Offprint from
Advances and Technical Standards in Neurosurgery, Vol. 30
Edited by J.D. Pickard

Basic and Clinical Aspects of Olfaction

B. N. Landis[1,2], T. Hummel[2], and J.-S. Lacroix[1]

[1] Unité de Rhinologie-Olfactologie, Service d' Oto-Rhinologie-Laryngologie, Hopitaux Universitaires de Genève, Genève, Switzerland
[2] Smell and Taste Clinic, Department of Otolaryngology, University of Dresden Medical School, Dresden, Germany

With 1 Figure

Contents

Abstract

Disturbances of olfaction are a common occurrence in many neurological and neurosurgical patients and their correct diagnosis might be helpful in management and enhancement of quality of life. However, olfaction is seldom checked in most neurosurgical units and the ''smell bottles'' are often either absent or out of date. This chapter reviews systematically recent advances in our understanding of the anatomy, physiology (olfactory coding) and measurement of olfactory function in the human. The causes and symptoms of smell disorders, risk of damage to the olfactory system by various surgical procedures and, finally, the natural history of recovery and treatment of smell disorders, for example after trauma, are discussed.

Keywords: Olfaction; smell disorder; anatomy; physiology; olfactory coding; measurement of olfactory function; craniotomy.

Anatomy

Although this review focuses on the olfactory system, it is necessary to mention, at least briefly, other sensory channels involved in chemosensory perception. All the senses can be stimulated by chemicals, which in fact, typically activate not only one but several of the ''chemical senses''. For example, nicotine not only activates the olfactory nerves, but also produces activation of the intranasal chemosensory trigeminal system.

Main Olfactory System

Olfactory perception starts at the level of the olfactory epithelium in the roof of the nasal cavity. Olfactory receptor neurons (ORN) are embedded within the respiratory epithelium and send their axons through the cribriform plate towards the olfactory bulbs. ORN carry olfactory receptors (OR) which are the key to olfactory information processing (see below). In the olfactory bulb ORN axons synapse with second order neurons, the

mitral cells. The wiring between the olfactory epithelium and the olfactory bulb is characterized by a convergence of ORN axons. Specifically, all ORN carrying the same OR converge in the same site within the bulb, called ''glomerulus''. Axons from the mitral cells follow the olfactory tract and divide into two bundles. Most fibers directly project to the pyriform and entorhinal cortices as well as to the amygdalae (all structures formerly subsumed under the term ''limbic system'') whereas a minority of fibers project through the thalamus towards the orbito-frontal cortex [1].

Compared to other sensory modalities the olfactory system has some particularities. First, the majority of the olfactory fibers do not cross but project ipsilaterally in the brain. Second, most olfactory fibers bypass the thalamus and project very rapidly and directly in the pyriform cortex, amygdalae, and entorhinal cortex which are implicated in emotional and memory processing [2]. This difference in central anatomy has been claimed to be partly responsible for the emotional load olfactory memories can carry [3]. In contrast to other sensory modalities, no main olfactory cortex has yet been found. Numerous works indicate the orbitofrontal cortices to be an important relay in olfactory information processing [4].

Trigeminal System

The trigeminal system provides the somato-sensory innervation to the nasal mucosa. Somato-sensory input from the skin, the nasal and oral cavities, respectively, is mediated by the trigeminal system. Since most odorous compounds stimulate trigeminal nerve endings, at least at higher concentrations, this system is almost always co-activated in the perception of odors. With few exceptions almost all odorants have been shown to exhibit trigeminal activation to some extent [5] (e.g., mint has a somewhat fruity odor, but also evokes a typical cooling effect which is mainly trigeminally mediated). The main modalities supplied by the trigeminal system are temperature, pain, touch, and irritation. Testing the chemosensory intranasal trigeminal system psychophysically is more complex than olfactory testing. Since olfactory thresholds are always lower than the trigeminal thresholds for a given substance, olfactory biases are obvious.

The olfactory system is unable to localize the site of stimulation when one nostril receives clean air and the other nostril simultaneously receives an odor at the same time. In contrast, trigeminal stimulation can be localized. This difference is used to solve the bias inherent to trigeminal testing. Using lateralisation paradigms, trigeminal function can be easily and rapidly measured in a clinical context [6, 7]. Since the olfactory and trigeminal systems are so closely related anatomically and physiologically, there is a strong interaction between the two systems [8, 9]. In patients with olfactory loss, the trigeminal function is also weakened [10, 11]. Older literature on trigeminal trans-sections also discusses its impact on olfactory

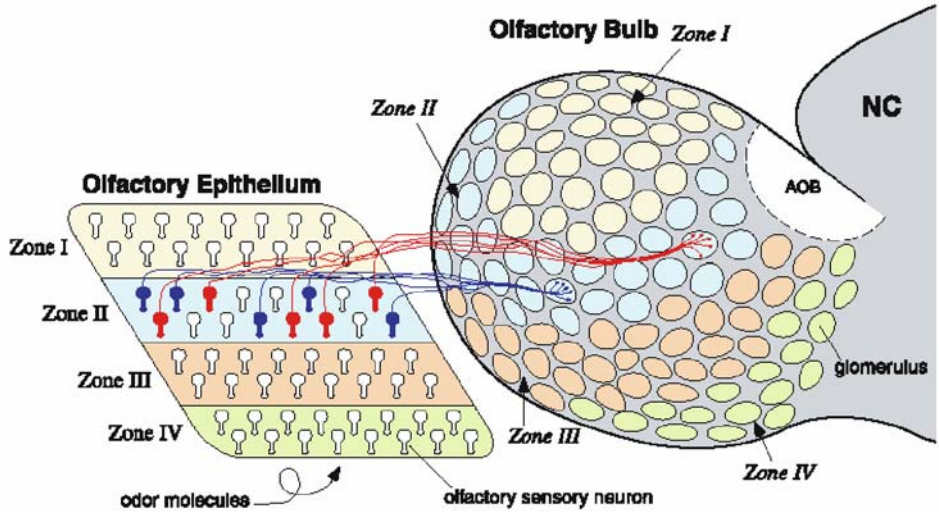

Fig. 1. Schematic diagram illustrating the axonal connectivity pattern between the nose and the MOB. The OE in mice is divided into four zones (zones I through IV) that are defined by the expression of odorant receptors. Olfactory sensory neurons in a given zone of the epithelium project to glomeruli located in a corresponding zone (*zones I* through *IV*) of the MOB. Axons of sensory neurons expressing the same odorant receptor (red or dark blue) converge to only a few defined glomeruli. *NC* Neocortex; *AOB* accessory olfactory bulb. Reprinted (abstracted/excerpted) with permission from Mori K, Nagao H, Yoshihara Y (1999). The olfactory bulb: coding and processing of odor molecule information. Science 286 (5440): 711–715. Copyright (1999) AAAS

function [12]. However, patients with complete trigeminal loss are extremely rare and no large study has so far been conducted to investigate the effects of trigeminal loss on olfactory function.

Gustatory System

The gustatory system provides the five basic tastes; sweet, sour, salty, bitter, and umami (glutamate). The latter, which resembles mainly the taste of chicken soup, has long been claimed in the Asian literature to be a basic taste quality [13, 14], whereas the western scientific community considered umami mainly as a ''taste enhancer''. This controversy was resolved when monosodium glutamate receptors were found on the tongue surface acting as specific taste receptors [15]. Molecular biological knowledge about taste receptors started to emerge a few years ago. Most basic taste qualities are not mediated by just one receptor type; several receptors act, for example, as sweet receptors. Many other taste modalities have been postulated (metallic taste, fat taste) and are currently under investigation. Future research is expected to clarify the coding mechanisms in taste perception.

Taste receptors are located within the taste buds, which are situated on all papillae except the filiform type. The highest densities of taste buds are found on the tongue and palate but they are also found throughout the entire oral cavity, hypopharynx and subglottic larynx [16]. Like ORNs, gustatory sensory receptor cells have the ability to regenerate [17]. Neural supply for these cells is provided by the facial, glossopharyngeal, and vagal nerves. The facial nerve innervates the anterior two thirds of the tongue, while the glossopharyngeal and vagal nerves innervate the posterior third of the tongue, as well as the hypopharynx and larynx. Like olfaction, taste fibers project ipsilaterally into the basal ganglia and brain stem. All gustatory fibers (facial, glossopharyngeal and vagus) innervating the oral-pharyngeal cavity converge into the nucleus solitarius within the brain stem.

Vomeronasal System

In 1813, Jacobson described a mucosal organ located on each side of the nasal septum and which was subsequently named ''Jacobson's organ'' [18, 19]. Later, the vomeronasal organ (VNO, consisting of vomeronasal epithelium, nerve, and accessory olfactory bulb) was shown to mediate effects attributed to pheromones [20]. A pheromone is a chemical molecule or compound which is secreted by one member of a species and, as soon as it is perceived by another member of the same species, elicits physiological, behavioral, or endocrinological effects [21, 22]. According to the original definition of Karlson and Lüscher [20] such effects must be species-specific. While the functionality and biological relevance in most animals is well documented, there is ongoing debate about the functional significance of the vomeronasal pouch in humans. Some authors claim to find neuronal activity within the vomeronasal epithelium [23] while many other studies suggest that the vomeronasal duct is nonfunctional in humans, with some vomeronasal nerves missing and lack of accessory olfactory bulbs in adults [24–27]. Furthermore, a vomeronasal duct is not always present in humans; recent investigations revealed that approximately 60% of humans have one [25]. Nevertheless, a few papers indicate that pheromonal-like effects occur in humans [28, 29] and several vomeronasal-like receptor genes have been found in the human genome, one of which is expressed in the olfactory epithelium (V1r) [30]. It is not yet known whether these receptors are functional or not. Their expression, however, indicates that putative ''human pheromones'' may act via the main olfactory system.

Olfactory Coding

The question of olfactory information encoding has been a concern for a long time. One main problem was to find a theory or model that would

predict the odorous properties of a given molecule. Although the fragrance industry spends a lot of money on the creation of new – and hopefully smelly – molecules, no model exists which could predict the smell of any given molecule. The search for new odorants is still a very expensive procedure based on trial and error. Therefore, a universal model of stereochemical – odor interaction would greatly assist the search for new odorants.

Several models have been proposed to explain how the olfactory system discriminates between odorants. In the early sixties Mozell hypothesized that the chromatography of a molecule would determine its processing [31, 32]. According to Mozell, the olfactory receptors, which are located on the cilia of the olfactory neurons, are covered by a mucous layer and odorants have to cross this mucus before reaching the receptor cell. His theory was based on experiments using frog olfactory epithelium. Although no clear evidence has been presented that absorption of odorants is irrelevant to its interaction with the receptors, this theory has received less attention during recent years. Nevertheless, recent work on humans suggests that absorption could have implications for olfactory perception [33]. Another model indicates that olfactory recognition is mainly based on a few basic odors and that combination of these odors encodes the olfactory information [34, 35]. This model claims that olfaction works according to physiological principles similar to those governing vision. This assumption was mainly based on experiments on specific anosmias to isovaleric acid. Further experiments with other odorants were not able to confirm this model. Another theory receiving interest from the media is an old idea [36] reactivated by Turin [37]. According to this theory, olfactory coding could be based on vibration properties of the odorants. Recent work, however, indicates that this model can not predict the olfactory characteristics of a given molecule [38].

Since odorants are chemical structures, the existence of a ligand–receptor interaction has been claimed for many years, and was finally substantiated in 1991 by the discovery of a large family of seven transmembrane receptor proteins, expressed exclusively in the olfactory neuroepithelium. These olfactory receptors (ORs) are encoded by approximately 1000 genes in the mouse, or approximately 1% of its genome [39]. While the mouse expresses approximately 850 of these genes, the rest being pseudogenes, humans have far fewer functional ORs (approximately 350) [40]. Although this seems to indicate a loss in function, the simple equation ''less receptors = less function'' is currently under debate and some studies argue that humans have a very high preservation rate for specially important ORs [41–43].

The discovery of the OR superfamily led to a renaissance of olfactory research. During the last decade, potential OR binding sites [44] and the topographical organization and distribution of the ORs within the olfac-

tory epithelium have been partly identified [45–47]. A recent finding has been the astonishingly high degree of organization found within the peripheral olfactory system. The first striking observation was that, among all the potentially expressible OR, every ORN expresses only one single OR gene [48, 49]. Furthermore, axons from all ORN expressing the same OR, whatever their location within the olfactory epithelium, project into two glomeruli in each olfactory bulb. This organization is called glomerular convergence [50]. Thus, a large glomerular map in the bulb, containing hundreds of glomeruli, will correspond to all OR expressed in the olfactory neuroepithelium. Molecular and electrophysiological studies revealed that OR are not selective for only one odorant, but numerous molecules bind with varying affinities to a certain OR. A given receptor may bind to a molecule with a given carbon chain length, but may lose binding affinity as the agonist's chain length increases. Similarly, the OR binding affinity for a molecule may dramatically change upon modification of the functional groups (aldehydes, ketones, acids, esters, alcohols, etc) of this molecule [51, 52]. In addition, every odorant is recognized not by one but by several ORs simultaneously, depending on its particular chemical properties. At the level of the glomerular map this leads to a specific activation pattern for each odorant [53]. This odor-specific activation pattern is believed to be responsible for the recognition of and distinction between different odorants [54].

However, as previously mentioned and although the olfactory receptor theory adequately explains how olfactory coding could work, olfactory research is still a long way away from predicting the odor of a molecule based solely on the stereo-chemical properties of the latter.

Measurement of Olfactory Function

Similar to other sensory modalities, olfactory testing procedures will yield information which is either based on subjects' insights (''subjective'' or ''psychophysical'' tests) or on more ''objective'' techniques less biased by the subjects' observations. Since the subjects' self assessment of olfactory function is unreliable, testing of olfactory function is necessary [55].

Psychophysical Methods of Olfactory Testing

The basic principle of psychophysical testing of olfaction is to expose a subject to an olfactory stimulus and to interpret the responses or reactions of the tested subject.

This procedure has numerous advantages in clinical application, but also important limitations. The most valuable advantage compared to objective testing methods in daily clinical life is the rapidity which allows psychophysical tests to serve as quick screening tools for olfactory dysfunction

[56]. More extensive testing sets, which can also be used for clinical research, allow graduation of the olfactory disorder. Fundamentally, every collection of odors is a potential olfactory test. Nevertheless, research during the last three decades [57, 58] has ruled out the importance of a well validated and reliable testing device. Whatever a clinical test consists of, it should reliably distinguish between anosmic, hyposmic, and normosmic subjects. Thus, the test should be based on normative data acquired and validated on large samples of healthy and diseased subjects. This includes comparison of the results with other validated tests and a good test-retest-reliability. These requirements apply to only a few olfactory tests available worldwide [57–63], since many tests of olfactory function do not comply with these criteria [64].

The best-validated olfactory tests include the UPSIT (University of Pennsylvania Smell Identification Test) [57, 59], the CCCRC-test (Connecticut Chemosensory Clinical Research Center) [58], and the ''Sniffin' Sticks'' [61, 62]. The latter one is a European test, while the first two were created in North America.

Most tests are based on a forced choice paradigm. An odorant is presented at supra-threshold concentration and the subject has to identify the odor from a list of descriptions of odors (e.g. the subject gets rose odor to smell, and is asked whether the perceived odor was ''banana,'' ''anis,'' ''rose,'' or ''lilac''). This forced-choice procedure controls the subjects' response bias. It also (potentially) allows the detection of malingerers since even anosmic subjects will produce a few ''correct'' answers provided in a random selection of items. However, this method is unreliable for medicolegal investigations since well-read or hyposmic malingerers may overcome these pitfalls. The result of the test corresponds to the sum of the correctly identified items. This test design is called a smell identification test, and is the most widely used way of testing [57–63, 65] probably because it is the most easy to understand. Most tests are based on the identification of 16 to 40 odors – the more items tested the more reliable the results. Identification tests are known to have a cultural connotation. Tests used in North America, for example, are composed of odors many of which are unfamiliar to continental Europeans or Asians (e.g., root beer, or wintergreen). The odors tested should therefore be adapted to the patients cultural background [66] in order to avoid unfamiliarity.

The two other widely used test designs are threshold tests and tests of odor discrimination. The idea of threshold tests is to expose a subject repeatedly to ascending and descending concentrations of the same odorant and to identify the least detectable concentration for this individual odor. Other designs are based on logistic regression [67, 68]. Discrimination tests mainly consist of a 3-alternative forced choice technique. Two of the administered odors are identical, one is different. The subjects' task

is to detect the different one. In principal, tests for odor threshold/odor discrimination are non-verbal. In addition, they can be used repetitively – which is more difficult with odor identification tests.

Generally, identification and discrimination tests are believed to reflect central olfactory processing while thresholds are thought rather to reflect peripheral olfactory function. Accordingly, it has been claimed by several authors [69–74] that patients with diseases of the central nervous processing of odorous information exhibit selective disturbances of discrimination and identification while threshold results are normal. Although this idea of a certain pattern pathognomonic for ''central'' olfactory disturbances seems attractive, the vast majority of studies have yet failed to confirm such typical pathology-associated patterns [75, 76]. The only, so far reliable and recurrent test pattern in olfactory disturbance is a low threshold and normal identification and discrimination in patients with chronic sinunasal problems [77].

Besides the solid body of literature and its clinical convenience, the psychophysical tests have one main limitation. As soon as the patient's collaboration is not guaranteed, interpretation of test results becomes difficult or even impossible. Such cases include mainly willful non-collaboration in cases of malingering, or for demented, unconscientious, or inexperienced patients. In order to acquire olfactory information in such cases, more objective testing methods have been developed which rely less on the subjects' cooperation.

Electrophysiological/Imaging Techniques Used to Test Olfactory Testing

Electro-Olfactogram (EOG)

Electro-olfactograms (EOG) are electrical potentials of the olfactory epithelium that occur in response to olfactory stimulation. The EOG represents the sum of generator potentials of ORN. While this response has been used extensively in olfactory research in animals (e.g., [78]), there are only a handful of reports describing the properties of the human EOG. Among other results, EOGs have been used to provide evidence for the dominant role of the central nervous system in olfactory desensitisation [79], for the functional characterisation of the olfactory epithelium [80], the specific topographical distribution of ORN, the expression of ORN in response to exposure to odorants [81], and the characterisation of certain odorants as OR antagonists [82]. However, the EOG so far has not been systematically used in patients with olfactory dysfunction. This is partly due to the topographical specificity of EOG responses, meaning that EOGs to certain odorants may be recorded only at certain epithelial sites. Thus, the subjects' odorous impressions may not always be reflected by the presence of an EOG response. In addition, the presence of an EOG may not always

represent an odorous sensation. Specifically, EOGs can be recorded in subjects with congenital anosmia [83], or EOGs are present at certain threshold levels when the subjects do not yet perceive an odor [84]. Having said this, EOGs may be extremely helpful in terms of elucidating pathological processes at the mucosal level [85].

Chemosensory Event-Related Potentials (CSERP)

Event-related potentials are EEG-derived poly-phasic signals. They are caused by the activation of cortical neurons which generate electro-magnetic fields [86]. As the EEG is a noisy signal which contains activity from many cortical neurons, ERP need to be extracted from this background activity. In other words, the signal-to-noise ratio needs to be improved. The classical approach to this problem involves averaging of individual responses to olfactory stimuli such that random activity would cancel itself out while all non-random activation would remain. In addition, stimuli are typically presented with a steep onset (<20 ms) in an extremely well-controlled, monotonous environment such that stimulus onset synchronizes the activity of as many cortical neurons as possible.

Olfactory ERP (1) are direct correlates of neuronal activation, unlike the signals that are seen, for example, in functional MR imaging, (2) have an extremely high temporal resolution in the range of micro-seconds, (3) allow the investigation of the sequential processing of olfactory information, and (4) can be obtained independently of the subject's response bias, i.e., they allow the investigation of subjects who have difficulties to respond properly (e.g., children, aphasic patients).

Based on a system developed by Kobal [87, 88], odors are applied intranasally. Presentation of odorous stimuli does not simultaneously activate mechano- or thermo-receptors in the nasal mucosa since odor pulses are embedded in a constantly flowing air stream. In contrast to audition or vision, to date no early ERP have been recorded in response to olfactory stimuli (for review see [89]) but only late near-field ERP, i.e. responses from cortical neurons. Peaks of the late near-field ERP fall into two groups. Earlier peaks like N1 encode a greater number of exogenous stimulus characteristics than of later, so-called endogenous components. That is, earlier components encode stimulus intensity or stimulus quality (e.g., "What is the nature of this stimulus?"), whereas later components are more related to the frequency, or the salience of the stimulus ("What is the meaning of this stimulus?") [86, 90–92].

Olfactory ERP are recorded all over the scalp. In terms of the topographic distribution of olfactory ERP, amplitudes exhibit characteristic patterns with a centro-parietal maximum for both amplitudes N1 and P2 [93] (compare [94–96]). Using magneto-encephalographic techniques [97]

Kobal and co-workers conducted a series of experiments which addressed the question of the generation of olfactory ERP. Cortical generators of the responses to trigeminal stimulation with CO_2 were localized in the secondary somato-sensory cortex [98]. Other work indicated [99, 100] that olfactory stimuli activate anterior-central parts of the insula, the para-insular cortex, and the superior temporal sulcus [101].

Clinical testing with chemosensory ERP [89] typically includes the recording of responses to olfactory (e.g., hydrogen sulfide, and phenyl ethyl alcohol) and trigeminal (e.g., CO_2) stimuli. This procedure has been adopted by the working group ''Olfaction and Gustation'' of the German ENT Society [102]. So far, in all investigated anosmic patients, intranasal trigeminal ERPs could be obtained after stimulation with CO_2 – although with significantly smaller amplitudes than in healthy controls [10]. In contrast, no olfactory ERPs could be detected in anosmic patients after stimulation with the odorants hydrogen sulfide and vanillin [103, 104]. Results from ERP investigations provide significant information in the testing of malingering patients. In a recent study, olfactory short-term recognition memory was assessed in patients with unilateral temporal lobe epilepsy and stereotactic electroencephalography (SEEG) recordings prior to surgery. Such recordings from the amygdala indicated the presence of chemosensory evoked potentials [267].

FMRI, PET, and MSI

Recent progress in the field of imaging presented the opportunity to study the functional topography of the human olfactory system in detail [106–108]. There are three major techniques being used: positron emission tomography (PET) [109–111], functional magnetic resonance imaging (FMRI) [112–114], and magnetic source imaging (MSI) based on magneto-encephalography [99, 101]. While bio-magnetic fields directly reflect electrophysiological events, PET and FMRI reflect either changes in blood flow or changes in metabolism which are epiphenomena of neuronal activity. Other major differences between these techniques relate to the temporal and spatial resolution. All three techniques have been used extensively to perform basic research, e.g., on olfactory induced emotions, odor memory, mechanisms of sniffing [109], or age- and sex-related differences in terms of olfactory function [115]. However, in order to become relevant for routine clinical investigations [116], these intriguing techniques await further standardization.

Causes and Symptoms of Smell Disorders

Since olfactory disorders or even total olfactory loss are far less of a handicap than blindness or deafness for the person concerned, there have not

been many attempts to estimate the percentage of people with olfactory problems. Initial surveys were done with questionnaires and rapid smell tests. They revealed that approximately 1–3% of the population has an olfactory problem [117, 118]. Since most of the decrease in olfactory function, like any other sensory function, is due to aging [119], this high incidence was not so astonishing in an aging society with an increasing mean age. In these first attempts to evaluate the epidemiology of olfactory problems, olfactory function was tested rather rudimentarily. Consecutive studies yielded much higher percentages of the population concerned by olfactory dysfunctions [120]. Importantly, olfactory disorders seem to affect more younger people than previously thought and most anosmic or hyposmic subjects either do not realize that they have an olfactory disorder or are simply not sufficiently handicapped to consult a physician [121, 122]. Current consensus is that approximately 5 percent of the general population suffer from anosmia, unrelated to chronic nasal problems. Although the highest incidence is found in the age group above 65 years, anosmia is astonishingly frequent in subjects between 45 and 65 years of age. Results are similar for the distribution of hyposmia, with a mean percentage of approximately 20% of the general population exhibiting mild or moderate smell dysfunction [120–122]. Recent studies underlined the potential alteration of quality of life consecutive to olfactory impairment [123–125]. Although not all patients with olfactory impairment seek medical help due to decreased quality of life, some may experience hazardous events in daily life like eating spoiled food or undetected smoke or gas leaks [126].

Most Common Causes

Several reports have been published on the frequency of the diverse origins of olfactory dysfunction. A recent survey conducted in Austria, Switzerland and Germany [127] revealed that approximately 50% of patients with olfactory dysfunction seen in ENT clinics are due to sinunasal problems. Further frequent causes of olfactory dysfunction are related to traumatic and post-URTI events.

Olfactory Loss Following Infections of the Upper Respiratory Tract (URTI)

As mentioned above, epidemiological questions surrounding olfactory disorders within the general population have only recently been addressed. Previous contributions to the epidemiology of olfactory loss included retrospective analyses of specialized ‘‘Smell and Taste Centers’’ on their respective data bases [128–130]. With some minor differences, these reports show similar findings about the main causes of olfactory disorders. Apart from

posttraumatic and sinunasal origin, post-URTI olfactory loss is among the major causes of olfactory dysfunction.

The patient's history typically starts with a cold, during which he loses his sense of smell. Not particularly bothered during the cold, the patient becomes suspicious about the smell loss when, one or two months after all sinunasal symptoms have abated, normal olfactory function does not return. This is usually the moment when the patient seeks medical advice, either from their general practitioner or from an ENT specialist. Unfortunately, very few studies focused on the epidemiology and prognostic outcome of post-URTI olfactory disorders [131–134]. Currently, no good data indicate which agent in such upper tract respiratory infections (URTI) leads to olfactory lesions. It is not even clear whether toxicity originates from a virus or bacteria, or from the immune response directed against olfactory neuroepithelium. Some authors claim that viral rather than bacterial infections are responsible for olfactory disturbances, and observe a higher incidence of dysosmias after spring and summer URTI [132]. Furthermore, women above 45 years of age seem to be affected at a higher percentage than men [132, 135, 136] – which brings up the potential olfactory protective effect of estrogens [137]. Nevertheless, the effect of estrogen on olfactory function remains an open debate [122, 138].

Clinically, it is important to know, and to inform patients with post-URTI olfactory anosmia or hyposmia, about the possibility of parosmia. Parosmia (also termed troposmia), the unpleasant distortion of odorous sensations, tends to occur two to three month after the URTI, although it appears sometimes to occur directly after the URTI. The real frequency of parosmia is probably higher than previously believed, in particular because patients do not always mention it to their physician [139, 140]. According to our clinical experience, up to 25% of subjects with URTI olfactory dysfunction experience parosmia or phantosmia.

Posttraumatic Olfactory Loss

Posttraumatic olfactory disorders represent approximately 20% of the patients seen in "Smell and Taste Clinics" [124]. Most posttraumatic olfactory dysfunctions are said to occur after occipital trauma, although no clear data on olfactory dysfunctions after lateral impacts exist. The current explanation is that "coup-contre-coup" lesions or tearing of the filae olfactoriae leads to anosmia or hyposmia. Although the entity of posttraumatic olfactory loss had already been described by the end of the last century it has, like most olfactory disorders received little systematic attention [141]. This might also be due to the modest olfactory complaints of severely poly-traumatized patients during their hospitalization. Olfactory loss seems to correlate with the severity of the trauma [142–145], although several

authors pointed out the fact that there is considerable individual variability in terms of the vulnerability of olfactory structures [145, 146]. Thus, even minor trauma can lead to anosmia whereas severe brain injuries may not alter olfaction. Probably, the injured parts of the olfactory system are most often the filae olfactoriae which cross the cribriform plate. However, central structures such as the orbitofrontal cortex and gyrus rectus have also been found to be affected after head trauma [142]. Similar to post-URTI olfactory impairment, these patients are prone to develop parosmia and phantosmia several months after the trauma. Clinical experience shows that most patients with posttraumatic olfactory disturbance typically become aware of the alteration after some delay. It is usually several weeks after the injury, when the major health problems have resolved and patients are discharged from the hospital, that they begin to complain of taste or smell loss. This is probably due to increased attention to olfaction once the general health status improves.

Sinunasal Causes

The third large group of patients who seek counseling for olfactory problems are patients suffering from concomitant sinunasal problems. Approximately 20% of all patients in smell and taste consultations have lost or impaired olfactory function due to a nasal problem [124]. Nasal polyposis has been known for a long time to decrease olfactory abilities due to the mechanical obstruction of nasal cavity restricting the airflow to the olfactory cleft [77, 129, 147–151]. During the last two decades, as a result of better olfactory tests, mild olfactory impairments could also be identified in other groups of patients with sinunasal diseases such as allergic and uncomplicated chronic rhinosinusitis [77, 152, 153]. In contrast to posttraumatic and post-URTI olfactory dysfunctions, these patients rarely exhibit parosmia or phantosmia.

Neurodegenerative Causes

Olfactory loss is common in patients with idiopathic Parkinson's disease (IPD) [154–156]. While a decreased sniff volume seems to contribute to the diminution of olfactory function [157], electrophysiological recordings in response to passive olfactory stimulation clearly established the presence of olfactory impairment in IPD [158, 159]. This olfactory deficit is so reliable that it can be used as a marker of IPD [75]. In other words; if a patient with normal olfactory function presents with IPD symptoms the diagnosis should be re-investigated [160, 161]. It can also be assumed that olfactory loss precedes the onset of motor symptoms by 4–6 years [162, 163] so that IPD may be the reason for "idiopathic olfactory loss" in some patients. Ol-

factory loss is also observed regularly in Alzheimer's disease, but at a much lower frequency and is less pronounced in multiple system atrophy, Huntington's disease, and motor neuron disease [161]. Little or no olfactory deficit is seen in cortico-basal degeneration, progressive supranuclear palsy, or essential tremor [161, 164].

Idiopathic

According to the retrospective epidemiological studies of Taste and Smell Clinics, the diagnosis of idiopathic – unknown – origin of smell impairment accounts for almost 20% of the cases, with the sampling bias discussed above. This seems simply to reflect the poor understanding of factors interfering with olfaction. With further insight and research this percentage should logically decrease. A considerable number of these idiopathic causes might be due to sinunasal disease, post URTI dysosmias following an almost undetected URTI, or neurodegenerative diseases [165].

Less Frequent Causes

Endocrine Diseases

Diabetes is probably one of the best investigated endocrine diseases concerning olfactory disorders [121, 166–168]. Most studies reveal slight olfactory deficiencies in diabetic patients especially at threshold levels indicating a peripheral patho-mechanism compatible with a possible diabetic microangiopathy or peripheral polyneuropathy. However, olfactory impairment in diabetes is relatively mild. Two recent studies conducted with identification tests in large study samples did not find that diabetic patients exhibit a decreased ability to identify odors compared to healthy controls [121, 122]. Several other endocrine diseases such as hypothyroidism [169, 170], adrenocortical insufficiency (Addison's disease) [171] or pseudohypoparathyroidism [172], have been reported to cause olfactory disorders. Many endocrine diseases have been reported to cause hyposmia but rarely lead to anosmia.

Epilepsy

Epileptic patients have been repeatedly tested with all possible olfactory testing modalities, and the general findings were that epileptic patients perform similar to controls with regard to odor thresholds [173, 174]. In contrast, more centrally believed tasks such as odor identification, discrimination or memory tests revealed that epileptic patients have olfactory impairments predominating on the side of the epileptic focus [74, 174–176].

Furthermore, olfactory evoked potentials have been shown to be altered in epileptic patients [177]. This latter study showed increased latencies in olfactory ERP ipsilateral to the epileptic lesion. These latencies were even longer when the lesion was right-sided. Taken together the data indicate that decreased olfactory function in epileptic patients is primarily due to centrally altered olfactory structures whereby the temporal lobe is the main lesion site. Studies on olfactory function in patients with frontal epileptic lesions, however, are lacking.

General Pathologies

Long lists of general pathologies causing olfactory disorders can be found in most reviews and textbooks of smell and taste disorders [172, 178]. Nevertheless, only few studies on specific pathologies have been conducted, sometimes on small sample sizes using unreliable olfactory tests, and sometimes with contradictory outcomes. Besides the above mentioned endocrine diseases, metabolic disorders such as kidney [72] and liver [122, 179, 180] affections have been associated with decreased olfactory function. Olfactory disturbances in those patients are especially interesting, since they are discussed as a potential cause of malnutrition with a more general impact on the patients' health [181].

Post-Surgery/Anesthesia

Anosmia may occur after general anesthesia during the course of surgical interventions not necessarily associated with nasal surgery [122, 182]. Further research should clarify whether surgery under general anesthesia presents a risk of anosmia. For surgical interventions in the sinu-nasal region, anosmia as complication has been estimated to occur in 1% of the cases [183] although this risk has probably been overestimated as indicated by the results of two large studies [184, 185].

Drug-Induced/Toxic

Numerous toxins have been implicated as causes of olfactory disorders [186]. Nevertheless, this information has been mainly accumulated on the basis of case reports. Knowledge about drugs inducing smell and taste disorders is also mainly based on case reports, but several major groups of drugs have been identified as likely to cause problems. Among these, cardiovascular drugs [187], anti-hypertensive drugs [188, 189], and antibiotics [172, 190] are the most frequently mentioned. Usually, the chemosensory side effects disappear when the medication is discontinued.

Congenital

Currently we distinguish between congenital anosmia occurring as an isolated defect or occurring within the context of a syndrome [191]. Isolated congenital anosmia seems to occur more often than previously believed. Apart from the typical patient history of no odor memories, only MR imaging leads to a more definitive diagnosis [192, 193]. In the frontal imaging planes just tangential to the eye bulbs, hypoplastic or aplastic olfactory bulbs can be visualized. This plane also allows an evaluation of the olfactory sulcus which is flattened if the olfactory bulb is absent or aplastic. This is a useful indicator of congenital anosmia, especially since the bulb is not always easy to identify. Among cases of congenital anosmia as part of a syndrome, the Kallmann-Syndrom [194] is the disorder in which it is most frequently encountered. This is an anosmia associated with hypogonadotropic hypogonadism clinically characterized by infertility and anosmia, where infertility can be reversed by substitution of gonadotropins [195].

Congenital anosmia is typically discovered during early puberty. It is a matter of speculation whether olfaction starts to be more important in this period compared to younger years.

Symptoms

Although this distinction is a matter of debate, the discrimination between qualitative and quantitative olfactory disorder have proven helpful in clinical practice. This distinction is mainly based on the patient's history and psychophysical test results.

Quantitative Olfactory Disorders

Normosmia/Hyposmia/Anosmia: Normosmia is the subjectively perceived normal olfactory function, usually defined as the ability to detect the great majority of tested odors in a given olfactory test. Hyposmia means the decrease of this olfactory function and anosmia the total loss of any olfactory function. Beside total anosmia, specific anosmias have been described, where only certain odors are not perceived and most odors are smelt normally [196]. The term functional anosmia was chosen since many subjects with severe olfactory loss appear to be able to still perceive a few single odors. Nevertheless, those rare and weak olfactory impressions are too poor to be of any help to these patients in daily life.

Qualitative Olfactory Disorders

The term ''qualitative olfactory disorder'' reflects the qualitatively changed perception of odorous sensation. They are frequently, but not necessarily, associated with quantitative olfactory disorders.

Parosmia describes the distorted perception of smells in presence of an odor source. In other words, parosmias are triggered by odors. This is a symptom occurring particularly often in post-URTI or posttraumatic olfactory disorders. Mostly odors are distorted into unpleasant odors (although some exceptions seem to exist: TH, personal communication). For example, to parosmic patients, coffee smells like burnt plastic. The exact explanation of the molecular modifications leading to parosmia is as yet unknown. Even the site of parosmia generation (olfactory epithelium, olfactory bulb, or other central-nervous olfactory structures) is not clear. Important clinically, is the observation that most parosmic impressions tend to diminish over months and finally disappear after years.

Phantosmia describes the distorted perception of smells in the absence of an odor source. Most often, phantosmias occur after trauma or URTI and consist of unpleasant odors occurring without being elicited through environmental odor sources. Phantosmias are rarely triggered but menstruation- and stress-related phantosmias have been reported [197]. Similar to parosmia, there is no exact explanation as yet of the molecular modifications leading to phantosmia; also, the site of its generation remains unclear. Phantosmias also have a tendency to disappear over the course of years.

Surgical Risks to the Olfactory System

Endoscopic Sinus/Transnasal Surgery

Chronic rhinosinusitis is the most common chronic inflammatory disease and is frequently associated with impaired sense of smell [198, 199]. When symptomatic patients do not improve on medical treatment, endoscopic sinus surgery (ESS) may be proposed. Nasal polyposis is considered as the ultimate stage of chronic rhinosinusitis for which the mainstay of treatment is medical, but in which ESS plays a part in the majority of cases resistant to medication. Assessment of preoperative olfactory function is important since patients suffering from chronic rhinosinusitis are not always aware of their olfactory dysfunction, and occurrence of olfactory loss or disorders after endonasal surgery has been reported to be as high as 1% [183, 200, 201]. Nevertheless, this may be an overestimation, as recent studies suggested [184, 185]. Regarding bilateral choanal atresia, surgical repair at relatively advanced ages (8–10 years) was not associated with olfactory improvement [202]. This observation suggests that early sensory exposure could be important for the normal development of olfactory function.

In most cases, ESS is associated with significant improvement of rhinosinusitis symptoms and olfactory function [184, 185]. However, absence

or deterioration of olfactory detection thresholds in patients with chronic rhinosinusitis after ESS have been reported [203, 204]. Post-ESS olfactory dysfunction could be due to several mechanisms with persistent mucosal inflammation/edema in the region of the olfactory epithelium being one possible explanation [205]. In addition to post-operative edema, local polyp recurrence, scar tissue, or granulation could also contribute to the absence of improvement in the sense of smell [206].

The olfactory mucosa of patients suffering from long lasting chronic rhinosinusitis could be altered by a variety of toxic inflammatory mediators. In parallel, repetitive URTIs probably alter the neuroepithelium even further [131]. Furthermore, the olfactory epithelium can degenerate in chronic rhinosinusitis and may be replaced by the respiratory epithelium [207]. Furthermore, all surgeons performing ESS should be aware of the risk of iatrogenic injuries of the olfactory epithelium associated with extensive ethmoidectomy [208].

Craniotomy

This paragraph focuses only on the interventions with access to the anterior fossa, since these are most likely to affect olfaction. As stated by Passagia [209], the olfactory structures constitute a natural obstacle to the exploration of the anterior fossa. Therefore, anosmia is a frequent complication of surgical approaches to this region [209]. Nevertheless, techniques have been described which potentially preserve olfaction [210, 211]. One crucial point in preservation of olfactory structures is to respect the blood supply to the olfactory bulb [209]. Whereas leaks of cerebrospinal fluid can be treated without destruction of olfactory structures, oncologic surgery for ethmoidal adenocarcinoma or esthesioneuroblastoma usually leads to anosmia [212, 213]. Meningiomas, which preferably grow in midline structures and especially within the olfactory groove region, are potentially dissectible with preservation of olfaction [209]. However, most reports on olfactory impairment after surgery of the anterior fossa have been conducted on small samples [214] and olfactory function has rarely been measured properly [209]. Welge-Luessen *et al.* [215] have recently published a study focusing on the olfactory outcome after meningeoma surgery. They pointed out that preservation of olfaction ipsilateral to the tumor is extremely difficult. They also showed a correlation between preserved postoperative olfactory function and tumor size. Overall, it seems that preservation of olfactorily eloquent structures might be possible when the tumor size is small. Nevertheless, olfactory function seems to be very vulnerable and seems sometimes altered even though the surgeon did not touch the olfactory structures. This corroborates findings by Delank [146] on posttrau-

matic cadavers, that olfactory tracts and bulbs in certain people are severed even after minor tearing.

Recovery of Smell Disorders

Age-related and congenital anosmia do not usually exhibit recovery. Sinunasal smell disorders are treatable and will be extensively discussed in the next paragraph. Toxic- and drug-induced smell disorders may recover once the drug intake is interrupted [190]. Two of the most important causes of olfactory dysfunction, post-URTI and posttraumatic causes, have received relatively little attention concerning their recovery rate. This is partly due to difficulties obtaining reliable epidemiological data on the real frequency of post-URTI olfactory disorders. Most patients with transitory or recovered post-URTI smell disorders probably do not seek medical help. The following recovery data apply to patients seen in Smell and Taste Clinics and are usually the ones with the most tenacious smell disorders. Several authors described recovery rates for post-URTI and posttraumatic disorders to be highest within the first year [133, 216–218]. According to this literature post-URTI disorders have a slightly better prognosis compared to posttraumatic disorders, mainly because they often cause hyposmia rather than anosmia. Total recovery is observed in approximately 5% of the cases, while up to 60% of all patients experience partial recovery of some olfactory function over the following years. The remaining patients do not have any improvement of chemosensory function. Although olfactory neurons have the ability to regenerate [17, 219], the exact mechanisms favoring such spontaneous recovery are not understood.

It is currently impossible to predict an individual outcome with regard to recovery. Clinically, one has the impression that younger patients might have better recovery rates but no solid data support this hypothesis [136]. For quite a while the presence of parosmia and phantosmia has been interpreted as a sign of plasticity and regeneration within the olfactory system. Recent retrospective data, however, do not support this clinical impression [220]. In contrast to the quantitative olfactory disorders, the qualitative disorders have a far better prognosis of spontaneous disappearance. Parosmias tend to decrease to a bearable level after approximately one year [139]. However, recent work revealed that more than 50% of the parosmias are still present after 2 years [220]. Over time, parosmia seems to lose its devastating effect on quality of life. To summarize, the best current therapeutic attitude towards post-URTI and posttraumatic olfactory disorders is to correctly inform the patient, without removing all hope of recovery, but not promising a quick and complete recovery. The patients should receive satisfactory olfactory testing. Follow-up investigations give both the physician and the patient the possibility to observe improvements.

Treatment of Olfactory Disorders

Surgical

The effect of surgery on quantitative olfactory disorders has already been mentioned above. Beside the routine surgery indicated in advanced and medication resistant nasal polyposis, ESS has also been proposed in very particular cases of qualitative olfactory disorders [221, 222]. Leopold was the first to describe the selective excision of the olfactory epithelium in patients suffering from very handicapping phantosmias. These cases, less than two dozen so far, have been carefully selected, and ESS in phantosmia is far from being routinely indicated. Interestingly, the histological analysis of these epithelia revealed numerous neuromas within the olfactory epithelium. Whether these neuromas are the substrate of the phantosmia is not clear. One report also treated parosmia with selective resection of the olfactory bulb [223] and a recent paper rediscovered the technique used by Leopold to treat parosmia [224]. These latter authors were unable to analyze the excised tissue and apparently ignored the existence of Leopold's work. This underlines the fact that this procedure should be reserved to experienced surgeons and is far from being a routine operation.

Conservative/Medication

Conservative Therapy of SND Related Olfactory Loss

Antibiotics: Putrid acute sinusitis is most frequently the result of infection by streptococcus pneumoniae, haemophilus influenzae, and moraxella catarrhalis which are relatively sensitive to antibiotic therapy. However, in the chronic form of putrid sinusitis, staphylococcus aureus and pseudomonas aeruginosa are much more important. Whenever possible, antibiotic therapy should only be started after the bacteria have been identified and tested for resistance to antibiotics. It is important to note that in chronic putrid sinusitis antibiotic treatment is not always successful.

Steroids: Among many other effects corticosteroids act as anti-inflammatory drugs, the anti-inflammatory effects being produced via a number of different pathways including inhibition of phospholipase A2 through induction of lipocortin [225]. They reduce submucosal edema and mucosal hypersecretion and thereby increase nasal patency. Systemically administered steroids are of help in many sinu-nasal disease (SND) patients [129, 226–228]. For example, Stevens reported that systemic administration of steroids was effective in 12 of 24 patients with SND-related olfactory loss [229]. In addition to the anti-inflammatory activity it has been postulated that corticosteroids directly improve olfactory function [230, 231] by modulating the function of ORN through effects on olfactory Na, K-ATPase [225]. In fact, also based on our own experience, systemic ste-

roids are often helpful even in patients without nasal obstruction due to polyps or obvious inflammatory changes (compare [229, 232]).

Steroids may be administered systemically or topically. With regard to idiopathic olfactory dysfunction, systemic administration is often applied for diagnostic purposes [233]. If systemic steroids improve olfactory function, treatment is typically continued with locally administered steroids. Although systemic steroids are usually more effective than locally administered steroids [230, 234], prescription of systemic steroids over an extended period of time is rarely warranted due to their side effects [150, 232]. While there are no exact recommendations, it is possible, however, to repeatedly administer short courses of systemic steroids with an interval of 6–12 months between courses.

A number of studies indicate the usefulness of topical steroids [153, 226, 228, 235]; however, the role of topical steroids in the treatment of SND related olfactory loss has been questioned [230, 233, 234, 236–239]. So far, no factors predicting a favorable response to topical steroids have been identified. It is not entirely clear why systemic steroids have a higher therapeutic efficacy compared to topical steroids [129, 234]. One reason may relate to the deposition of the spray in the nasal cavity. In fact, it has been shown that only a small amount of nasally applied drugs reaches the olfactory epithelium which is situated in an effectively protected area of the nasal cavity [240–242]. This situation can be slightly improved by the application of sprays in "head-down-forward position" [230, 239].

Other treatments: In addition to the use of steroids there are other therapeutic approaches to restoration of olfactory loss. They include the use of anti-leukotrienes [243], saline lavages [244], or approaches which have received less vigorous scientific investigation, e.g., dietary changes [245], acupuncture [246], anti-allergy immunotherapy [247] and herbal treatments.

Conservative Therapy of Post-URTI/Posttraumatic Olfactory Loss

Post-URTI smell dysfunction seems to be due to an impairment of ORN, both in function and in numbers [248, 249]. While numerous treatments have been tried in post-URTI anosmia (e.g., zinc, vitamin A; see below), no pharmacological therapy has been established so far (see [250–252]). The situation is similar for posttraumatic olfactory loss where therapeutic options are lacking. The absence of conservative treatment for certain forms of olfactory dysfunction is underlined by the fact that, when "parosmia" is present [253, 254], in some patients surgical removal of the olfactory epithelium may be considered as a cure [255].

Having said this, there are still numerous candidates for the pharmacological treatment of olfactory dysfunction, one being *alpha-lipoic acid* (aLA) which is used in the treatment of diabetic neuropathy [256]. The ef-

fect of aLA is well described both in experimental animals and in humans (for review see [257]). It is known to stimulate the expression of nerve growth factor, substance P, and neuropeptide Y [258–260]. It enhances motor nerve conduction velocity as well as microcirculation [261, 262]. Further, due to its potent anti-oxidative effects, aLA also has neuroprotective capabilities indicating that aLA is suited to treat neural damage involving free radicals [263]. Preliminary work has already indicated that it may be useful in post-URTI olfactory loss when administered at a dose of 600 mg/d over a period of 4–7 months [136]. Other encouraging pilot studies have been performed with the NMDA-antagonist *caroverine* [135] administered at a dose of 120 mg/d for 4 weeks. Potential mechanisms for the hypothesized effect included reduced feedback inhibition in the olfactory bulb as a consequence of NMDA-antagonistic actions, or antagonism of an excitotoxic action of glutamate.

Although frequently mentioned as a therapeutic option, studies on *zinc* treatment for olfactory dysfunction have produced negative results [135, 250] (see also [264]). It may, however, be of therapeutic value in patients with severe zinc deficiency, e.g., in hemodialysis. In studies in postmenopausal women *estrogens* have been reported to provide a certain protection against olfactory disturbances [130]. However, as mentioned above, recent studies [138] indicate that estrogens are probably ineffective in the treatment of olfactory loss. Finally, although discussed frequently, the potential therapeutic use of orally administered *vitamin A* [251, 265] is questionable unless appropriate double-blinded studies become available.

A different approach to the treatment of olfactory disorders is the detection and treatment of underlying causes. This approach may also involve the replacement of drugs suspected of affecting the sense of smell [172, 266, 267]. Other possible treatments may include, for example, acupuncture [246].

Acknowledgements

The authors would like to thank Professor Ivan Rodriguez for his helpful comments on the basic olfactory sections (one and two). This work was partly supported by a grant from the Deutsche Forschungsgemeinschaft (DFG HU441/2-1) to TH and by a grant from the Swiss National Fund for Scientific Research FNSRS (n° 3100A0-100621-1) to JSL.

References

1. Dodd J, Castellucci VF (1991) Smell and taste: The chemical senses. Principles of neural sciences. In: Kandel ER, Schwartz JH, Jessel TM (eds) Elsevier Science Publishing Co, New York, p 512–529
2. Turner BH, Mishkin M, Knapp M (1980) Organization of the amygdalope-

tal projections from modality-specific cortical association areas in the monkey. J Comp Neurol 191: 515–543
3. Herz RS (2000) Scents of time. The Sciences 34–39
4. Zatorre RJ *et al* (1992) Functional localization and lateralization of human olfactory cortex. Nature 360: 339–340
5. Doty RL *et al* (1978) Intranasal trigeminal stimulation from odorous volatiles: psychometric responses from anosmic and normal humans. Physiol Behav 20: 175–185
6. Hummel T *et al* (2003) Effects of olfactory function, age, and gender on trigeminally mediated sensations: a study based on the lateralization of chemosensory stimuli. Toxicol Lett 140–141: 273–280
7. Hummel T (2000) Assessment of intranasal trigeminal function. Int J Psychophysiol 36: 147–155
8. Cain WS (1974) Contribution of the trigeminal nerve to perceived odor magnitude. Ann NY Acad Sci 237: 28–34
9. Cain WS, Murphy CL (1980) Interaction between chemoreceptive modalities of odour and irritation. Nature 284: 255–257
10. Hummel T *et al* (1996) Loss of olfactory function leads to a decrease of trigeminal sensitivity. Chem Senses 21: 75–79
11. Gudziol H, Schubert M, Hummel T (2001) Decreased trigeminal sensitivity in anosmia. ORL J Otorhinolaryngol Relat Spec 63: 72–75
12. Krause F (1895) Die Physiologie des Trigeminus nach Untersuchungen an Menschen, bei denen das Ganglion Gasseri entfernt worden ist (Schluss). Munch Med Wochenschr 27: 628–631
13. Ikeda I (1909) On a new seasoning. J Tokyo Chem Soc 30: 820–836
14. Ikeda K (2002) New seasonings. Chem Senses 27: 847–849
15. Chaudhari N, Landin AM, Roper SD (2000) A metabotropic glutamate receptor variant functions as a taste receptor. Nat Neurosci 3: 113–119
16. Witt M, Reutter K, Miller IJ Jr (2003) Morphology of the peripheral taste system. Handbook of olfaction and gustation. In: Doty RL (ed) Marcel Dekker, Inc, New York, p 651–678
17. Beidler LM, Smallman RL (1965) Renewal of cells within taste buds. J Cell Bio 27: 263–272
18. Jacobson L, Trotier D, Døving KB (1998) Anatomical description of a new organ in the nose of domesticated animals by Ludvig Jacobson (1813). Chem Senses 23: 743–754
19. Cuvier G (1811) Rapport – Fait à l'Institut, sur un Mémoire de M. Jacobson, intitulé: Descripion anatomique d'un organe observé dans les mammifères. Annales du Muséum d'Histoire Naturelle Paris. Tome 18: 412–424
20. Karlson P, Lüscher M (1959) ''Pheromones'': a new term for a class of biologically active substances. Nature 183: 55–56
21. Schaal B *et al* (2003) Chemical and behavioural characterization of the rabbit mammary pheromone. Nature 424: 68–72
22. Dorries KM, Adkins-Regan E, Halpern BP (1997) Sensitivity and behavioral responses to the pheromone androstenone are not mediated by the vomeronasal organ in domestic pigs. Brain Behav Evol 49: 53–62

23. Monti-Bloch L, Grosser BI (1991) Effect of putative pheromones on the electrical activity of the human vomeronasal organ and olfactory epithelium. J Steroid Biochem Molec Biol 39: 573–582
24. Witt M *et al* (2002) On the chemosensory nature of the vomeronasal epithelium in adult humans. Histochem Cell Biol 117: 493–509
25. Knecht M *et al* (2001) Frequency and localization of the putative vomeronasal organ in humans in relation to age and gender. Laryngoscope 111: 448–452
26. Witt M *et al* (2000) Characterization of the adult human vomeronasal organ using immunohistochemical and electrophysiological measures. Chem Senses 25: 668
27. Knecht M *et al* (2003) Assessment of olfactory function and androstenone odor thresholds in humans with or without functional occlusion of the vomeronasal duct. Behav Neurosci 117: 1135–1141
28. Stern K, McClintock MK (1998) Regulation of ovulation by human pheromones. Nature 392: 177–179
29. Savic I *et al* (2001) Smelling of odorous sex hormone-like compounds causes sex-differentiated hypothalamic activations in humans. Neuron 31: 661–668
30. Rodriguez I *et al* (2000) A putative pheromone receptor gene expressed in human olfactory mucosa. Nat Genet 26: 18–19
31. Mozell MM (1964) Evidence for sorption as a mechanism of the olfactory analysis of vapours. Nature 203: 1181–1182
32. Mozell MM, Jagodowicz M (1973) Chromatographic separation of odorants by the nose: retention times measured across in vivo olfactory mucosa. Science 181: 1247–1249
33. Sobel N *et al* (1999) The world smells different to each nostril. Nature 402: 35
34. Amoore JE (1967) Specific anosmia: a clue to the olfactory code. Nature 214: 1095–1098
35. Henning H (1916) Der Geruch. Johann Ambrosius Barth, Leipzig
36. Dyson GM (1938) The scientific basis of odour. Chem Ind 57: 647–651
37. Turin L (1996) A spectroscopic mechanism for primary olfactory reception. Chem Senses 21: 773–791
38. Keller A, Vosshall LB (2004) A psychophysical test of the vibration theory of olfaction. Nat Neurosci 7: 337–338
39. Buck L, Axel R (1991) A novel multigene family may encode odorant receptors: a molecular basis for odor recognition. Cell 65: 175–187
40. Gilad Y *et al* (2003) Human specific loss of olfactory receptor genes. Proc Natl Acad Sci USA 28: 28
41. Menashe I *et al* (2003) Different noses for different people. Nat Genet 34: 143–144
42. Gilad Y *et al* (2003) Natural selection on the olfactory receptor gene family in humans and chimpanzees. Am J Hum Genet 73: 489–501
43. Gilad Y *et al* (2004) Loss of olfactory receptor genes coincides with the acquisition of full trichromatic vision in primates. PLoS Biol 2: E5

44. Man O, Gilad Y, Lancet D (2004) Prediction of the odorant binding site of olfactory receptor proteins by human-mouse comparisons. Protein Sci 13: 240–254
45. Strotmann J *et al* (1994) Olfactory neurones expressing distinct odorant receptor subtypes are spatially segregated in the nasal neuroepithelium. Cell Tissue Res 276: 429–438
46. Vassar R, Ngai J, Axel R (1993) Spatial segregation of odorant receptor expression in the mammalian olfactory epithelium. Cell 74: 309–318
47. Ressler KJ, Sullivan SL, Buck LB (1993) A zonal organization of odorant receptor gene expression in the olfactory epithelium. Cell 73: 597–609
48. Vassar R *et al* (1994) Topographic organization of sensory projections to the olfactory bulb. Cell 79: 981–991
49. Nef P *et al* (1992) Spatial pattern of receptor expression in the olfactory epithelium. Proc Natl Acad Sci USA 89: 8948–8952
50. Mombaerts P *et al* (1996) Visualizing an olfactory sensory map. Cell 87: 675–686
51. Zhao H *et al* (1998) Functional expression of a mammalian odorant receptor. Science 279: 237–242
52. Araneda RC, Kini AD, Firestein S (2000) The molecular receptive range of an odorant receptor. Nat Neurosci 3: 1248–1255
53. Uchida N *et al* (2000) Odor maps in the mammalian olfactory bulb: domain organization and odorant structural features. Nat Neurosci 3: 1035–1043
54. Malnic B *et al* (1999) Combinatorial receptor codes for odors. Cell 96: 713–723
55. Landis BN *et al* (2003) Ratings of overall olfactory function. Chem Senses 28: 691–694
56. Hummel T *et al* (2001) Screening of olfactory function with a four-minute odor identification test: reliability, normative data, and investigations in patients with olfactory loss. Ann Otol Rhinol Laryngol 110: 976–981
57. Doty RL, Shaman P, Dann M (1984) Development of the University of Pennsylvania Smell Identification Test: a standardized microencapsulated test of olfactory function. Physiol Behav 32: 489–502
58. Cain WS *et al* (1988) Evaluation of olfactory dysfunction in the Connecticut Chemosensory Clinical Research Center. Laryngoscope 98: 83–88
59. Doty RL *et al* (1984) University of Pennsylvania Smell Identification Test: a rapid quantitative olfactory function test for the clinic. Laryngoscope 94: 176–178
60. Kobal G *et al* (1996) ''Sniffin' sticks'': screening of olfactory performance. Rhinology 34: 222–226
61. Hummel T *et al* (1997) 'Sniffin' sticks': olfactory performance assessed by the combined testing of odor identification, odor discrimination and olfactory threshold. Chem Senses 22: 39–52
62. Kobal G *et al* (2000) Multicenter investigation of 1,036 subjects using a standardized method for the assessment of olfactory function combining tests of odor identification, odor discrimination, and olfactory thresholds. Eur Arch Otorhinolaryngol 257: 205–211

63. Kondo H *et al* (1998) A study of the relationship between the T&T olfactometer and the University of Pennsylvania Smell Identification Test in a Japanese population. Am J Rhinol 12: 353–358
64. Lecanu JB *et al* (2002) Valeurs normatives du test olfactométrique Biolfa. Ann Otolaryngol Chir Cervicofac 119: 164–169
65. Briner HR, Simmen D (1999) Smell diskettes as screening test of olfaction. Rhinology 37: 145–148
66. Ho WK *et al* (2002) Change in olfaction after radiotherapy for nasopharyngeal cancer – a prospective study. Am J Otolaryngol 23: 209–214
67. Lotsch J, Lange C, Hummel T (2004) A simple and reliable method for clinical assessment of odor thresholds. Chem Senses 29: 311–317
68. Linschoten MR *et al* (2001) Fast and accurate measurement of taste and smell thresholds using a maximum-likelihood adaptive staircase procedure. Percept Psychophys 63: 1330–1347
69. Hawkes CH, Shephard BC (1993) Selective anosmia in Parkinson's disease? Lancet 341: 435–436
70. Koss E *et al* (1987) Olfactory detection and recognition in Alzheimer's disease. Lancet 1: 622
71. Koss E *et al* (1988) Olfactory detection and identification performance are dissociated in early Alzheimer's disease. Neurology 38: 1228–1232
72. Frasnelli JA *et al* (2002) Olfactory function in chronic renal failure. Am J Rhinol 16: 275–279
73. Hornung DE *et al* (1998) The olfactory loss that accompanies an HIV infection. Physiol Behav 15: 549–556
74. Jones-Gotman M, Zatorre RJ (1988) Olfactory identification deficits in patients with focal cerebral excision. Neuropsychologia 26: 387–400
75. Mesholam RI *et al* (1998) Olfaction in neurodegenerative disease: a meta-analysis of olfactory functioning in Alzheimer's and Parkinson's diseases. Arch Neurol 55: 84–90
76. Daum RF *et al* (2000) Riechprüfung mit "Sniffin' Sticks" zur klinischen Diagnostik des Morbus Parkinson. Nervenarzt 71: 643–650
77. Klimek L *et al* (1998) Lateralized and bilateral olfactory function in patients with chronic sinusitis compared with healthy control subjects. Laryngoscope 108: 111–114
78. Ottoson D (1956) Analysis of the electrical activity of the olfactory epithelium. Acta Physiol Scand 35: 1–83
79. Hummel T, Knecht M, Kobal G (1996) Peripherally obtained electrophysiological responses to olfactory stimulation in man: electro-olfactograms exhibit a smaller degree of desensitization compared with subjective intensity estimates. Brain Res 717: 160–164
80. Leopold DA *et al* (2000) Anterior distribution of human olfactory epithelium. Laryngoscope 110: 417–421
81. Wang L, Chen L, Jacob T (2004) Evidence for peripheral plasticity in human odour response. J Physiol 554: 236–244
82. Spehr M *et al* (2004) The HOR17-4 signalling system – one receptor, dual capacity. Chem Sens (in press)

83. Rawson NE *et al* (1995) Functionally mature olfactory receptor neurons from two anosmic patients with Kallmann syndrome. Brain Res 681: 58–64
84. Hummel T, Mojet J, Kobal G (1997) Electro-olfactograms are present when odorous stimuli have not been perceived. Chem Senses 22: 196
85. Knecht M, Hummel T (2004) Recording of the human electro-olfactogram. Physiol Behav 83: 13–19
86. Picton TW, Hillyard SA (1988) Endogenous event-related potentials. EEG-handbook, revised series, vol. 3. In: Picton TW (ed) Elsevier, Amsterdam, p 361–426
87. Kobal G, Plattig KH (1978) Methodische Anmerkungen zur Gewinnung olfaktorischer EEG-Antworten des wachen Menschen (objektive Olfaktometrie). Z EEG-EMG 9: 135–145
88. Kobal G (1981) Elektrophysiologische Untersuchungen des menschlichen Geruchssinns. Thieme Verlag, Stuttgart
89. Kobal G, Hummel T (1991) Olfactory evoked potentials in humans. Smell and taste in health and disease. In: Getchell TV *et al* (eds) Raven Press, New York, p 255–275
90. Pause BM *et al* (1996) The nature of the late positive complex within the olfactory event-related potential. Psychophysiology 33: 168–172
91. Krauel K *et al* (1998) Attentional modulation of central odor processing. Chem Senses 23: 423–432
92. Donchin E *et al* (1986) Cognitive psychophysiology and human information processing. Psychophysiology: systems, processes and applications. In: Coles MGH, Donchin E, Porges SW (eds) Guilford Press, New York
93. Kobal G, Hummel T, Van Toller S (1992) Differences in chemosensory evoked potentials to olfactory and somatosensory chemical stimuli presented to left and right nostrils. Chem Senses 17: 233–244
94. Pause B, Sojka B, Ferstl R (1996) The latency but not the amplitude of the olfactory event-related potential (OERP) varies with the odor concentration. Chem Senses 21: 485
95. Murphy C *et al* (1998) Age effects on central nervous system activity reflected in the olfactory event-related potential. Evidence for decline in middle age. Ann NY Acad Sci 855: 598–607
96. Lorig TS *et al* (1996) The effects of active and passive stimulation on chemosensory event-related potentials. Int J Psychophysiol 23: 199–205
97. Williamson SJ, Kaufman L (1987) Analysis of neuromagnetic signals. Handbook of electroencephalography and clinical neurophysiologgy, volume 1, Methods of brain electrical and magnetical signals. In: Gevins AS, Rèmond AA (eds) Elsevier, Amsterdam, p 405–448
98. Huttunen J *et al* (1986) Cortical responses to painful CO2-stimulation of nasal mucosa: a magnetencephalographic study in man. Electroenceph Clin Neurophysiol 64: 347–349
99. Kettenmann B *et al* (1996) Magnetoencephalographical recordings: separation of cortical responses to different chemical stimulation in man. Funct Neurosci [EEG Suppl] 46: 287–290

100. Kettenmann B *et al* (1997) Multiple olfactory activity in the human neocortex identified by magnetic source imaging. Chem Senses 22: 493–502
101. Ayabe-Kanamura S *et al* (1997) Measurement of olfactory evoked magnetic fields by a 64-channel whole-head SQUID system. Chem Senses 22: 214–215
102. Welge-Lussen A (1999) Chemosensorisch evozierte Potentiale – Anwendung und Bedeutung im klinischen Alltag. HNO 47: 453–455
103. Kobal G, Hummel T (1998) Olfactory and intranasal trigeminal event-related potentials in anosmic patients. Laryngoscope 108: 1033–1035
104. Peters JM *et al* (2003) Olfactory function in mild cognitive impairment and Alzheimer's disease: an investigation using psychophysical and electrophysiological techniques. Am J Psychiatry 160: 1995–2002
105. Hudry J *et al* (2003) Olfactory short-term memory and related amygdala recordings in patients with temporal lobe epilepsy. Brain 126: 1851–1863
106. Savic I (2002) Imaging of brain activation by odorants in humans. Curr Opin Neurobiol 12: 455–461
107. Zald DH, Pardo JV (2000) Functional neuroimaging of the olfactory system in humans. Int J Psychophysiol 36: 165–181
108. Kettenmann B, Hummel T, Kobal G (2001) Functional imaging of olfactory activation in the human brain. Methods and frontiers in chemosensory research. In: Simon SA, Nicolelis MAL (eds) CRC Press, Baco Raton, Florida, USA, p 477–506
109. Small DM *et al* (1997) Flavor processing: more than the sum of its parts. Neuroreport 8: 3913–3917
110. Kareken DA *et al* (2004) Olfactory system activation from sniffing: effects in piriform and orbitofrontal cortex. Neuroimage 22: 456–465
111. Savic I, Berglund H (2004) Passive perception of odors and semantic circuits. Hum Brain Mapp 21: 271–278
112. Sobel N *et al* (2000) Time course of odorant-induced activation in the human primary olfactory cortex. J Neurophysiol 83: 537–551
113. Poellinger A *et al* (2001) Activation and habituation in olfaction – an fMRI study. Neuroimage 13: 547–560
114. Anderson AK *et al* (2003) Dissociated neural representations of intensity and valence in human olfaction. Nat Neurosci 6: 196–202
115. Yousem DM *et al* (1999) The effect of age on odor-stimulated functional MR imaging. Am J Neuroradiol 20: 600–608
116. Henkin RI, Levy LM, Lin CS (2000) Taste and smell phantoms revealed by brain functional MRI (fMRI). J Comput Assist Tomogr 24: 106–123
117. Wysocki CJ, Gilbert AN (1989) National Geographic Smell Survey: effects of age are heterogenous. Ann NY Acad Sci 561: 12–28
118. Hoffman HJ, Ishii EK, MacTurk RH (1998) Age-related changes in the prevalence of smell/taste problems among the United States adult population. Results of the 1994 disability supplement to the National Health Interview Survey (NHIS). Ann NY Acad Sci 855: 716–722
119. Doty RL *et al* (1984) Smell identification ability: changes with age. Science 226: 1441–1443

120. Murphy C *et al* (2002) Prevalence of olfactory impairment in older adults. JAMA 288: 2307–2312
121. Brämerson A *et al* (2004) Prevalence of olfactory dysfunction: the skovde population-based study. Laryngoscope 114: 733–737
122. Landis BN, Konnerth CG, Hummel T (2004) A study on the frequency of olfactory dysfunction. Laryngoscope 114: 1764–1769
123. Miwa T *et al* (2001) Impact of olfactory impairment on quality of life and disability. Arch Otolaryngol Head Neck Surg 127: 497–503
124. Temmel AF *et al* (2002) Characteristics of olfactory disorders in relation to major causes of olfactory loss. Arch Otolaryngol Head Neck Surg 128: 635–641
125. Hummel T, Nordin S (2004) Olfactory disorders and their consequences for quality of life – A review. Acta Oto-Laryngologica, in press
126. Santos DV *et al* (2004) Hazardous events associated with impaired olfactory function. Arch Otolaryngol Head Neck Surg 130: 317–319
127. Damm M *et al* (2004) Riechstörungen – Epidemiologie und Therapie in Deutschland, Österreich und der Schweiz. HNO 52: 112–120
128. Quint C *et al* (2001) Patterns of non-conductive olfactory disorders in eastern Austria: a study of 120 patients from the Department of Otorhinolaryngology at the University of Vienna. Wien Klin Wochenschr 113: 52–57
129. Seiden AM, Duncan HJ (2001) The diagnosis of a conductive olfactory loss. Laryngoscope 111: 9–14
130. Deems DA *et al* (1991) Smell and taste disorders: a study of 750 patients from the University of Pennsylvania Smell and Taste Center. Arch Otorhinolaryngol Head Neck Surg 117: 519–528
131. Jafek BW *et al* (1990) Postviral olfactory dysfunction. Am J Rhinol 4: 91–100
132. Sugiura M *et al* (1998) An epidemiological study of postviral olfactory disorder. Acta Otolaryngol [Suppl] 538: 191–196
133. Faulcon P *et al* (1996) Anosmie secondaire à une rhinite aiguë: sémiologie et évolution à propos d'une série de 118 patients. Ann Otolaryngol Chir Cervicofac 116: 351–357
134. Duncan HJ, Seiden AM (1995) Long-term follow-up of olfactory loss secondary to head trauma and upper respiratory tract infection. Arch Otolaryngol Head Neck Surg 121: 1183–1187
135. Quint C *et al* (2002) The quinoxaline derivative caroverine in the treatment of sensorineural smell disorders: a proof-of-concept study. Acta Otolaryngol 122: 877–881
136. Hummel T, Heilmann S, Huttenbrink KB (2002) Lipoic acid in the treatment of smell dysfunction following viral infection of the upper respiratory tract. Laryngoscope 112: 2076–2080
137. Dhong HJ, Chung SK, Doty RL (1999) Estrogen protects against 3-methylindole-induced olfactory loss. Brain Res 824: 312–315
138. Hughes LF *et al* (2002) Effects of hormone replacement therapy on olfac4-tory sensitivity: cross-sectional and longitudinal studies. Climacteric 5: 140–150

139. Portier F *et al* (2000) Sémiologie, étiologie et évolution des parosmies: à propos de 84 cas. Ann Otolaryngol Chir Cervicofac 117: 12–18
140. Frasnelli J, Hummel T (2004) Olfactory dysfunction and daily life. Eur Arch Otorhinolaryngol 5: 5
141. Legg JW (1873) A case of anosmia following a blow. Lancet 2: 659–660
142. Yousem DM *et al* (1999) Posttraumatic smell loss: relationship of psychophysical tests and volumes of the olfactory bulbs and tracts and the temporal lobes. Acad Radiol 6: 264–272
143. Zusho H (1982) Posttraumatic anosmia. Arch Otolaryngol 108: 90–92
144. Frank Greiffenstein M, John Baker W, Gola T (2002) Brief report: anosmia and remote outcome in closed head injury. J Clin Exp Neuropsychol 24: 705–709
145. Sumner D (1964) Post-traumatic anosmia. Brain 87: 107–120
146. Delank KW, Fechner G (1996) Zur Pathophysiologie der posttraumatischen Riechstörungen. Laryngorhinootologie 75: 154–159
147. Fein BT, Kamin PB, Fein NN (1966) The loss of sense of smell in nasal allergy. Ann Allergy 24: 278–283
148. Doty RL (1997) Olfaction. Nasal Polyposis – An inflammatory disease and its treatement. In: Mygind N, Lildholdt T (eds) Munksgaard, Copenhagen, p 153–159
149. Landis BN *et al* (2003) Retronasal olfactory function in nasal polyposis. Laryngoscope 113: 1993–1997
150. Hotchkiss WT (1956) Influence of Prednisone on nasal polyposis with anosmia. Arch Otolaryngol 64: 478–479
151. Klimek L *et al* (1997) Olfactory function after microscopic endonasal surgery in patients with nasal polyps. Am J Rhinol 11: 251–255
152. Apter AJ *et al* (1995) Allergic rhinitis and olfactory loss. Ann Allergy Asthma Immunol 75: 311–316
153. Stuck BA *et al* (2003) Mometasone furoate nasal spray improves olfactory performance in seasonal allergic rhinitis. Allergy 58: 1195
154. Ansari KA, Johnson A (1975) Olfactory function in patients with Parkinson's disease. J Chron Dis 28: 493–497
155. Ward CD, Hess WA, Calne DB (1983) Olfactory impairment in Parkinson's disease. Neurology 33: 943–946
156. Doty RL, Deems D, Steller S (1988) Olfactory dysfunction in Parkinson's disease: A general deficit unrelated to neurologic signs, disease stage, or disease duration. Neurology 38: 1237–1244
157. Sobel N *et al* (2001) An impairment in sniffing contributes to the olfactory impairment in Parkinson's disease. Proc Natl Acad Sci USA 98: 4154–4159
158. Barz S *et al* (1997) Chemosensory event-related potentials in response to trigeminal and olfactory stimulation in idiopathic Parkinson's disease. Neurology 49: 1424–1431
159. Hawkes CH, Shephard BC (1998) Olfactory evoked responses and identification tests in neurological disease. Ann NY Acad Sci 855: 608–615
160. Hawkes CH, Shephard BC, Daniel SE (1999) Is Parkinson's disease a primary olfactory disorder? QJM 92: 473–480

161. Hawkes C (2003) Olfaction in neurodegenerative disorder. Mov Disord 18: 364–372
162. Berendse HW *et al* (2001) Subclinical dopaminergic dysfunction in asymptomatic Parkinson's disease patients' relatives with a decreased sense of smell. Ann Neurol 50: 34–41
163. Sommer U *et al* (2004) Detection of presymptomatic Parkinson's disease: combination of olfactory tests, transcranial sonography, and 123 I-FP-CIT-SPECT. Mov Disord, in press
164. Müller A *et al* (2002) Olfactory function in idiopathic Parkinson's disease (IPD): results from cross-sectional studies in IPD patients and long-term follow-up of de-novo IPD patients. J Neural Transm 109: 805–811
165. Heilmann S, Huettenbrink KB, Hummel T (2004) Local and systemic administration of corticosteroids in the treatment of olfactory loss. Am J Rhinol 18: 29–33
166. Jorgensen MB, Buch NH (1961) Studies on the sense of smell and taste in diabetics. Arch Otolaryngol 53: 539–545
167. Weinstock RS, Wright HN, Smith DU (1993) Olfactory dysfunction in diabetes mellitus. Physiol Behav 53: 17–21
168. Le Floch JP *et al* (1993) Smell dysfunction and related factors in diabetic patients. Diabetes Care 16: 934–937
169. Doty RL (1986) Gender and endocrine-related influences on human olfactory perception. Clinical Measurement of Taste and Smell. In: Meiselman R (ed) MacMillan, New York, p 377–413
170. McConnell RJ *et al* (1975) Defects of taste and smell in patients with hypothyroidism. Am J Med 59: 354–364
171. Henkin RI, Bartter FC (1966) Studies on olfactory thresholds in normal man and in patients with adrenal cortical insufficiency: the role of adrenal cortical steroids and of serum sodium concentration. J Clin Invest 45: 1631–1639
172. Schiffman SS (1983) Taste and smell in disease (first of two parts). N Engl J Med 308: 1275–1279
173. Campanella G, Filla A, De Michele G (1978) Smell and taste acuity in epileptic syndromes. Eur Neurol 17: 136–141
174. Eskenazi B *et al* (1986) Odor perception in temporal lobe epilepsy patients with and without temporal lobectomy. Neuropsychologia p 553–562
175. Jones-Gotman M *et al* (1997) Contribution of medial versus lateral temporal-lobe structures to human odour identification. Brain 120: 1845–1856
176. Kohler CG *et al* (2001) Olfactory dysfunction in schizophrenia and temporal lobe epilepsy. Neuropsychiatry Neuropsychol Behav Neurol 14: 83–88
177. Hummel T *et al* (1995) Chemosensory event-related potentials in patients with temporal lobe epilepsy. Epilepsia 36: 79–85
178. Schiffman SS (1983) Taste and smell in disease (second of two parts). N Engl J Med 308: 1337–1343
179. Henkin RI, Smith FR (1971) Hyposmia in acute viral hepatitis. Lancet 1: 823–826

180. Kleinschmidt EG, Kramp B, Schwager A (1976) Functional study on the sense of smell in patients with chronic liver disease. Z Gesamte Inn Med 31: 853–856
181. Reaich D (1997) Odour perception in chronic renal disease. Lancet 350: 1191
182. Adelman BT (1995) Altered taste and smell after anesthesia: cause and effect? Anesthesiology 83: 647–649
183. Kimmelman CP (1994) The risk to olfaction from nasal surgery. Laryngoscope 104: 981–988
184. Damm M *et al* (2003) Olfactory changes at threshold and suprathreshold levels following septoplasty with partial inferior turbinectomy. Ann Otol Rhinol Laryngol 112: 91–97
185. Briner HR, Simmen D, Jones N (2003) Impaired sense of smell in patients with nasal surgery. Clin Otolaryngol 28: 417–419
186. Hastings L, Miller ML (1997) Olfactory loss to toxic exposure. Taste and smell disorders. In: Seiden AM (ed) Thieme, New York, p 88–106
187. Doty RL *et al* (2003) Influences of antihypertensive and antihyperlipidemic drugs on the senses of taste and smell: a review. J Hypertens 21: 1805–1813
188. Kharoubi S (2003) Anosmie toxi-médicamenteuse à la nifédipine. Presse Med 32: 1269–1272
189. Levenson JL, Kennedy K (1985) Dysosmia, dysgeusia, and nifedipine. Ann Intern Med 102: 135–136
190. Welge-Luessen A, Wolfensberger M (2003) Reversible anosmia after amikacin therapy. Arch Otolaryngol Head Neck Surg 129: 1331–1333
191. Jafek BW *et al* (1990) Congenital anosmia. Ear Nose Throat J 69: 331–337
192. Abolmaali ND *et al* (2002) MR evaluation in patients with isolated anosmia since birth or early childhood. AJNR Am J Neuroradiol 23: 157–164
193. Yousem DM *et al* (1996) MR evaluation of patients with congenital hyposmia or anosmia. Am J Radiol 166: 439–443
194. Kallmann FJ, Schoenfeld WA, Barrera SE (1944) The genetic aspects of primary eunuchoidism. Am J Ment Defic 48: 203–236
195. Wustenberg EG *et al* (2001) Normosmie bei Kallmann Syndrom – Ein Fallbericht. Laryngorhinootologie 80: 85–89
196. Amoore JE (1991) Specific anosmias. Smell and taste in health and disease. In: Getchell TV *et al* (eds) Raven Press, New York, p 655–664
197. Kaufman MD, Lassiter KR, Shenoy BV (1988) Paroxysmal unilateral dysosmia: a cured patient. Ann Neurol 24: 450–451
198. Lanza DC, Kennedy DW (1997) Adult rhinosinusitis defined. Otolaryngol Head Neck Surg 117: S1–7
199. Togias A (1999) Mechanisms of nose-lung interaction. Allergy 54[Suppl] 57: 94–105
200. Stevens CN, Stevens MH (1985) Quantitative effects of nasal surgery on olfaction. Am J Otolaryngol 6: 264–267
201. Haddad FS *et al* (1985) Intracranial complications of submucous resection of the nasal septum. Am J Otolaryngol 6: 443–447
202. Gross-Isseroff R *et al* (1989) Olfactory function following late repair of choanal atresia. Laryngoscope 99: 1165–1166

203. Hosemann W *et al* (1993) Olfaction after endoscopic endonasal ethmoidectomy. Am J Rhinology 7: 11–15
204. Rowe-Jones JM, Mackay IS (1997) A prospective study of olfaction following endoscopic sinus surgery with adjuvant medical treatment. Clin Otolaryngol 22: 377–381
205. Downey LL, Jacobs JB, Lebowitz RA (1996) Anosmia and chronic sinus disease. Otolaryngol Head Neck Surg 115: 24–28
206. Min YG *et al* (1995) Recovery of nasal physiology after functional endoscopic sinus surgery: olfaction and mucociliary transport. ORL J Otorhinolaryngol Relat Spec 57: 264–268
207. Lee SH *et al* (2000) Olfactory mucosal findings in patients with persistent anosmia after endoscopic sinus surgery. Ann Otol Rhinol Laryngol 109: 720–725
208. Jafek BW, Murrow B, Johnson EW (1994) Olfaction and endoscopic sinus surgery. Ear Nose Throat J 73: 548–552
209. Passagia JG *et al* (1999) Surgical approaches to the anterior fossa, and preservation of olfaction. Adv Tech Stand Neurosurg 25: 195–241
210. Spetzler RF *et al* (1993) Preservation of olfaction in anterior craniofacial approaches. J Neurosurg 79: 48–52
211. Suzuki J, Yoshimoto T, Mizoi K (1981) Preservation of the olfactory tract in bifrontal craniotomy for anterior communicating artery aneurysms, and the functional prognosis. J Neurosurg 54: 342–345
212. Dulguerov P, Allal AS, Calcaterra TC (2001) Esthesioneuroblastoma: a meta-analysis and review. Lancet Oncol 2: 683–690
213. Dias FL *et al* (2003) Patterns of failure and outcome in esthesioneuroblastoma. Arch Otolaryngol Head Neck Surg 129: 1186–1192
214. Bakay L, Cares HL (1972) Olfactory meningiomas. Report on a series of twenty-five cases. Acta Neurochir (Wien) 26: 1–12
215. Welge-Luessen A *et al* (2001) Olfactory function in patients with olfactory groove meningioma. J Neurol Neurosurg Psychiatry 70: 218–221
216. Bonfils P, Corre FL, Biacabe B (1999) Sémiologie et étiologie des anosmies: à propos de 306 patients. Ann Otolaryngol Chir Cervicofac 116: 198–206
217. Costanzo RM, DiNardo LJ, Zasler ND (1995) Head injury and olfaction. Handbook of Olfaction and Gustation. In: Doty RL (ed) Marcel Dekker, New York, p 493–502
218. Murphy C, Doty RL, Duncan HJ (2003) Clinical disorders of olfaction. Handbook of olfaction and gustation. In: Doty RL (ed) Marcel Dekker, New York, p 461–478
219. Gradziadei PPC, Monti-Graziadei GA (1978) Continuous nerve cell renewal in the olfactory system. Handbook of sensory physiology, vol. IX. In: Jacobson M (ed) Springer, Wien, New York, p 55
220. Hummel T *et al* (2004) Qualitative olfactory dysfunction: frequency and prognostic significance. Abstractbook AchemS p 89 (Poster 339)
221. Leopold DA *et al* (1991) Successful treatment of phantosmia with preservation of olfaction. Arch Otolaryngol Head Neck Surg 117: 1402–1406

222. Leopold DA, Loehrl TA, Schwob JE (2002) Long-term follow-up of surgically treated phantosmia. Arch Otolaryngol Head Neck Surg 128: 642–647
223. Markert JM, Hartshorn DO, Farhat SM (1993) Paroxysmal bilateral dysosmia treated by resection of the olfactory bulbs. Surg Neurol 40: 160–163
224. Bonfils P *et al* (2004) Traitement chirurgical d'une parosmie post-rhinitique. Ann Otolaryngol Chir Cervicofac 121: 47–50
225. Fong KJ *et al* (1999) Olfactory secretion and sodium, potassium-adenosine triphosphatase: regulation by corticosteroids. Laryngoscope 109: 383–388
226. Golding-Wood DG *et al* (1996) The treatment of hyposmia with intranasal steroids. J Laryngol Otol 110: 132–135
227. Tos M *et al* (1998) Efficacy of an aqueous and a powder formulation of nasal budesonide compared in patients with nasal polyps. Am J Rhinol 12: 183–189
228. Mott AE *et al* (1997) Topical corticosteroid treatment of anosmia associated with nasal and sinus disease. Arch Otolaryngol Head Neck Surg 123: 367–372
229. Stevens MH (2001) Steroid-dependent anosmia. Laryngoscope 111: 200–203
230. Mott AE, Leopold DA (1991) Disorders in taste and smell. Med Clin North Am 75: 1321–1353
231. Klimek L, Eggers G (1997) Olfactory dysfunction in allergic rhinitis is related to nasal eosinophilc inflammation. J Allergy Clin Immunol 100: 159–164
232. Jafek BW *et al* (1987) Steroid-dependent anosmia. Arch Otolaryngol Head Neck Surg 113: 547–549
233. Heilmann S, Hüttenbrink KB, Hummel T (2004) Local and systemic administration of corticosteroids in the treatment of olfactory loss. Am J Rhinol 18: 29–33
234. Ikeda K *et al* (1995) Efficacy of systemic corticosteroid treatment for anosmia with nasal and paranasal sinus disease. Rhinology 33: 162–165
235. Meltzer EO *et al* (1998) Subjecive and objective assessments in patients with seasonal allergic rhinitis: effects of therapy with mometasone furoate nasal spray. J Allergy Clin Immunol 102: 39–49
236. El Naggar M *et al* (1995) Effect of Beconase nasal spray on olfactory function in post-nasal polypectomy patients: a prospective controlled trial. J Otolaryngol 109: 941–944
237. Blomqvist EH *et al* (2003) Placebo-controlled, randomized, double-blind study evaluating the efficacy of fluticasone propionate nasal spray for the treatment of patients with hyposmia/anosmia. Acta Otolaryngol 123: 862–868
238. Heilmann S *et al* (2004) Untersuchung der Wirksamkeit von systemischen bzw. topischen Corticoiden und Vitamin B bei Riechstörungen. Laryngo-Rhino-Otol 86: 1–6
239. Benninger MS *et al* (2004) Techniques of intranasal steroid use. Otolaryngol Head Neck Surg 130: 5–24
240. Hardy JG, Lee SW, Wilson CG (1985) Intranasal drug delivery by spray and drops. J Pharmacy Pharmacol 37: 294–297

241. Newman SP, Moren F, Clarke SW (1987) Deposition pattern from a nasal pump spray. Rhinology 25: 77–82
242. McGarry GW, Swan IR (1992) Endoscopic photographic comparison of drug delivery by ear-drops and by aerosol spray. Clinical Otolaryngology 17: 359–360
243. Parnes SM, Chuma AV (2000) Acute effects of antileukotrienes on sinonasal polyposis and sinusitis. Ear Nose Throat J 79: 18–20, 24–25
244. Bachmann G, Hommel G, Michel O (2000) Effect of irrigation of the nose with isotonic salt solution on adult patients with chronic paranasal sinus disease. Eur Arch Otorhinolaryngol 257: 537–541
245. Rundles W (1946) Prognosis in the neurologic manifestations of pernicious anemia. Blood 1: 209–219
246. Tanaka O, Mukaino Y (1999) The effect of auricular acupuncture on olfactory acuity. Am J Chin Med 27: 19–24
247. Stevenson DD *et al* (1996) Aspirin desensitization treatment of aspirin-sensitive patients with rhinosinusitis-asthma: long-term outcomes. J Allergy Clin Immunol 98: 751–758
248. Moran DT *et al* (1992) Ultrastructural histopathology of human olfactory dysfunction. Microsc Res Tech 23: 103–110
249. Yamagishi M, Fujiwara M, Nakamura H (1994) Olfactory mucosal findings and clinical course in patients with olfactory disorders following upper respiratory viral infection. Rhinology 32: 113–118
250. Henkin RI *et al* (1976) A double-blind study of the effects of zinc sulfate on taste and smell dysfunction. Am J Med Sci 272: 285–299
251. Yee KK, Rawson NE (2000) Retinoic acid enhances the rate of olfactory recovery after olfactory nerve transection. Brain Res Dev Brain Res 124: 129–132
252. Hendriks APJ (1988) Olfactory dysfunction. Rhinology 26: 229–251
253. Nordin S *et al* (1996) Prevalence and assessment of qualitative olfactory dysfunction in different age groups. Laryngoscope 106: 739–744
254. Leopold D (1995) Distorted olfactory perception. Handbook of olfaction and gustation. In: Doty RL (ed) Marcel Dekker Inc. New York, p 441–454
255. Jafek BW, Murrow B, Linschoten M (2000) Evaluation and treatment of anosmia. Curr Opin Otol Head Neck Surg 8: 63–67
256. Reljanovic M *et al* (1999) Treatment of diabetic polyneuropathy with the antioxidant thioctic acid (alpha-lipoic acid): a two year multicenter randomized double-blind placebo-controlled trial (ALADIN II). Alpha Lipoic Acid in Diabetic Neuropathy. Free Radic Res 31: 171–179
257. Packer L, Kraemer K, Rimbach G (2001) Molecular aspects of lipoic acid in the prevention of diabetes complications. Nutrition 17: 888–895
258. Hounsom L *et al* (1998) A lipoic acid-gamma linolenic acid conjugate is effective against multiple indices of experimental diabetic neuropathy. Diabetologia 41: 839–843
259. Hounsom L *et al* (2001) Oxidative stress participates in the breakdown of neuronal phenotype in experimental diabetic neuropathy. Diabetologia 44: 424–428

260. Garrett NE *et al* (1997) alpha-Lipoic acid corrects neuropeptide deficits in diabetic rats via induction of trophic support. Neurosci Lett 222: 191–194
261. Coppey LJ *et al* (2001) Effect of antioxidant treatment of streptozotocin-induced diabetic rats on endoneurial blood flow, motor nerve conduction velocity, and vascular reactivity of epineurial arterioles of the sciatic nerve. Diabetes 50: 1927–1937
262. van Dam PS *et al* (2001) Glutathione and alpha-lipoate in diabetic rats: nerve function, blood flow and oxidative state. Eur J Clin Invest 31: 417–424
263. Lynch MA (2001) Lipoic acid confers protection against oxidative injury in non-neuronal and neuronal tissue. Nutr Neurosci 4: 419–438
264. Seiden AM (1997) The intial assessment of patients with taste and smell disorders. Taste and smell disorders. In: Seiden AM (ed) Thieme, New York, p 4–19
265. Garrett-Laster M, Russell RM, Jacques PF (1984) Impairment of taste and olfaction in patients with cirrhosis: the role of vitamin A. Hum Nutr Clin Nutr 38: 203–214
266. Henkin RI (1994) Drug-induced taste and smell disorders. Incidence, mechanisms and management related primarily to treatment of sensory receptor dysfunction. Drug Saf 11: 318–377
267. Ackerman BH, Kasbekar N (1997) Disturbances of taste and smell induced by drugs. Pharmacotherapy 17: 482–496
268. Hudry J, Perrin F, Ryvlin P, Mauguière F, Royet J-P (2003) Olfactory short-term memory and related amygdala recordings in patients with temporal lobe epilepsy. Brain 126: 1851–1863