Fragrance: its biology and pathology

A strange and invisible perfume hits the sense
(Anthony and Cleopatra, II, ii)

Historical

Like fire, metals and the preservation of food, cosmetics and perfumes are thought to have been used for at least 200,000 years. The biological actions of perfumes and flavours are closely linked; a pleasant aroma stimulates the appetite and herbs useful in the culinary arts frequently possess olfactive qualities that render them valuable as perfume ingredients.

Perfume oils were not only used in primeval cosmetics but were also kept in purpose-made vessels not so very different from some present-day air fresheners; they were also incorporated in joss sticks and incense. Such uses were partly to cover 'evil' or simply undesirable smells in much the same way that until fairly recently judges in British courts sniffed at posies of fragrant flowers to cover the malodours of their courts.

Synthetic fragrances

In the last century it became apparent that there were many chemicals in nature with desirable olfactory properties, but that they were present at levels so low that concentrating them to a usable level was too expensive or impracticable. The age of 'synthetic' fragrances began when their structural chemistry was defined and synthetic routes were developed to produce them in large quantities.

Natural products are usually mixtures of chemicals and some can be potentially dangerous, but synthetic preparations can be produced with control not only of their basic constituents but also of impurities. Perfumes and their constituent chemicals are subjected to relatively little legislative control apart from that imposed on all chemicals. While perfume allergy must continue to be a matter of continuing research, the incidence of serious reactions in the total population is low. Other conditions, such as bergamot phototoxicity (Berlocque dermatitis) and persistent light reactions from musk ambrette, have been virtually eliminated due to the extraction of bergaptene (5-methoxypsoralen)—the active ingredient—from oil of bergamot, and from the advice of the International Fragrance Association not to use musk ambrette. The industry continues to monitor all incidents that are reported and to control or ban materials when appropriate.

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Clinical problems

Asthma and respiratory sensitisation

Perfumes probably do not cause asthma but may significantly diminish maximum expiratory flow rates in asthmatic subjects with hyperactive airways [1]. Similar effects are caused by inhaled substances with 'irritant' potential. The part played by the odoriferous characteristics of an individual chemical is difficult to define [2]: in four asthmatics, exposure to colognes resulted in worsening of their asthma as evidenced by lowering of the forced expiratory volume and in a survey of 60 asthmatics, 57 developed respiratory symptoms when exposed to one or more common odours. It is, of course, difficult to ascertain whether such worsening is organic or secondary to emotional stimuli consequent upon the appreciation of certain odours, or to anxiety over the possibility of a reaction. The patient might not be aware that irritant non-odoriferous chemicals may be present at the same time as odoriferous products and wrongly blame the latter. In practice, however, asthmatics who develop symptoms after becoming aware of certain odours should avoid them, whatever the mechanism involved.

Alzheimer's disease and Parkinson's disease

It is interesting that patients with Alzheimer's disease have poor odour perception. Their nasal neuroepithelium contains characteristic masses of abnormal neurites which react with two specific antibodies against the tangles and plaques of Alzheimer's disease, although there are no typical tangles in the olfactory neurons [3,4]. This does not mean that odours are the cause of Alzheimer's disease but rather that the disease affects the olfactory system.

Comparable clinical and pathological changes have been noted in Parkinson's disease.

Anosmia

While complete blockage of odour perception occurs with many inflammatory conditions, such as those resulting from viral infections and chemical irritants and paralysants, recent work indicates that odour inhibition can also be selective. Shirley and co-workers [5] have described selective blocking of the perception of some odours by concanavalin A. It is however, often

difficult to discriminate between true blocking of the olfactory mechanism and overriding central 'neutralising' from multiple messenger effects.

Olfactory mechanisms

Over 10,000 odours can be detected and identified by the human olfactory system. The odour threshold of chemicals varies by many orders of magnitude. The perception of odours is the result of a cascade of events that start at the fibrils of the sensory dendrites in the nose, proceed to the olfactory bulb and thence to the higher cortical centres where odours are consciously appreciated; the response is then actively terminated—it does not just fade away because the stimulus is removed. Burchell [6] has summarised the current concepts of these mechanisms. Cytochrome P450 monooxygenases play a significant role in the termination of enzyme activity. In addition, recent studies by Lancet *et al* [7] have identified an olfactory UDP-glucuronosyltransferase which catalyses the glucuronidation of some odorants and have shown that glucuronic acid conjugation abolishes the ability of odorants to stimulate olfactory adenylyl cyclase.

Much has been learnt about the early part of the process once it became possible to culture the olfactory nerve and study its molecular biology. How the higher cortical centres are involved is much less well understood. The primary event in the nerve is the binding of the odorant molecule to receptor protein molecules at the cilial endpoints of the apical dendrites of the olfactory neurons. Together, they form the olfactory neuroepithelium on the turbinate cartilages in the posterior region of the nasal cavity. The olfactory epithelium contains 10 to 100 million sensory cells which respond to different ensembles of smells. The binding of specific molecules to proteins is a biological mechanism intrinsic to many other biological processes (eg sensitisation). The binding of the molecule to its receptor then initiates a complex cascade of G-protein mediated events [6] and the consequent changes in the cell's metabolism induce electrical charges which are then transmitted to the olfactory bulb. The cortical appreciation of an odour is but one of these events which may, in turn, set off a cascade of related psychological sequelae, themselves perhaps also initiated or modified by the connection of the olfactory bulb to the limbic system. The termination of the olfactory stimulus may not be the end of the biological event; it may become inscribed in memory for a very long time, and possibly be still further modified by concurrent events to evoke conditioned reflex effects.

These observations have led to further questions: are the many different odours distinguished by a multiplicity of different odour receptor cells; or by specific protein receptors in otherwise similar receptor cells; or by differing biochemical reactions and metabolic pathways of the different odour-protein conjugates? It is probable that all these may operate but no doubt further mechanisms will be revealed in due course.

The olfactory nerve has been closely studied in the investigation of axoplasmic transport in neurons [8]. These cells have many advantages for such studies because the olfactory nerve is 'probably the simplest, most homogeneous and most easily accessible nervous tissue available for biochemical and axoplasmic transport studies'. Its cells undergo continuous turnover, being replaced by undifferentiated cells which develop into receptor neurons, with new axons growing out to reach the olfactory bulb [9]. Proteins and low molecular weight compounds, including amino-acids, are carried to synapses by axoplasmic transport, but the speed of such transport is much slower than that of odour perception. Although this mechanism may be one possible mode of entry for perfume into the nervous system, there is no definitive proof that such transport necessarily plays any part in the appreciation of smell. But it does present a potential route to the nervous system other than transport in the blood, and an alternative to the concept that the blood-brain barrier is the only significant factor that controls delivery to the central nervous system.

Social implications of perfume use

Perhaps the most typical considerations in the social sense, apart from masking or simple replacement of malodours, is the use of incense and the debatable role of pheromones in humans. It is interesting to speculate whether the use of incense arose solely from a concept of association of religious expresion with smoke and fire or the more esoteric concept that most incense contains 'remains of plants', viz essential oils which contain resenes, acids and complex resin alcohols.

Certain animal steroids are also found in plants and some synthetic monocyclic C_{16} molecules can rotate and produce steroid-like profiles [10]. Thus it is possible that the constituents of early incense were in some cases not dissimilar to pheromones. Why does pheromonal activity play little, if any, part in human responses? Stoddart [11] has suggested a mechanism based on the need in human social evolutionary terms for the 'bond of fidelity', and has discussed the part played in the masking of odours, including pheromones, by natural perfumes and the consequent masking of oestrus-advertising odours. At the same time he emphasises the 'ambivalences of humankind' towards odour and its suppression, accepting that this may involve association with our 'memory traces' and 'olfactory vestiges'.

Recent studies in the psychological aspects and biochemistry of fragrance have answered many interesting and important questions but have also presented us with even more problems concerning mechanisms. Their solution may well result not only in more and

better fragrances but may also help to clarify several areas of medical and clinical research.

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