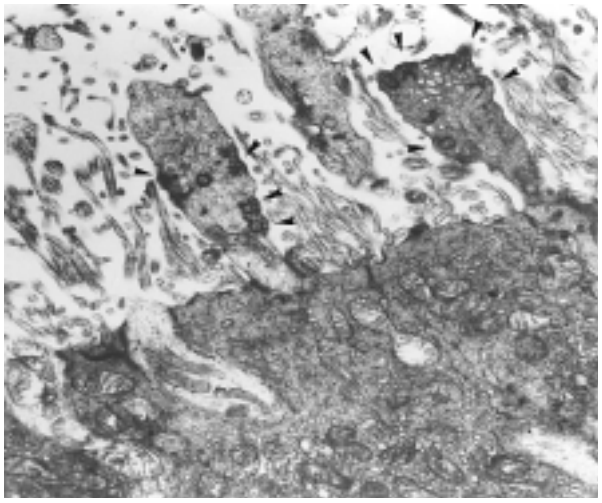

Fig 2. Olfactory cilia emerge (arrows) from the entire border of the olfactory vesicle (3.5 × 6.000).

Two other cell types make up the olfactory epithelium, the sustentacular and basal cells. These cells, although lacking the functional importance of the neurosensory cells, also have important tasks. The sustentacular cell has a secretory capacity, as shown in various animals. It seems that this secretion is a response to a specific smell. This secretory capacity has only been demonstrated in laboratory experiments with animals; in human beings this function has not been demonstrated yet.[11-13]

The sustentacular cells lengthen vertically. The external or distal segment occupies the epithelial surface, with its nuclei in the more superficial region. The cell body gradually narrows downward to allow space for the neurosensory cells, which constitute a second, deeper file. The sustentacular cells—of cylindric aspect, spindly and perpendicular to the epithelium surface—are supported by the basal membrane and the layer of basal cells in the deepest layer. Their other end, as has been explained, appears in the free surface of the mucosa.

In the apical cytoplasm, which extends between the free surface and the nuclear zone, the most external part is practically "empty" of organelles. However, immediately below there are abundant smooth endoplasmic reticula arranged in several layers forming concentric circles. Within these circular formations we can find abundant mitochondria, scant granular endoplasmic

reticula, free ribosomes, the Golgi apparatus, and secretory vacuoles. This apical cytoplasm composition of the sustentacular cell leads us to support the criteria that concede a principal secretory role to this cell element, with secretion possibly through the microvilli. It seems that a pigment of this secretion is what gives the olfactory zone its characteristic yellowish tone. In addition to nutrition, protection, and neurosensory cell support functions, this cell possesses, as we have said, a clear secretory function, differentiated from that of the Bowman glands.

Basal cells are arranged in the deepest zone of the epithelium over the basal membrane. They are polygonal, are small, and have a rounded nucleus in a central position. Their hyaloplasm is dense, with abundant free polyribosomes and organelles: mitochondria, Golgi apparatus, and moderate granular endoplasmic reticula.

The basal cell layer may be lacking in more or less extensive areas of the epithelium. These cellular elements are of great importance because they can change into sustentacular or neurosensory cells, thus replacing any deficits that may arise.[14] In the case of destruction of olfactory epithelium, an immediate regeneration occurs, and new basal cells appear on the basal membrane. It is believed that the origin is the cellular elements of the Bowman glands,[15] which by the degree of nucleus osmiophilia, are thought to differentiate 2 types of basal cells with different orientation, toward neurosensory or sustentacular cells.

In our ultrastructural basal cell observations, we have not found a specific evolutionary orientation of this cell type.[16] The different osmiophilia of the basal cell nuclei, their structure, and the more or less secretory character of some of the cytoplasmic formations do not suggest such an evolutionary orientation.

At present 2 types of basal cells are accepted: smooth and spherical. It seems that smooth basal cells are transformed by mitosis into spherical basal cells. These then separate from the basal membrane, migrate, and produce receptor neurons or sustentacular cells.[16-19]

Basal cells definitely germinate cells with the capacity of transformation. When it is necessary, they regenerate the other 2 olfactory epithelium cell types. Constant replacement of the epithelium is thus produced.

The basal cells surround the neuronal axons before they exit from the epithelium. As soon as they pass the basal membrane, the axons are covered by Schwann's membrane. The basal membrane is a condensation of collagen of the lamina propria, whose function is to separate this clearly from the epithelium.

Electron microscopy has facilitated the discovery of a fourth type of cell in the olfactory epithelium, the microvillous cell.[12,19-21]

Epithelial Surface

The surface of the epithelium is covered by a hydrolipid mucous film. The olfactory vesicles are submerged here with their olfactory cilia and the digitations of the microvilli emitted by the sustentacular cells.[22]

The mucous covering, the specialized prolongations of the neurosensory cells (vesicles and olfactory cilia), and the sustentacular cells (microvilli) submerged in it possess a special surface-to-center organization, that is, from the lumen to the apical cytoplasm of the sustentacular cells. At the surface we first find the most superficial mucous layer. This is a homogeneous zone, a poorly defined amorphous layer differing in thickness according to the zone and having little electronic density. Sections of the distal cilia segments appear here, the more abundantly the greater the depth. Slide samples show that these have only small central tubular fibers. At times only a single circular element is seen, of similar or even greater diameter than that of 2 central tubules fibers together. This suggests a terminal cut in which the 2 central tubules have joined into a final blister, which is the swelling or final ball observed[22] at the end of the cilia distal segment by electron sweep microscopy. These distal cilia parts are placed longitudinally parallel to the epithelium surface, forming a relatively thick layer.

Just below this superficial zone, numerous cilia with additional tubular elements appear: 4 (the 2 central and 2 peripheral tubules), 6, 8, and so forth. These increase gradually until they demonstrate the typical structure of 9 peripheral double tubular fibers and 2 central fibers. This structure is common to the cilia of whatever localization in all animal species. That is, the complete cilia—9(2) + 2—do not convert abruptly into distal segments with only 2 central tubules but rather gradually lose the peripherals at different levels. As the total size of the cilia adapts to the quantity of tubules that are left, its thinning is progressive until it reaches the final sections with only the central tubules. These are then conserved unchangingly in the distal longitude.

It is not rare to find 2 groups of complete ciliary tubules (9 peripheral and 2 central) surrounded by a common ciliary membrane. It has not been possible to determine whether the 2 cilia separate after running together for a short trajectory or whether, in contrast, they remain united throughout their longitude. In some cases these double cilia maintain a perfect organization within the membrane, the 2 circles of 9 tubules and the 2 central ones clearly marked in each cilium. However, in some images, although the 10 and 8 + 4 in total do exist, they seem relatively disorganized, lacking a precise structure of 2 circular groups.[23]

In the plane that immediately underlies the superfi-

cial mucous covering, the most distal extremes of the olfactory vesicles begin to appear. A few basal bodies and the birth of the corresponding cilia can be distinguished here, even in the most apical vesicle zones. The sustentacular cell microvilli do not reach this level or do so only in small numbers.

These microvilli begin to abound just below. They can be simple, double, or multiple, representing authentic branches that part from a common trunk. They are all aligned in the same direction, approximately perpendicular to the epithelium surface. At times they are so abundant that virtually no space is left between them, whereas adjacent areas have slight density in which the microvilli look like algae in the sea.

At this level there are a great many olfactory vesicles with their typical club or drumstick shape. At times their profiles are softer and more rounded, and sometimes they look like inverted pyramids. Two electronic densities can be perceived, with one vesicle group markedly darker than the others. The more electrodense areas are more infrequent and are scattered throughout the layer, not accumulated. Inside are found the organelles and formations cited in all descriptions of olfactory vesicle ultrastructure: abundant mitochondria (some quite large), small vesicles and granules, microtubules, centrioles, and basal bodies.

In transverse cuts of olfactory vesicles, the olfactory cilia can frequently be seen branching out in 4 or 5 opposite directions, forming a star pattern. On the other hand, it is not rare to count from 6 to 8 cilia that emerge almost from the neck up to the most apical part of the vesicle in longitudinal cuts. In our estimation, between 25 and 40 basal bodies and cilia emerge from each.

Olfactory cilia frequently separate from the vesicle perpendicular at their origin, immediately curving toward the surface. However, other cilia emerge parallel to the greater vesicle axis and do not separate totally from it until the apical zone.

When the olfactory vesicle approaches the epithelial surface, it becomes significantly thinner before entering the epithelial thickness as a dendrite. It thus forms a neck in which the neurotubules are generally more visible because a great number are included in a smaller space. After this, the vesicle enters the epithelium between 2 sustentacular cells, to which it is closely united by a 3-element complex. Almost no organelles are found here, in this most apical zone of the sustentacular cells, from which the microvilli emerge.

Lamina Propria

Two formations characterize the lamina propria of the olfactory mucosa: the fascicles or bundles of olfactory axons and Bowman's glands. The olfactory nerve bundles are a set of neurosensory cells united in their trajectory toward the bulb. They are covered by the sheath of Schwann, have no myelin, and are thicker the farther away from the epithelium they are located.

When studying neurosensory cell images, we could see that the axon enters deeply between the basal cells and the basal feet of the sustentacular cells; then various axons join together in a bundle and penetrate the basal membrane together. In this intraepithelial nerve bundle formation, the sustentacular cells can be considered to be ependymal cells and the basal cells to be central nervous system astrocytes or peripheral nervous system Schwann cells. As soon as these nerve bundles penetrate the basal membrane, they are surrounded by Schwann cells in the lamina propria. These bundles gradually unite in the lamina propria, with the nearest bundles forming more and more important nerve elements until the union of various fascicles constitutes a true filum olfactorium. As is known, these olfactory fila lead the peripheral neurosensory cell axon through the openings of the ethmoid cribrum up to the olfactory bulb. At that point, the fila form a synapse in the glomeruli of the apical dendrites of the mitral cells and with the dendrites of tufted cells.

Nerve fillets of amyelinic fibers are very frequent. In addition, typically myelinic fibers in which the highly electrodense myelin conduct can be seen perfectly are not rare. These are found in very close parallel concentric layers, differentiating themselves from the membrane of a Schwann cell. Likewise, notable mixed fillets can also be seen; in these, amyelinic and clearly myelinic fibers exist, separated by only fine connective endoneural-type walls. Part of the nerve fibers observed in the lamina propria of the olfactory mucosa are not sensory elements, but are fibers of the sympathetic system or the trigeminal system.[24]

Bowman's glands are branching tubular structures in which a few more or less flat cells are ordered in a concentric string around the lumen of the gland. They make up the adenomere responsible for fabricating the secretory product. These cellular elements possess very abundant smooth endoplasmic reticula, while they lack or have few granular endoplasmic reticula. This indicates that the secretion is lipid or saccharide, not protein. In the cytoplasm of these glandular cells, numerous "grains" or secretory vesicles appear. They range in color from almost transparent to grayish, or a last almost-black type of great electrodensity, depending on whether the secretion is mucosa, serosa, or pigmentation. The glands are usually located near the basal membrane, that is, in the surface of the lamina propria near the epithelium.

The intraluminal surface is generally wide and lon-

Fig 3. Retrograde HRP transport (epithelium-bulb) is evident in all cases. A partial topographic relation exists between the injection zone in the olfactory mucosa and the bulb. *Olfactory nerve layer; **glomerular layer with different glomerulus label degrees: glomerulus with soft HRP label (arrow) and glomerulus with intense HRP label (double arrow).

gitudinally extensive. It penetrates the basal membrane and runs through the epithelium to the external surface, where it releases its content. Secretion quantity is related to greater or lesser functional activity, according to the necessity of diluting odorous molecules.

We can see 2 types of glandular cells: clear ones and others that are darker because of more abundant nuclear chromatin and much more frequent protoplasmatic organelles. This can be interpreted as a distinct functional situation of the same cell type, in which the clear cells are latent or resting and the dark ones are actively secreting. This whole group is surrounded by the gland basal membrane, which is a concentrated connective layer that is pale gray under an electron microscope. The membrane limits the periphery of the basal gland cells and is comparable with the basal membrane of the epithelia.

As is true in all sites, the lamina propria connective tissue is abundant. There are many collagen fibers, a few elastic fibers, and very numerous fibrocytes and fibroblasts. The collagen fibers are abundantly dispersed among the nerve fillets. The fibrocytes emit their formations as a membrane, making coverings that surround the entire nerve fillet (perineuro) peripherally. In addition, others extend among the various bundles of the same fillet (mesoneuro) and a third type sheath all the nerve bundle independently (endoneuro).

The vascular component of the olfactory mucosa, although abundant, is not as ample as in respiratory mucosa. There are fewer arterioles; veins are less frequent and lacking in cavernous structures; and the erectile vascular system frequent in the rest of the nasal mucosa is missing. However, apart from these differences, the capillary network is likewise rich in the lamina propria of this olfactory mucosa.

Olfactory Bulb and Olfactory Centers

The olfactory nerves are distributed throughout the periphery of the bulb, forming its outer layer, or the olfactory nerve layer. Its axons then reach the second (or glomerular) layer, where they form a synapse in the glomeruli with the apical dendrites of mitral and tufted cells. The relations established between the axons of the first olfactory neurons and the mitral cell dendrites have been studied to define glomerular structure. It has been found that in the differentiation of the mitral cell, a superproduction of its dendrites occurs, with a posterior selection of the useful primary apical dendrites and elimination of the excess. The synapse of these useful dendrites with the peripheral receptor neuron axons constitutes the mature glomerulus.[25]

The olfactory bulb is an extremely organized formation, perfectly studied by Ramón y Cajal,[26] whose basic general structure remains unalterable. It is made up of 7 successive layers, which from outside in are as follows. The first layer, or olfactory nerves, is formed by the olfactory nerve axons, which penetrate parallel to the bulb surface and then curve toward the center to enter the second layer. In the second (or glomerular) layer, the receptor neuron axons form a synapse with the mitral cell apical dendrites; the group of these unions forms a spherical conglomerate called a glomerulus. Near the glomeruli some cellular elements called periglomeruli cells are found; Schoenfeld et al[27] and Liu and Shipley[28] demonstrated that these cells transmit information between the glomeruli and the outermost tufted cells, forming an intrabulbar association system. In the third (or external plexiform) layer, the middle and internal tufted cells are found, and they act as second neurons, or relief neurons, of the olfactory pathway,

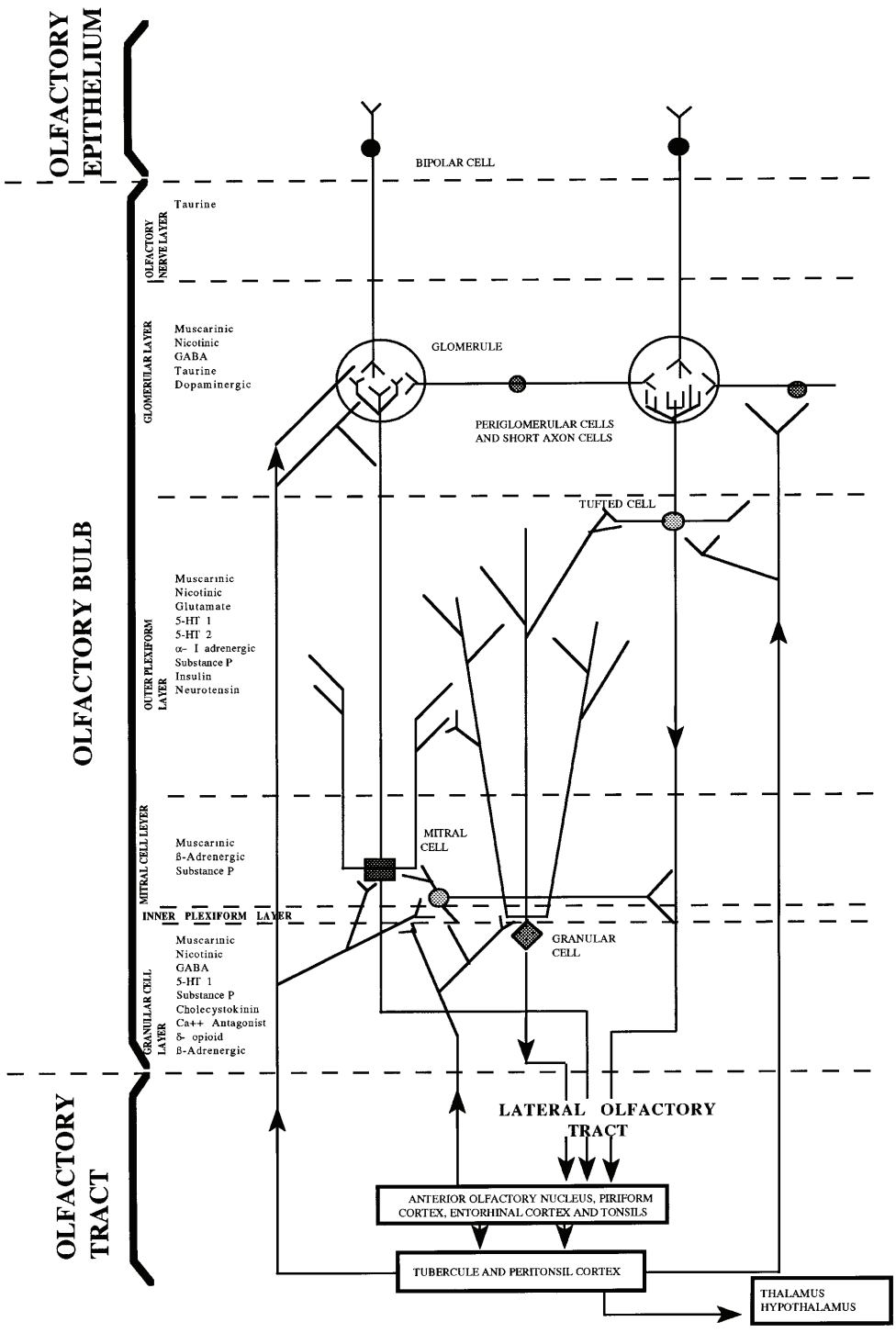

Fig 4. Schema of olfactory pathway. HT, Hydroxytryptamine.

which transports information to the retrobulbar areas. In this layer secondary dendrites of mitral and tufted cells connect among themselves in branches, and these connections even contact the granule dendrites. The fourth layer is made up of mitral cells, which are the principal relief neurons (second neurons) of the olfactory pathway in the bulb. The fifth layer, or internal plexiform, is a fine layer containing few cells, crossed by dendrites

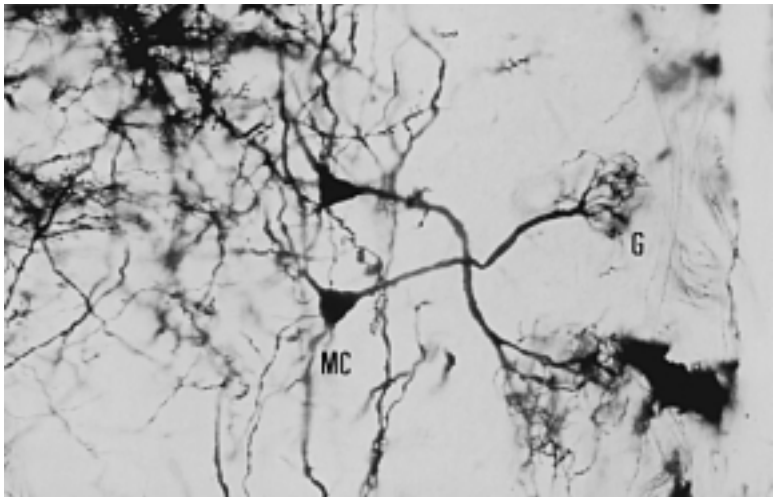

Fig 5. Some 30,000 first neurons contact about 25 mitral cells (MC) at a synapse point. Argentic stain showing some mitral cells with their dendritic processes branching in the glomerular layer (G).

and axons of the bulb cells. The sixth (or granule cell) layer contains great cellular richness. Its cells, called granules, are abundant elements; they have been divided into clear and dark granules, both having a different distribution in the bulb and a different time origin.[29] The axon traces divide the layer into numerous islands containing the cellular bodies. The granules are the most numerous cells in the bulb; they have no axon but rather apical dendrites that contact in the external plexiform layer with those of the mitral and tufted cells. The granules are formed principally in the postnatal period and continue proliferating in the adult.[30-32] The seventh (or subependymal) layer is the deepest olfactory bulb layer. It is of notable importance during development, but its role in the adult is as yet unknown.

In addition to the 4 classic cells of the olfactory bulb (periglomerular, tufted, mitral, and granule), many other cell types have been described. These have been named after the authors who first described them, or for their form and relations, but they are all grouped together as short axon cells.[9] The bulb contains a great diversity of neurotransmitters, and some of its cells have more than 1 neurotransmitter phenotype.[19,33,34]

It seems certain that a partial topographic relation exists between the olfactory mucosa and the bulb, although a consensus has not been reached among all authors. In our experience, anterograde and retrograde HRP transport was evident in all cases (Fig 3).[6,7,35] Analysis of the data from both HRP axon transport systems leads to the conclusion that there is a correlation between the injection and captation zones. However, there are always other unforeseen captation zones. This seems to indicate that the topographic relation between the olfactory mucosa (first neuron) and the different glomerulus bulb zones (second neuron) is not strict.

The second neuron, or deuteroneuron, of the olfactory pathway is represented by the mitral bulb cell, located in the fourth bulb layer or mitral cell layer (Fig 4). The tufted cells of the external plexiform layer also act as second neurons. It is essential to consider how the first and second neurons form a synapse; some 30,000 first neurons contact about 25 mitral cells at the synapse point (Fig 5). From this perspective, the olfactory receptor can be considered as a functional subunit of the bulb glomerulus.[36]

Each neurosensory cell of the epithelium is a receptor that expresses a specific smell, and the different receptors of the same smell are widely distributed throughout the olfactory epithelium. However, wherever they are, they project their axons to only a few, specific glomeruli of the olfactory bulb.[37]

The olfactory bulb receives fibers from neurons located in the higher brain regions, which possibly reach the bulb in greater numbers than those it receives from the olfactory epithelium.[34] Cholinergic and GABAergic fibers arrive from the horizontal limbus of the diagonal band, serotoninergic fibers from the raphe, noradrinenergic from the locus ceruleus region, and histaminergic fibers from the hypothalamus.[37]

The efferent fibers exit the bulb through the lateral olfactory tract (Fig 4); their objectives or targets are the anterior olfactory nucleus, the primary olfactory cortex or piriform cortex, the entorhinal cortex, and the tonsils. These structures are intercommunicated in a complex manner with the olfactory bulb.[38]

The third neurons are found in the olfactory paleo-

cortex: the anterior olfactory nucleus and olfactory tubercle, piriform cortex, and peritonsil cortex. The second neuron axons through the lateral olfactory tract principally reach the piriform and the peritonsil cortex. From the olfactory paleocortex, the third neurons send connections to the thalamus, hypothalamus, and tonsil complex.

The anterior olfactory nucleus is subdivided into various zones that receive different names based on their orientation with respect to the anterior limbus of the anterior commissure. Projections that cross the anterior commissure exit from some zones to contact the anterior olfactory nucleus and the bulb of the other hemisphere. With these contralateral connections, the anterior olfactory nucleus is the first olfactory structure that has a bilateral representation.[39]

The existence of end projections from the olfactory tract to the neocortex is well confirmed, although the complexity of the neocortical projections has not yet been perfectly established. Projections reach the orbitofrontal neocortex directly from the piriform cortex and indirectly through the thalamus and the hypothalamus. Olfactory tract projections reach the somatogustative neocortex through the thalamus. It has been demonstrated that the neocortical areas of the superior temporal sulcus of both hemispheres is activated by olfactory stimuli.[39]

CONCLUSIONS

1. Our findings in the structure of the olfactory mucosa coincide with those presented in classical references.
2. Our study of the connections between olfactory receptors of the epithelium and the bulb glomeruli confirms the existence of a convergent information system. It further demonstrates a point-by-point relation between the 2, although this should not be considered exclusive or strict.
3. Otolaryngologists need to possess a basic knowledge of the olfactory tract structure to understand olfactory alterations.

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Microscope- and Endoscope-assisted Paranasal Sinus Surgery

This international preparation course will be held February 17-19, 2000. The professor and chairman is H. Rudert, MD, Department of Otorhinolaryngology–Head and Neck Surgery and the professor and co-chairman is B. Tillmann, MD, Center of Clinical Anatomy, Department of Anatomy.

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