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Review Article

Olfaction: a review

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Introduction

Olfaction is the sensation arising from the nasal cavity following stimulation of the olfactory epithelium by volatile compounds. Olfactory disturbance is common: some two million Americans suffer from a loss, diminution, or distortion of their sense of smell, taste or both (Neurological and Communicative Disorders and Stroke Council, 1991). Olfaction helps to protect us from harmful substances, such as environmental contaminants and spoiled food. It contributes to the livelihoods of cooks, wine tasters, firefighters, chemists and industrial workers, as well as nutritional status and general quality of life (Schiffman, 1983). Odour-evoked memories have been found to be more emotional than verbally-cued memories (Herz and Cupchik, 1995). In one study of 750 consecutive patients with anosmia 68 per cent thought that a disordered sense of smell affected their quality of life and 56 per cent felt it altered their daily living (Deems *et al.*, 1991).

Kant proclaimed 'To which organic sense do we owe the least and which appears to be the most dispensable? The sense of smell (Kant 1978).' Darwin postulated that loss of olfactory acuity was part of the evolutionary process (Darwin 1898). Freud and others argued that smell had been left behind and sight had taken priority (Stoddart, 1992). These views may underestimate the influence of olfaction on our lives. The olfactory pathway projects to the limbic system and it is not surprising that olfactory perception consists not only of odours, but the experiences and emotions associated with them and therefore olfaction is not simply a biological and psychological phenomenon, it is cultural and hence a social and historical phenomenon (Classen, 1994). 'When I lost my sense of smell it was like being struck blind . . . you smell . . . maybe not consciously, but as a rich unconscious background to everything else' (Sacks, 1987).

Since antiquity, aromatics have been employed across cultures, for purposes as diverse as seduction, healing, hunting, inducing hallucinations, banqueting, anointing the dead, in amphitheatres, in images of love, in literature and communication with spirits. The Egyptians' most famous perfume, Kyphi, was a blend of 16 ingredients which reputedly had the power to relieve anxiety, heal the soul and was burnt in sacrifice to Re, the Sun God (Rackham, 1960).

The Greek gods Aphrodite and Eros were 'fragrant' and Mount Olympus was itself deemed a place of fragrance (Homer, The Iliad, see Murray, 1924). Christianity, despite initial resistance, gradually incorporated many traditional olfactory practices and beliefs, St. Paul declaring that 'We are the aroma of Christ, of God, among those who are being saved' (Paul, New Testament). The practice of purification with incense is still observed today. Olfaction, knowledge and wisdom were interlinked in the classical world; the origin of the word sagacious from the Latin sagax, implies a keen sense of smell and intelligence.

The Arabian physician Avicenna (980–1037) linked bad smell with disease. The cause of the plague was deemed to be the foul odour caused by putrefaction; 'And when evyl substance shal putrefie . . . their stinke may cause great mortalitie' (Norton, 1975). The physician Hector Gavin conducted 'olfactory tours' in 19th century London and his contemporary Chadwick thought that, 'all smell is disease'.

In humans, eccrine glands are primarily responsible for cooling and apocrine glands exude part of their cell into the lumen of the gland and are primarily responsible for body smell. Sometimes, the breakdown of the oily secretions from sebaceous glands by bacteria can also produce a smell. Stoddard argues that humans are highly scented as the apocrine glands are centred around discrete organs (Stoddard, 1992). Russell *et al.* (1980) took the axillary secretions from one group of women and placed them on the upper lip of another group and found that they developed synchronous menstrual cycles (Russell *et al.*, 1980). Bruce (1959) found that

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newly pregnant mice lose their litters if they were brought into contact with the scent of unfamiliar (non-mate) male mice (Bruce, 1959).

The relentless manipulation of olfaction in today's consumer society, includes the suppression or augmentation of body smell with deodorants or perfumes and colognes, 'home sweet home', juxtaposed with the smell of pollution, industry or traffic. Antagonists which block the ability to perceive certain odours (Artis, 1986), artificial flavourings which paradoxically reduce the spectrum of flavours in the original and, odours which act as behaviour modifiers, are in common use (Anon, 1991, 1992) (Synnott, 1993).

Anatomy and genetics

The olfactory neuroepithelium is an area of 2–10 cm^2 located high in the nasal vault which covers some of the superior turbinate, the superior nasal septum and the majority of the cribriform plate and it often has a yellowish hue. There is dispute about the cause of the colour, whether it is from the granules in Bowman's glands, carotenoids in the mucosa, phospholipids or their breakdown products (Douek, 1974), or secondary to lysosomes in the base of the supporting cells (Williams, 1995). It is composed of olfactory sensory neurons (OSN's), sustentacular or supporting cells which ensheath the receptor neurons – these maintain the normal extracellular potassium levels needed for neuronal activity (Kimmelman, 1993), and basal cells which replace the neuroepithelium approximately every 40 days. There are high levels of cytochrome-P450 and detoxifying enzymes in the supporting cells which may play a part in removing odorants from the area.

The olfactory neuron dendrite is bipolar with a round cell body and has 10–23 cilia on its surface which are up to 200 μ long and may overlap with the cilia of adjacent neurons (see Figures 1 and 2). The cilia have a 9 plus 2 pattern of microtubules characteristic of motile cilia but towards the tip there is only a central pair. The exposed part of the olfactory dendrites and cilia has a membrane with high concentrations of intramembranous particles in comparison to non-olfactory cilia (Williams, 1995). The olfactory organ is unique in the central nervous system, being the only part in direct contact with the environment and in its ability to regenerate damaged or lost neurons (Firestein *et al.*, 1996). The olfactory sensory neuron tapers into an unmyelinated axon and synapses in the olfactory bulb (see Figure 3).

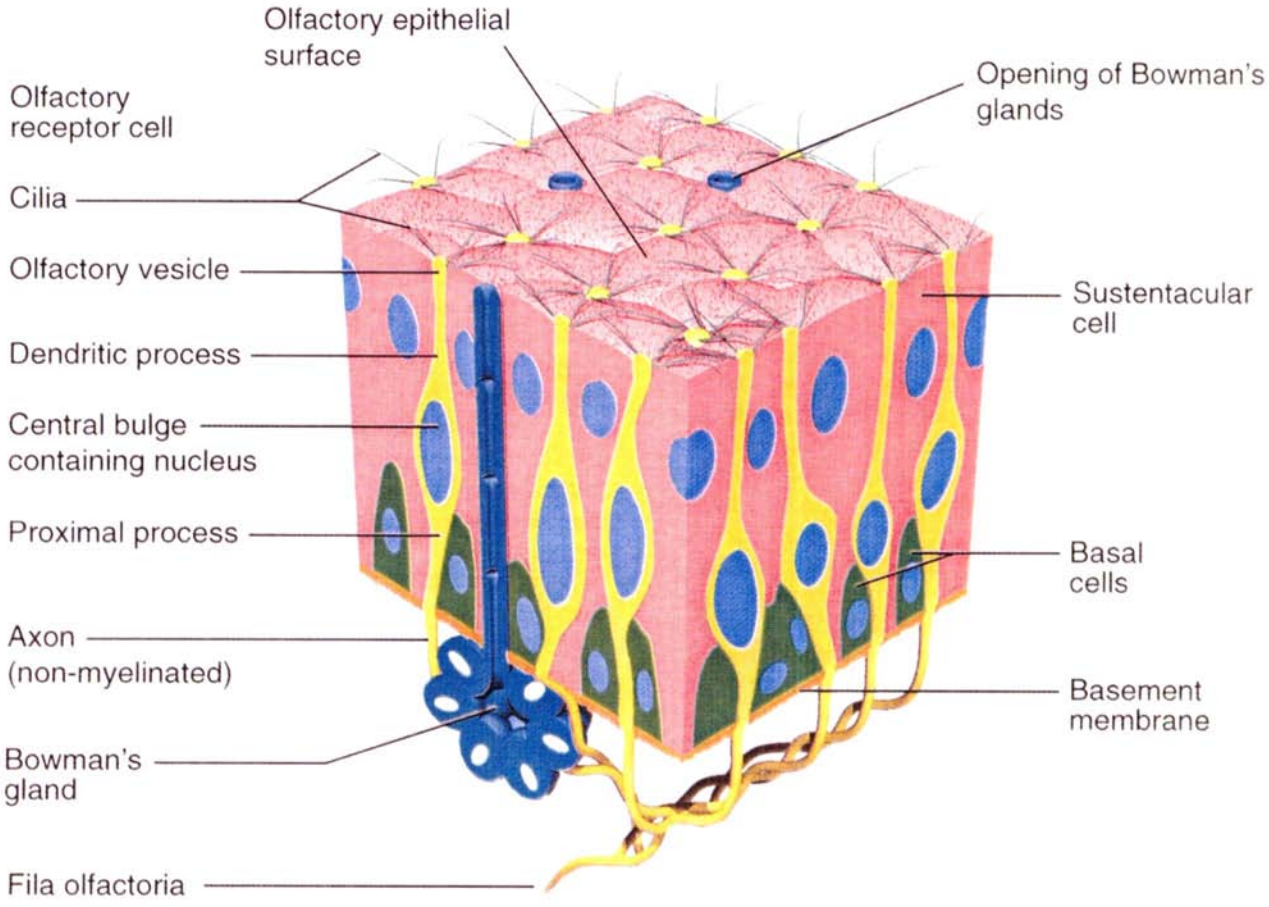

FIG. 1
Line diagram of olfactory mucosa. (Courtesy of *Human Histology* by Alan Stevens and Jim Lowe, Mosby)

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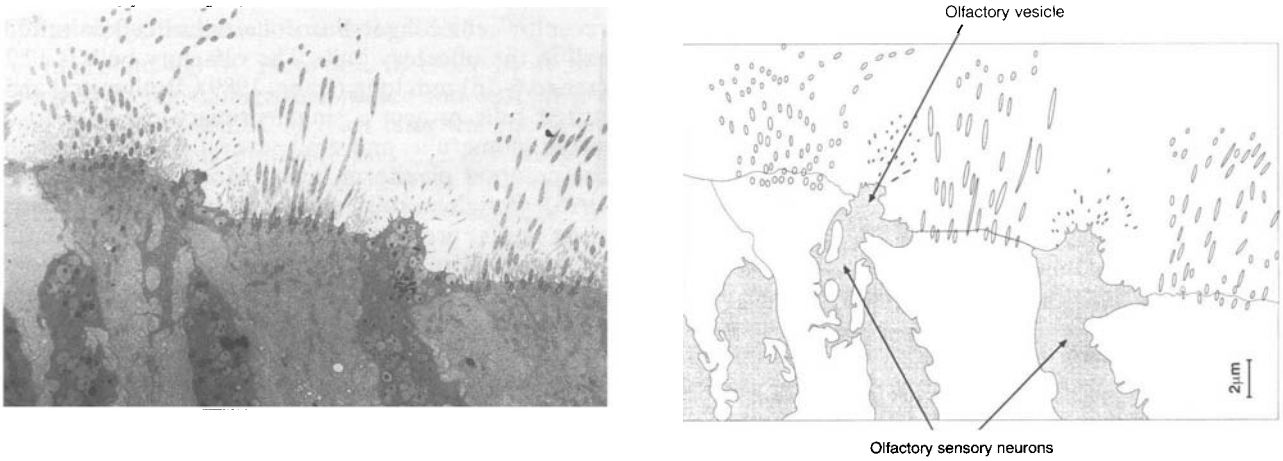

FIG. 2
a. Transmission electron micrograph of olfactory mucosa. (Bar = 2μm)
b. Line diagram of 2a.

The lifespan of an olfactory receptor neuron is approximately one month and it is likely that apoptosis, regulated cell death, is important in maintaining a balance between cell proliferation and death. However, studies with ^{3}H thymidine and bromodeoxyuridine have shown that some cells can stay alive for longer than this, particularly if they are not exposed to pollutants (Williams, 1995). Olfactory receptor neurons can be identified using polyclonal antibodies against olfactory marker protein (Chuah and Zheng, 1987). Basal cells are small polygonal cells in contact with the underlying basement membrane and are the stem cells for receptor and sustentacular cells. They may play a vital role in regeneration after viral damage. Cells at all stages of differentiation, whether neuronal precursors, immature OSNs or mature OSNs, undergo apoptosis (Holcomb *et al.*, 1996) and this reflects events elsewhere in the nervous system where many more neurons are produced than remain after they have made synaptic connections (Oppenheim, 1991). The underlying lamina propria contains olfactory nerve fascicles and mucus-secreting tubuloalveolar Bowman's glands.

A gene family for olfactory receptors and their surface proteins has been found (Buck and Axel, 1991) and there appear to be few interspecies differences in gene sequences. These odorant receptors have very diverse amino acid sequences expressed from about 500 genes and, as they can discriminate between 10 times that number of odours it is likely that each odour receptor interacts with several different odours. It is uncertain whether the large number of compounds which can be recognized can be matched by the number of specific receptor proteins, each a product of a separate gene and expressed on different cells (Lancet, 1994), or whether olfactory receptor neurons can express several receptor proteins, or whether each olfactory receptor protein has broad binding specificities. Different genes appear not to be co-expressed in any individual neuron (Ngai *et al.*, 1993) or at most only one or two olfactory receptor alleles are transcribed in any one cell (Chess *et al.*, 1994). It is also uncertain whether the ability to distinguish different odorants is due to exact receptors for individual odorants, whether receptor proteins themselves help to organize a map of olfactory connections with the help of unknown guidance molecules to orientate axons and their connections to the olfactory bulb (Lewin, 1994; Bargmann, 1996), or whether receptors are less specific and there is processing in the olfactory bulb or centrally. Electrophysiological studies suggest that, given a high enough concentration, each olfactory sensory neuron (OSN) may recognize a range of different odours but only a limited number (Sicard and Holley, 1984). *In situ* hybridization studies have shown that OSNs which express the same receptor are found infrequently throughout the epithelium (Vassar *et al.*, 1993) although over a wide area (Mombaerts, 1996). There appears to be some spatial mapping of odorant receptor gene expression into broad zones that are the same on both sides of the nose (Ressler *et al.*, 1993) but within these zones there is no apparent pattern in the distribution of neurons expressing a given receptor (Mombaerts, 1996).

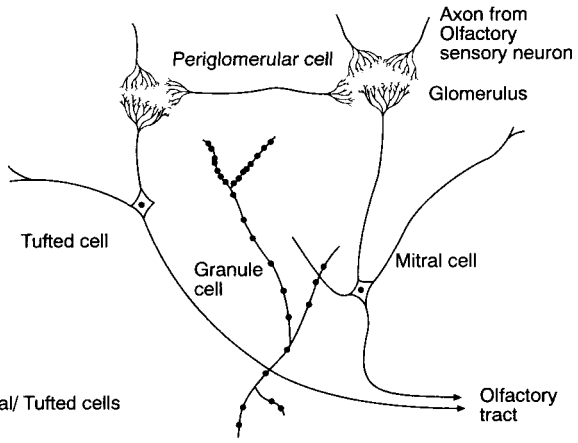

FIG. 3
Line diagram of basic cell connections in the olfactory bulb.

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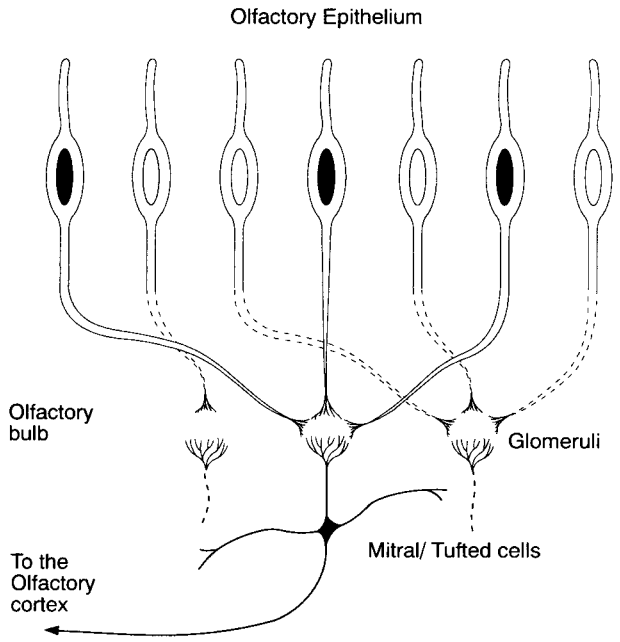

FIG. 4
Convergence of olfactory neurons with the same receptor specificity onto a specific glomerulus.

Retrograde studies of labelled neurons have suggested that there is some pattern formation. Axons traced from mouse olfactory sensory neurons which express a given odorant receptor have been found to project to topographically fixed loci within the large number of glomeruli in the olfactory bulb (Mombaerts *et al.*, 1996) (Figure 3). Further spatial mapping of glomeruli occurs in the olfactory bulb (Kauer and Cinelli, 1993) and recordings from mitral cells confirm this (Mori *et al.*, 1992). In the mouse, convergence from five million OSNs to 2,000 glomeruli has been found (Royet *et al.*, 1988). It has been postulated, and supported by *in situ* hybridization techniques with different odour receptor probes, that each of the axons from each OSN which expresses the same odorant receptor may converge on the same glomerulus (Vassar *et al.*, 1993) (Figure 4). This raises the question as to whether odorant receptors determine the projection pathways of the OSNs, and if this is the case then olfactory receptors are likely to be expressed before neural connections are made to the bulb (Mombaerts *et al.*, 1996). Experiments which have genetically altered receptor sequences suggest that while olfactory receptors are one determinant of axonal paths this effect may not be absolute (Mombaerts *et al.*, 1996).

Twin studies have had problems differentiating environmental from genetic effects. It is uncertain whether certain subsets of olfactory receptors become active in response to certain odours (Segal and Topolski, 1995).

When neuronal axons penetrate the cribriform plate they become covered by Schwann cells. One Schwann cell contains five to 10 fibres, but occasionally up to 100 (Lang, 1989). Olfactory sensory neurons are bipolar and about 15,000 olfactory receptor cells converge on one mitral cell or tufted cell in the olfactory bulb. The olfactory bulb is 12.2 (range 6–16) mm long (Lang, 1989). Both mitral and tufted cells project a single primary dendrite to a single glomerulus and emit several dendrites within the external plexiform layer (Mori and Yoshihara, 1995). Periglomerular cells, granule cells and short axon cells are interneuron-connecting glomeruli (Figure 3). Granule cells connect to mitral cells and inhibit them. From the olfactory bulb tract the main axons originate in the mitral or tufted cells and give off striae which pass to the olfactory tubercle and then projections go to the amygdala, the pre-pyriform cortex, the anterior olfactory nucleus and the entorhinal cortex as well as the hippocampus, hypothalamus and thalamus. The olfactory axons have both convergent and divergent projections and are not point to point as are the visual or somatosensory systems (Mori and Yoshihara, 1995).

The vomeronasal organ

Otherwise known as the organ of Jacobson (Jacobson, 1811), the vomeronasal organ is vestigial in humans but can be seen as a pit on the inferior part of the nasal septum. In some species, rodents in particular, there are central connections to accessory olfactory bulbs and reproductive physiology is closely linked to its function. It is present and functions in new world monkeys, dogs and cats (Breipohl *et al.*, 1979). One of the most detailed reviews of the vomeronasal organ in different species is described by Wysocki (1979) who concludes that while there is no evidence of a recognized central connection in man, no firm conclusions can be drawn regarding its presence in old world primates. It can be shown in the foetus but there are no proven central connections in humans (Nakashima *et al.*, 1985) in spite of claims to this effect (Taylor, 1994). Johnson *et al.* (1985) examined 100 humans and found a nasal pit in 39 per cent and went on to examine 27 post mortem specimens and failed to find any central connection.

Embryology

On day 24 a pit forms on either side of the anterior end of the neural groove and this becomes the nasal pit. Receptor cells are present by the seventh week and these make connection with the forebrain. Electron microscopic studies show that receptor cells differentiate early and sprout basal axons which pierce the basal lamina and grow back to synapse with secondary neurones in the olfactory bulb (Williams, 1995). When the dendrites reach the surface, their ends expand and become the base of the olfactory cilia, and the other cells in the epithelium have differentiated and are functional at birth.

Physiology, transduction and cognition

In around 400 BC Plato described odours as 'half-formed' being thinner than water and coarser than air and Galen, some 200 years later was the first to claim that it was the brain and not the nose that perceived smell (Eastwood, 1981). Humans can detect more than 10,000 different odours and discriminate between 5,000 (Ressler *et al.*, 1994). The only other part of the human body which can discern between so many different molecules is the immune system. The olfactory epithelium has several million olfactory sensory neurons. The hydrophilic olfactory mucus constrains the incoming odorant molecules with respect to absorption, solubility and chemical reactivity, but once dissolved the odorant can interact with the receptor cell(s). Odorant binding proteins (OBPs) bind and solubilize hydrophobic molecules, increasing their concentration up to 10,000 times that in ambient air. They are low molecular weight soluble proteins which are concentrated in the nasal mucus of most vertebrates or the sensillar lymph of insects. There are usually two to three types of OBPs in most vertebrates and there are significant sequence similarities between them and a superfamily or soluble carrier proteins called lipocalins (Pelosi, 1994). One model of the OBP molecule has seven transmembrane domain structures, as do most G-protein coupled receptors (Buck and Axel, 1991; Ressler *et al.*, 1994). The OBPs may also remove the odorant molecules after transduction, which occurs after specific interactions between the odorant molecules and receptor proteins on the surface of the olfactory cilia. OBPs have been found in a variety of other tissues and may also have a role in detoxification or signalling (Boudjelal *et al.*, 1996). Olfactory transduction is probably then mediated via a unique olfactory epithelium G_{olf}-protein coupled cascade, with cAMP and/or IP_3 (phosphoinositide specific phosphodiesterase C) as an intracellular second messenger, exciting an ion channel in the cilia, which depolarizes the olfactory neuron. Recently, through molecular cloning, a cyclic nucleotidegated olfactory channel has been identified (Hatt, 1996). Some odorants have been found to activate cAMP specifically and others to activate IP_3 (Hatt, 1996), it is not known if these affect the same or different membrane ion channels. Recently Kendrick *et al.* (1997) have found that in sheep which recognize their lambs' odour within two days of birth, the mitral cells become increasingly responsive to this odour (Kendrick *et al.*, 1997). They also found and propose that nitric oxide released from both mitral and granule cells, which potentiates glutamate release from mitral cells through reciprocal synapses, may underlie the formation of olfactory memories.

The precise mechanism by which the vast number of smells is recognized and discriminated is unknown, but possible theories include; specific odorants exciting specific receptors which are randomly grouped or aggregated, differing solubilities of odorant allowing a temporospatial distribution of the odorant across the olfactory mucosa (Adrian, 1954), or a response to the molecules' vibration spectra within an inelastic electron tunnel formed by olfactory receptors and their associated G-protein (Turin, 1996). The structure-based theories on their own cannot explain differences in smell between identical substances such as acetophenone and its fully deuterated analogue acetophenone-d8 (Turin, 1996). The vibration theory has received media prominence recently (Rosin, 1995), it proposes that it is the vibrational frequency of a molecule which is detected when it attaches to a receptor. This detects that vibrational mode and allows electrons to jump across the receptor and then trigger the neuron. It might be possible for one receptor to detect a range of vibrational energies. The olfactory mucosa of mammals is high in enzymes including cytochrome P-450 glutathione and UDP-transferase (Lazard *et al.*, 1991) and these may play a part in metabolizing odorants.

Adaptation is a characteristic of olfaction and in the past has been thought to be due to receptor phosphorylation which modulates the normal signal transduction and activation of the adenyl cyclase/cyclic AMP second messenger system. More recent work suggests that the effect is downstream and a modulation of the cAMP-gated channel from Ca^{2+} feedback (Kurahashi and Mwnini, 1997). It has recently been found that even odourless substances can, by cross-adaptation, alter the perception of another compound (Pierce *et al.*, 1996).

Olfactory ability is unaffected by left central, parietal and posterior brain excisions (Zatore, 1990) and as patients with right parietal and

TABLE I
THE DEFINITION OF OLFACTORY DYSFUNCTION. ADAPTED FROM KIMMELMAN (1993)

Olfactory dysfunction	Definition
Total anosmia	Inability to detect any qualitative olfactory sensation
Partial anosmia	Ability to detect some, but not all, qualitative olfactory sensation
General or total hyposmia	Decreased sensitivity to all odourants
Hyposmia	Decreased sensitivity to some, but not all, odourants
Specific anosmia	Many individuals lack the ability to detect specific odourants smelt by others (Amoore, 1977)
Dysosmia	Distortion in odour perception; (EITHER parosmia or phantosmia)
Parosmia or cachosmia	The presence of an unpleasant odour when a normally presented odour is presented
Phantosmia	Perception of an odour in the absence of an olfactory stimulus
General, total hyperosmia or multiple chemical sensitivity	Increased sensitivity to odours, multiple chemical sensitivity, a doubful entity (Doty, 1994)
Partial hyperosmia	Increased sensitivity to only some odours
Olfactory agnosia	Inability to classify, contrast, or identify an odour sensation verbally, even though the ability to distinguish between odourants or to recognise them may be normal

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temporal lesions have difficulty lateralizing odorants, the right cortex is the suggested olfactory processing area (Bellas, 1989). Whole scalp neuromagnetic signals to olfactory stimulation suggest that the area around the superior temporal sulci of both hemispheres is involved in olfactory processing (Kettenmann *et al.*, 1996). Established odour associations can last at least one year, three times as long as for visual stimuli (Schiffman, 1983).

Odorants have biological meaning, a child preferring its mother's smell at six to 10 days (MacFarlane, 1975), this also mediating the child's attachment between three and five years of age (Schall, 1980). The child begins to show odour preferences between two and seven years (Engen, 1974).

Olfaction differs from the common chemical senses in the nasal and oral cavities which originate from free nerve endings scattered throughout their lining and provide the sensation of irritation or burning when stimulated by items such as ammonia or chilli peppers. This is mediated by branches of the trigeminal nerve and the glossopharyngeal nerve which all input to the spinal trigeminal nucleus, thalamus and somatosensory cortex. This is also useful for identifying malingerers (see Olfactory testing).

Abnormal olfactory function

Life has a 'flat' quality for the anosmic patient, distinguishing foods by their texture and colour (such as the lumpiness of sour milk), and avoiding perfume for fear of over-application. A reduced ability to smell is not uncommon as one study showed that approximately half of 65–80-year-old people are affected (Doty *et al.*, 1984a). Parosmia and phantosmia/cacosmia from the Greek kakos 'bad' osme 'smell', can be even more disturbing than anosmia. Patients are more likely to be female, older, and associations include a history of an influenza-like illness, head trauma, nasal disease, or temporal pathology (Scott, 1989).

Taste

As three quarters of 'flavour' is contributed by olfaction, many patients confuse 'taste' with 'flavour' and present with dysgeusia when their problem is dysosmia, and whilst 74 per cent of dysosmics complained of dysgeusia, only four per cent have been found to have an objective gustatory deficit (Deems *et al.*, 1991). Patients with specific dysgeusia, for example for bitter, or dysgeusia triggered by eating, are less or more likely to claim concurrent dysosmia, respectively. If the patient can detect sweet, sour, salt and bitter tastes then general gustatory dysfunction is unlikely to be present (Deems *et al.*, 1991).

Age-related olfactory changes

Physiological changes and subjective deficits in olfactory function should be borne in mind to prevent all such dysfunction from being deemed pathological. Detection and recognition thresholds (being the lowest concentration at which an odorant is detected or correctly identified, respectively) and trigeminal thresholds are elevated in elderly individuals and have been shown to deteriorate in a longitudinal study (Ship *et al.*, 1996). Olfactory dysfunction for food odours, is believed to contribute significantly in anorexia, malnutrition and subsequent weight loss in the elderly (Engen, 1974) (Schiffman, 1983). Olfactory warning systems such as the detection of coal gas (Chalke, 1958) and the trigeminal sensitivity to CO_2 (Stevens, 1982) are diminished with age. Age-related olfactory loss appears to begin at 60, becoming significantly worse after 70 (Doty *et al.*, 1984b). This is two to 10 times higher than for those in their 20's, and is exacerbated by illness or multiple medication. Suprathreshold losses of both pleasant and foul odour intensities are perceived half as strongly at 70 as at 20, and correct identification of odour is between 60 and 75 per cent that of younger subjects (Schiffman, 1991). Women consistently perform better than men in smell identification (Ship *et al.*, 1996).

Anatomical and physiological changes include a decrease in protein synthesis and structural alterations, such as intercalation of respiratory epithelium, in the olfactory neuroepithelium (Dodson, 1980), atrophy in the olfactory bulb and nerve (Brizzee, 1975), senile plaque and neurofibrillary tangle formation in the hippocampus and amygdala (Scheibel, 1975), hypothalamic degeneration (Macholdo-Salas, 1977) and increased intracellular hippocampal calcium (Landfield, 1984). Such changes can affect any part of the olfactory

TABLE II

THE MAJOR CAUSES OF OLFACTORY DYSFUNCTION AND SOME OF THEIR CHARACTERISTICS. ADAPTED FROM DEEMS *et al.* (1991)

Cause of disturbance	% of patients	% of these with medically measured loss of smell	Female:Male in this population	% with Dysosmia
Post upper respiratory tract infection	26	76	1.42	35
Idiopathic	22	53	1.10	33
Head trauma	18	86	0.68	40
Obstructive nasal and paranasal sinus disease	15	72	0.80	28
Congenital	4	100	0.76	0
Toxic chemical exposure	2	67	0.31	28
Oral infection	0.8	17	1.62	0
Other infection	0.5	25	2.43	25
Psychiatric	0.5	25	0.81	50

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pathway with normal ageing but may also be seen with disease, medications and pollutants (Bellas, 1989).

Causes of olfactory disturbances

There are three major classifications of olfactory disorders; transport (conductive), sensory and neural (Snow, 1991). 'Sensorineural' is used in practice when differentiation is difficult. Transport disorders interfere with the access of a chemical stimulus to the smell receptors and the commonest examples are inflamed nasal mucosa or nasal polyps. Sensory losses result from damage to the sensory organs (Schiffman, 1983). Factors which reduce cell turnover or directly modify cells include toxic chemicals, radiation, medications, neoplasms and viruses (see Table II). Neural losses result from interruptions in the peripheral or central nervous olfactory pathways, from head trauma, neoplasms and surgery.

Iatrogenic causes, accounting for a small percentage of olfactory disturbances, include medication, neurosurgery, radiotherapy, and nasal and paranasal sinus surgery.

Upper respiratory tract infections

A temporary loss of sense of smell often occurs with an upper respiratory tract infection, usually due to obstruction or oedema in and around the olfactory cleft and it will resolve with patency (usually one to three days). However, in a small percentage of otherwise healthy 40–60 year olds, 70–80 per cent of whom are women, olfaction never returns (Leopold, 1986). Invasion of the central nervous system via the olfactory nerves (Tomlinson, 1983) and olfactory destruction by viruses has been demonstrated (Goto, 1977). Biopsies reveal decreased or absent olfactory receptors (Yamagishi, 1988), and only a third of these patients recover (Hendriks, 1988).

Head trauma

Between five and 10 per cent of adults who sustain a head injury with a period of loss of consciousness have an olfactory loss, whereas 3.2 per cent and 1.2 per cent of children develop transient and permanent losses respectively (Leopold, 1991). The severity of the injury correlates with loss although even minor trauma can produce total anosmia (Hasegawa *et al.*, 1986). Frontal blows are a common site of trauma to result in olfactory loss but occipital blows, in themselves much less common, are five times more likely to result in total anosmia (Hendriks, 1988). Loss is usually immediate and recovery occurs in fewer than 10 per cent, most occurring within six months. Amnesia for greater than 24 hours is an indicator of a poorer prognosis. Between eight and 39 per cent show some recovery within three months, but it can take as long as seven years (Mott, 1991). After trauma the olfactory cells become distorted, axon and axon tangles proliferate, there are fewer cilia and there may be frontal cortex damage (Levin, 1985).

Obstructive nasal and paranasal sinus disease

The area through which air flows to get to the olfactory cleft is thought to be medial and anterior to the lower part of the middle turbinate and anatomical changes in this area such as mucosal swelling, or polyps can impair olfaction. The onset of olfactory dysfunction is more gradual but recovery is more likely than with deficits due to head trauma or with a total loss following an upper respiratory tract infection (Deems *et al.*, 1991). The mucosal oedema and swelling which occur secondary to chronic infective rhinosinusitis may respond with time or the appropriate medical treatment. Relief with a one to two week course of systemic steroids can be diagnostic as well as therapeutic.

Congenital

At about eight years of age children begin to discern between taste, pungency and irritating odours. Some individuals are born with an isolated loss to a particular chemical or group. Inherited causes are twice as common in females. Kallman's syndrome is associated with olfactory bulb agenesis and hypogonadotrophic hypogonadism. Congenital anosmia is also associated in some patients with Turner's syndrome and in patients with premature baldness, vascular headaches (Singh *et al.*, 1970), and other abnormalities (Lygonis, 1969). These patients score little more than chance in olfactory tests. These individuals often fastidiously clean both themselves and their surroundings, avoiding fragrances for fear of overuse (Leopold *et al.*, 1992). The diagnosis involves excluding the more common causes of dysfunction (Leopold *et al.*, 1992).

TABLE III
CATEGORIES OF TOXIC CHEMICAL-RELATED OLFACTORY DYSFUNCTION. ADAPTED FROM SCHIFFMAN (1993)

Compounds, dusts and processes	Examples
Metallurgical compounds and processes	Cadmium compounds, chromium, lead, magnetic elements, mercury, nickel, silver, steel, zinc
Dusts	Ashes, cement, chemicals, coke, grain, hardwoods, lime, silicosis
Nonmetallic inorganic compounds	Ammonia, CS_2, CO, chlorine, SO_2, H_2S, NO2, fluorides
Organic compounds	Acetates, acetone, benzene, benzine, chloromethanes, menthol, petroleum, solvents, trichloroethylene
Manufacturing processes	Acids (inorganic and organic) cement, asphalt, flour, tobacco, varnishes, cotton, paint, paper, peppermint, spices

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TABLE IV
CLASSES OF MEDICATION WHICH CAN EFFECT OLFACTION. ADAPTED FROM SCHIFFMAN (1993)

Drug class	Example
Local anaesthetic	Cocaine hydrochloride
Antihypertensives	Nifedipine
Antimicrobials	Streptomycin, amphotericin B, ethambutol
Antithyroids	Carbimazole, thiouracil
Opiates	Codeine, morphine
Antidepressants	Amitriptyline
Radiation therapy	To head
Sympathomimetics	Amphetamines
Vasodilators	Diltiazem
Other	Acetylcholine-like substances Strychnine
Amoebicides and antihelminthics	Metronidazole, nizidazole
Immunosuppressants	Methotrexate, azathioprine
Antirheumatics	Gold, levamisole, colchicine, allopurinol

Environmental pollutants/toxic chemical exposure (Table 3)

The strategic position of the olfactory receptors to monitor our external environment makes them particularly vulnerable to inhaled chemicals, especially if they are airborne (Schiffman, 1992a). Dysosmia can be induced by inhalation of steam or warm air (Deems *et al.*, 1991). Nasally-inhaled irritants can increase blood vessel permeability, alter mucoserous gland secretion and mucus flow, decrease respiratory epithelium cilia activity and suppress breathing rate. Temporary or permanent losses in olfactory sensitivity due to brief or prolonged exposure to pollutants can occur through modification of neurotransmitter levels or physiological or anatomical damage to the olfactory receptor. Both direct and passive smoking are associated with olfactory loss (Frye, 1990). The olfactory bulbs are particularly pollutant-sensitive, but under some circumstances olfactory receptor cell regeneration may be induced by environmental agents (Hinds, 1984). A review of substances which have been reported as possibly causing olfactory dysfunction by Amoore lists a wide range of organic and inorganic substances but many of these are circumspect case reports and do not prove causation (Amoore, 1984).

Psychiatric

Disturbance of the limbic to hypothalamic pathways in depressive patients may lead to olfactory dysfunction (Jesberger, 1988). Conversely 56 per cent of those with dysfunction feel affected psychologically and those with dysosmia and dysgeusia are 1.5 times more prone to depression (Deems *et al.*, 1991). Patients with the olfactory reference syndrome are obsessively concerned with minor odours which are often related to bodily smells and this often causes them to bathe frequently and overuse perfumes. In Marcel Proust syndrome the patient dramatically conjures up memories of odours, which interferes with daily routines.

Surgical

Pre-operative assessment of olfactory function is not standard practice (Kimmelman, 1994), although the risk of mild (mean 2.25 decrease in UPSIT) hyposmia and anosmia following nasal operations is 34 and 1.1 per cent respectively (Mott, 1991). Small series of patients, and inadequate objective measurements have meant that many studies in this area have been flawed (Kimmelman, 1994). Nasal and paranasal surgery can affect the olfactory pathway by direct trauma to the olfactory epithelium on the middle turbinate, septum or cribriform plate or by obstructing the airway with adhesions. Peri-operative or post-operative medication may also affect smell. The incidence of loss of sense of smell following topical nasal medication or the vehicle which preserves them is unknown but low (Quraishi *et al.*, 1997). Laryngectomy reduces airflow through the nasal cavity and reduces olfaction. Coincidental

TABLE V
CATEGORIES OF MEDICAL DISEASE AND OLFACTORY DYSFUNCTION. IN PART ADAPTED FROM SCHIFFMAN (1993)

Group of conditions	Examples
Nervous	Alzheimer's, Down's, epilepsy, multiple sclerosis, Parkinson's, head trauma, Korsakoff's psychosis, migraine, neoplasms
Congenital	Associated with choanal atresia, Kallmann's syndrome
Nutritional and metabolic	Chronic renal failure, liver disease, B12 deficiency, trimethylaminuria
Trauma	Cribriform plate fracture or tear of olfactory fibres in head injury, laryngectomy
Inflammatory	Rhinosinusitis, infective, allergic, sarcoid, Wegener's granulomatosis
Endocrine	Adrenal cortex insufficiency, Cushing's, hypothyroidism, diabetes, Turner's, Kallman's, primary amenorrhoea, X-linked ichthyosis
Local	Adenoid hypertrophy, allergic rhinitis, atopy, sinusitis and polyposis, bronchial asthma, Crouzon's and Sjogren's syndromes, leprosy, ozena
Neoplasms	Olfactory neuroblastoma, anterior skull base tumours
Degenerative	Age
Viral and infectious	Acute viral hepatitis, HIV, Influenza-like
Other	Amyloidosis and sarcoidosis, cystic fibrosis, familial, laryngectomy, psychiatric

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post-operative or pre-operative olfactory dysfunction could lead to litigation, especially if there has been inadequate pre-operative assessment or documentation (Kimmelman, 1994). Patients with chronic sinusitis and/or polyposis prior to surgery should have their sense of smell documented (and ideally tested if it is abnormal), and they should be told that complete restoration of their sense of smell cannot be guaranteed.

Patients undergoing rhinoplasty, septoplasty or nasal fracture reduction are also potentially at risk but this complication is so rare that most surgeons would not routinely warn their patients of this possibility. In a study by Kimmelman the type of surgery, intra-operative use of cocaine and different types of general anaesthesia did not affect olfactory acuity, and whereas one patient in 93 showed a decrease of six points on post-operative UPSIT testing, 13 patients experienced a similar increase (Kimmelman, 1994).

Medicines

Pharmacological substances have been reported as a cause of olfactory dysfunction after oral administration, systemic injection or topical application to the olfactory receptors (Table IV). Our current understanding of this is limited because:

(1) these effects occur in only a minority of patients;

(2) concomitant medical disease can contribute to the olfactory disorder;

(3) olfactory transduction and the involved neurotransmitters are currently poorly understood.

Drugs may affect receptor function, binding, or cell turnover in the olfactory epithelium (Henkin, 1994). Conversely, exogenous oestrogens may protect against olfactory dysfunction in post-menopausal women (Deems *et al.*, 1991).

Medical disease

Medical disease may cause olfactory dysfunction by decreasing the receptor cell turnover rate and has been reported after adrenalectomy, hypophysectomy, thyroidectomy and uraemia (Table V). Protein deprivation has resulted in a similar decrease in small bowel epithelium (Schiffman, 1983). Malnourishment resulting in niacin and zinc deficiency can have a similar effect but zinc therapy has not been found to be of therapeutic benefit (Deems *et al.*, 1991). A range of conditions listed in Table V have been reported as being associated with problems of olfaction, but the relative rarity of this problem in many of these conditions brings into question whether there is a true pathological association.

Neurodegenerative

The recognition and identification of threshold levels and memory of odours is severely affected in Alzheimer's disease (Knupfer and Spiegel, 1986), reflecting the presence of the characteristic plaques and tangles and neurotransmitter deficits in the olfactory pathways. The olfactory bulb is possibly the site of initial pathology in Alzheimer's disease (Pearson, 1985). Eichenbaum demonstrated that peripheral deficits preceed problems with odour detection (Eichenbaum, 1983). Transneural transport via olfactory pathways has been shown for diverse agents such as viruses (Esiri, 1984), aluminosilicates (Roberts, 1986), gold and dyes (Jackson, 1979), and amino acids (Baker, 1995). It has been postulated that the causative agent in Alzheimer's disease may act through such a route (Roberts, 1986).

Olfactory dysfunction has also been found early in the development of Parkinson's disease (Ward *et al.*, 1983) and is unrelated to neurological signs, disease stage or duration (Doty *et al.*, 1988). Anosmia in multiple sclerosis is rare (Doty *et al.*, 1984b).

Neoplasms

Intranasal tumours, such as inverted papilloma, adenocarcinoma, squamous cell carcinoma and olfactory neuroblastoma can produce local destruction in the olfactory cleft or block its airflow. Intracranial meningiomas, pituitary tumours and gliomas cause local destruction, 25 per cent of temporal lobe tumours produce an olfactory disturbance (Furstenberg, 1943).

Assessment of olfaction

In common with all medical assessments, a thorough history and examination is crucial in formulating the differential diagnosis, followed by further investigations. Complaints of loss of taste, for example, are usually related to olfactory loss (Deems *et al.*, 1991). The history accurately establishes the onset and progression of the olfactory disorder. A history of a partial or intermittent loss of smell is in keeping with mucosal disease as a result of allergy, infection or any pathology which can cause inflammation of the mucosa such as Wegener's granulomatosis or sarcoid. Treatment of the cause of the mucosal inflammation often, but not invariably, results in improvement. Examination distinguishes an airflow from a sensorineural problem and the olfactory cleft can be inspected using an endoscope. The following management structure includes the majority of possible relevant symptoms and signs.

History

Type of olfactory dysfunction
- Total loss, decrease, increase, distortion

Speed of onset of olfactory disturbance
- Rapid – viruses, trauma
- Slow – nasal/sinus disease e.g., polyps, neoplasms, are there concomitant nasal symptoms?
- Neurological symptoms – Visual loss/change, distortion/loss of facial sensation, headache, behaviour changes ⇒ Primary CNS involvement e.g., Alzheimer's, multiple sclerosis or extension of inflammation/neoplasm from nasal cavity to the orbit/anterior cranial fossa.

Previous medical history
- Preceding upper respiratory viral tract infection, trauma, neoplasm, surgery, radiotherapy
- Concomitant medical illness

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Social history
Occupation, chemical exposure, head trauma
Tobacco and alcohol consumption
Substance abuse
Nutrition – fad diets, malabsorption
Drug history
Past and current medication
Family history
Allergy, CNS abnormalities, nasal disorders

Examination

Signs of intranasal disease
Mucosal oedema, mucopus, granular mucosa, polyps olfactory mucosa visible with a nasal endoscope
Eyes – extraocular motility/ophthalmoscopy
Neck lymph nodes – malignancy/chronic inflammation, infection

Olfactory testing

There are several methods for characterizing the type and degree of olfactory loss. Interestingly, all can identify malingerers.

(1) Glass sniff bottles (Cheesman and Townsend, 1956; Doty and Gregor, 1986).

(2) Glass rods or strips of soaked blotting paper (Toyota *et al.*, 1978).

(3) Plastic squeeze bottles (Amoore and Ollman, 1983). The butanol threshold test requires forced choice testing between serial dilutions of butanol in distilled water. The strongest solution is four per cent butanol, which even the anosmic can smell due to excitation of the common chemical sense, the mixture being diluted progressively into thirds into seven different concentrations. The subject is started at the weakest concentration (bottle 7) and proceeds through the higher concentrations until five forced choices between the butanol and control bottle are correct. The malingerer will claim not to identify even the four per cent butanol (Cain, 1989). Phenyl ethyl alcohol (PEA) does not stimulate the trigeminal nerve and can be used in threshold testing.

(4) The odour identification test. This consists of eight different opacified bottles. The subject chooses the correct odorant from a list of 20 common foods or household products presented to them. The eighth bottle contains Vicks vapour rub to identify malingerers. Smell declines more with age than does taste, so results from these tests must be interpreted with respect to age and sex-matched controls. Odours which are culturally appropriate may help to improve the reproducibility of this test.

(5) The odorant confusion matrix (Wright, 1987) in which 10 single odorants are presented in random order. The subject chooses an option after each one from 10 options. This process is repeated in random order a further 10 times. A matrix is built up and the reproducibility of their response can be studied.

(6) The University of Pennsylvania smell identification test (UPSIT) (Doty *et al.*, 1984b), consists of 40 MCQs of common plant, food or household items with scratch-and-sniff microencapsulated odorants. The chance score is 10, with a lesser score indicating malingering (Seiden, 1992).

Investigations

Depending on the history and examination the following may have a place in management: thyroid function, adrenal function, CSF examination, full blood count, erythrocyte sedimentation rate, serum glucose, creatinine and allergy skin prick testing.

Biopsy of the olfactory neuroepithelium, immunohistochemistry and electron microscopy are used in research (Strahan, 1991) in an attempt to correlate histological and clinical signs, but this is not always successful, as patches of respiratory epithelium often co-exist within areas of olfactory neuroepithelium (Lovell *et al.*, 1982; Nakashima, 1984). As many as six specimens may be required (Jafek *et al.*, 1989). Endoscopically guided biopsy under local anaesthesia may give a better success rate (Lanza *et al.*, 1993). Olfactory biopsy is usually abnormal in congenital anosmia (Leopold *et al.*, 1992). Biopsy of olfactory epithelium has not been shown to reduce performance to olfactory tests (Lanza *et al.*, 1994).

Electrophysiology

Electrophysiological tests are not readily obtainable and are primarily used in research at present. The electro-olfactogram can only be obtained by placing the electrodes on the olfactory area and this reading represents a summation potential generated by the olfactory sensory neurons. The electrodes cause sneezing and local anaesthesia cannot be used because it will alter olfaction. Olfactory evoked potentials can be recorded from skull electrodes and depend on good stimulation techniques in order to avoid mechanical and thermal artefacts (Kobal and Hummel, 1996). The preferred method to date is based on thermostabilized switching, with a rise time that must not exceed 20 ms in order to avoid giving the subject any clues, and the stimulus onset has to be quick (<50 ms) in order to stimulate enough cortical neurons. It is important to distinguish which substance is used. For example, stimulation of the trigeminal nerve occurs with carbon dioxide, the olfactory system with hydrogen sulphide, and both from substances such as carvone, and each can effect event-related potentials to each other (Livermore *et al.*, 1992). The picture is complicated by the fact that many olfactory substances also stimulate the trigeminal system, particularly in high concentrations. The interstimulus interval should be longer than 30 s when averaging from repeated stimulation is needed. Gender and age can affect the amplitude and latency of olfactory evoked potentials (Evans *et al.*, 1995). Discrimination deteriorates with age, particularly over the age of 80 (Schiffman, 1992b).

Imaging

Plain X-rays are of little use in assessment, failing to detect minor mucosal oedema which can lead to dysfunction, overestimating disease in 34 per cent of

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cases and underestimating in 46 per cent. A coronal CT scan will outline the bony structure of the paranasal sinuses, anterior skull base, and cribriform plate (Kimmelmann, 1991), the presence of any choanal atresia (Leopold *et al.*, 1992), but it is of limited use in the absence of endoscopic signs of disease, as it will show up some certain forms of intracranial pathology whereas magnetic resonance imaging (MRI) will demonstrate the brain and soft tissues with more clarity. MRI is particularly useful in parenchymal brain lesions (Kimmelmann, 1991; Yousem *et al.*, 1996). In one report of 25 congenitally anosmic patients MRI showed an absence of olfactory bulbs and tracts in the majority, with hypoplasia in the remainder (Yousem *et al.*, 1996). Temporal and/or frontal lobe volume loss was found in 20 per cent.

Recently, functional MRI has demonstrated a significant increase in cerebral blood flow in the piriform cortex, orbitofrontal cortex, the inferior medial frontal lobe and their corresponding cortices when a subject smells (Koizuka *et al.*, 1994).

Treatment

This will depend upon the type of olfactory dysfunction and should be directed towards the diagnosis.

Conductive (transport)

The object is to remove the obstruction to odorant and allow access to the olfactory receptors. In allergic rhinitis or polyp disease a course of systemic steroids can often bring about an improvement, but this is often temporary without further treatment such as allergen avoidance, regular topical nasal steroids and non-sedative antihistamines. If medical treatment fails, a polypectomy, ideally endoscopically to remove polyps and minimize the removal of olfactory mucosa, may help to open the olfactory cleft (Yamagishi, 1988), but this may only provide significant sustained improvement in approximately 50 per cent (Downey *et al.*, 1996). Widespread polyposis is associated with a poorer prognosis because it reflects incomplete resolution of mucosal disease (Downey *et al.*, 1996). Conservative partial resection of the middle turbinate does not appear to affect olfaction (Biedlingmaier and Whelan, 1996).

Sensorineural

No drug treatment has shown efficacy in restoring olfactory function. Experimentally, substance P or acetylcholine is reputed to increase olfactory receptor sensitivity (Bouvet, 1988) and flavour amplification. The selection of natural odorous molecules by gas chromatography and then adding them to complementary foods can ameliorate mild hyposmia whilst increasing preference and intake of nutrient-dense food in the sick elderly (Schiffman, 1991). Unfortunately anosmic elderly patients, such as those with Alzheimer's do not respond to flavour amplification. Olfaction contributes 80 per cent of the sensation of flavour. Other qualities such as colour, texture, viscosity are also important, and frequent switching between foods allows maximum contact between tastants and receptor sites and prevents adaptation. It is important to speak to relatives about smoke and fire detectors, and the possibility of switching from natural gas to electricity for safety. The benefit of taking zinc is doubtful (Deems *et al.*, 1991), although one study suggested that those with renal or liver disease, who are deficient may be helped (Deems *et al.*, 1991). Vitamin A and B trials supplements do not help (Leopold, 1991). Phantosmia has been treated by excision of the olfactory epithelium from the underside of the cribriform plate (Leopold, 1991). It has been suggested that neurotrophins or pharmacological inhibitors of apoptosis in the olfactory epithelium may be found which will help in some anosmias yet to be determined (Holcomb *et al.*, 1996).

Conclusion

Despite its scope and effect on life, olfaction is still undervalued by the medical profession as our poor understanding of its mechanisms demonstrates. More research is needed to improve our understanding and develop treatment strategies.

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