Section of Laryngology

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Olfaction and its Disorders

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Recent Advances in the Pathology of Olfaction

Ear, nose and throat surgeons frequently see patients complaining of olfactory symptoms. Unlike deafness we have no audiogram that we can compare with other patients, that we can repeat with certainty or indeed that we can report to each other easily. The surgeon also knows that he is unlikely, in the majority of cases, to obtain improvement, while at the back of his mind lurks the danger of serious intracranial disease and the difficulties of psychiatric diagnosis. The symptoms are variable, and a classification is always helpful if only to render them more familiar:

(1) *Quantitative abnormalities:* Anosmia and hyposmia. Hyperosmia.
(2) *Qualitatative abnormalities (parosmia)*: Presence of bad smells. Alteration of smells. Single non-discriminating (SND) response.
(3) *Illusions, hallucinations and abnormal sense-memory:* These symptoms are caused by three main groups of conditions: local disease of nose and surrounding area; intracranial illness; psychiatric illness.

This paper deals only with abnormalities of smell resulting from disease of the nose.

Metabolic changes may affect the sense of smell, and we have long been familiar with the hypertrophic and hyperæmic effects which hormonal changes may induce in the respiratory mucosa of the nose. The different capacities for smelling the synthetic lactone, exaltolide, which are shown by males and females in the various periods of the life cycle have also been known for many years. These factors should not be over-estimated, although we should always bear in mind the possible effects of contraceptive pills and other drugs. In fact the majority of patients we see will suffer from some abnormality of the nose.

The nasal illnesses which may cause loss of smell are: structural abnormalities preventing access to the olfactory area, including nasal polyps and tumours; rhinitis, which may be allergic, vasomotor or chronic infective; post-influenzal anosmia; rare types of congenital anosmia.

We have tried to obtain material from the olfactory mucosa of patients suffering from a selected group of illnesses and to combine their clinical examination with light and electron microscopic inspection.

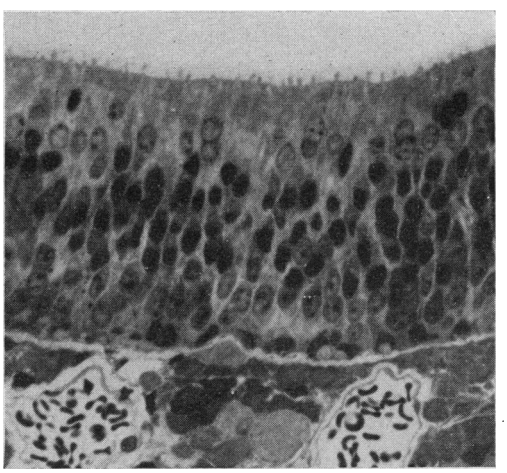

Fig 1 *Vertical section through the olfactory mucosa of a mouse to show receptor endings protruding from the surface of the epithelium, dark receptor cell bodies and nuclei in the middle zone of the epithelium, with nuclei of supporting cells above and the pale nuclei of basal cells below. Vascular tissue, nerves and gland cells are visible in the lamina propria at the base.* × 375

Clinical Examination

This included routine ENT examination, together with skull and sinus X-ray and olfactory tests using the olfactory spectrogram (Douek 1974).

Technique

In man the olfactory epithelium is limited to the upper surface of the superior turbinate, to a corresponding area of the nasal septum and to the under-surface of the cribriform plate in between. Its size is variable and its margins are indistinct, but once these difficulties are recognized, taking biopsies does not present impossible difficulties.

It is done under local or general anæsthesia with the patient placed in the usual position for nasal operations. The nostril is held open with a self-retaining speculum and the operating microscope focused on the olfactory area. A small biopsy is taken from the septal surface using a long thin pair of toothed dissecting forceps.

The tissue fragment is placed in a small quantity of physiological saline and gently flattened with a pair of mounted needles. In some cases it is found advantageous to carry out-this step on a millipore filter, making sure that the epithelial surface is uppermost. The specimen is then flooded with 3% glutaraldehyde in 0.2 mol/l. phosphate buffer (pH 7.3), and fixed for 4 hours. Subsequently the tissue is washed several times with 0.2 mol/l. phosphate buffer, treated with buffered 1% osmium tetroxide, dehydrated, embedded and sectioned for electron microscopy. Sections stained with uranyl acetate and lead citrate are examined with an RCA EMU-4A electron microscope. Somewhat thicker (1 μm) sections are also taken from the same tissue blocks, stained with toluidine blue and viewed with the light microscope. Comparative material taken from mice was also prepared in a similar manner.

Findings

Normal: The normal mucosa in all mammals including man (Naessen 1971) consists of a sensory epithelium containing bipolar receptor neurones, situated on a lamina propria of varying thickness in which to lie the olfactory axons, glands of Bowman, and various connective tissue elements. The olfactory epithelium itself consists of the sensory cells, the nuclei of which form several layers, surrounded by supporting cells with apically-positioned nuclei, and bounded beneath by a layer of basal cells (Fig 1). Some of the basal cells are immature in structural characteristics and are believed to give rise periodically to new receptors, at least in some species (Andres 1966, Moulton *et al.* 1970, Graziadei 1974,

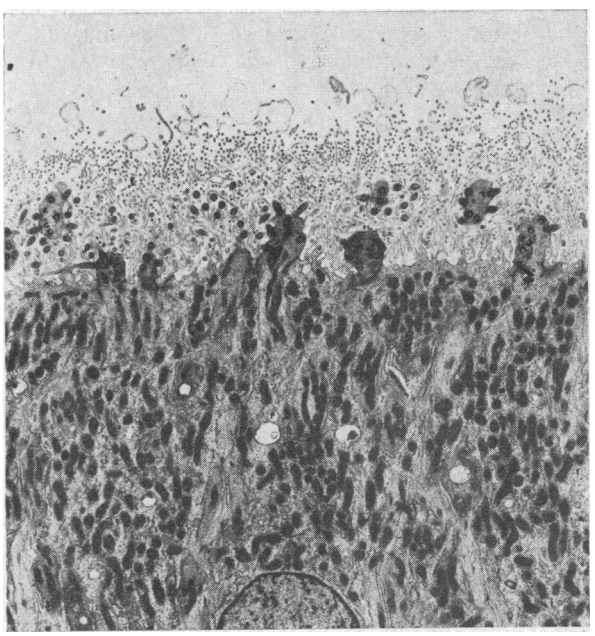

Fig 2 *Electron micrograph of the olfactory surface of a mouse, showing ciliated sensory endings and receptor dendrites, with the apices of supporting cells covered with microvilli.* × *2250*

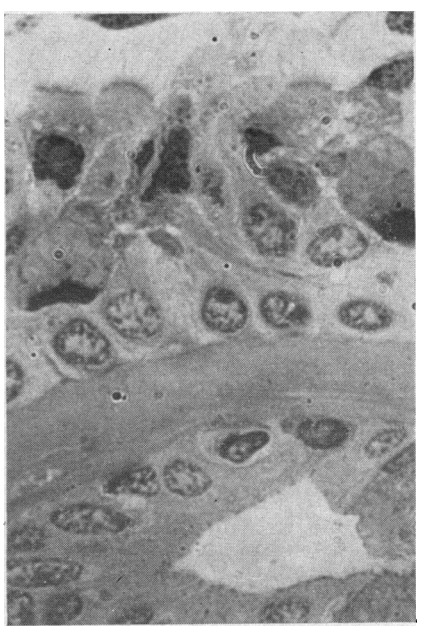

Fig 3 *Light micrograph of a biopsy from a case of post-influenzal anosmia, showing ciliated columnar epithelial cells situated above a thick collagenous lamina propria. A crypt containing possible sensory cell precursors is present at its base.* × *750*

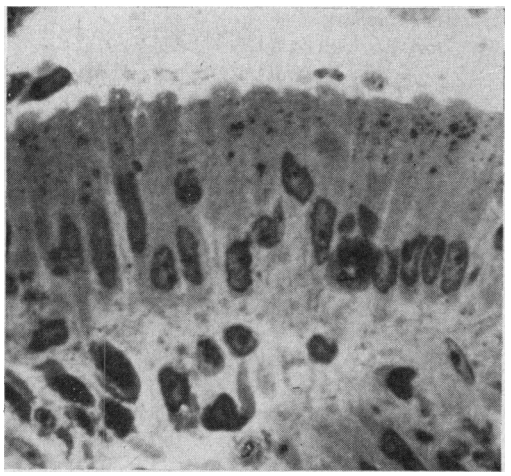

Fig 4 *Light micrograph of the olfactory epithelium from a case of congenital anosmia.* × *600*

Bannister & Dodson 1975). The sensory terminals of the olfactory dendrites bear numerous cilia (Fig 2), the trailing endings of which interweave among the many microvilli which mark the surfaces of the neighbouring supporting cells. Mucus, secreted by the subepithelial glands of Bowman, covers the sensory area.

Tissue from patients: The first patient suffered from vasomotor or allergic rhinitis, with much sneezing, profuse nasal secretions and a rather pale appearance of the mucosa. He had been unable to smell for ten years. The biopsy showed a normal olfactory surface, with numerous olfactory endings provided with cilia which often showed some malformation, being either rather short, or clustered together within a single cell membrane. The surfaces of the supporting cells protruded above the level of the receptor endings more than is usual, but otherwise appeared quite normal. Olfactory axons and associated Schwann cells were observed in the lamina propria, and Bowman's glands were also present.

The second patient who had undergone multiple sinus operations over many years suffered from a chronic infective rhinitis. He had no measurable sense of smell. No part of the biopsy showed true olfactory epithelium, the surface apparently being replaced by respiratory epithelium with ciliated columnar and goblet cells. Extensive tracts of dense collagenous tissue in the lamina propria indicated that considerable scar formation had occurred, and no olfactory axons were observed.

The third patient had influenza followed by complete anosmia. Examination showed a normal nose and the olfactory spectrogram indicated an SND response. The biopsy was abnormal (Fig 3), with signs of extensive scarring of the subepithelial tissue and replacement of the sensory epithelium with respiratory epithelium containing ciliated and goblet cells. Mucous and serous cells were visible in glandular crypts. Scattered in the basal regions of the epithelium and in the glandular crypts were pale oval or fusiform cells containing numerous mitochondria and sometimes clusters of centrioles near one end. These cells resemble immature receptor cells (*see* Discussion). No axons were detected in the subepithelial regions.

The fourth patient is very striking. He suffered from congenital anosmia. His biopsy when looked at by light microscopy seemed at first sight almost normal (Fig 4) but closer inspection with the electron microscope revealed that certain abnormalities existed in the structure of the receptor cells (Fig 5). The receptor endings although containing clusters of centrioles, were completely devoid of cilia, and did not project above the level of their attachments to the surrounding supporting cells. Their dendrites were rich in ribosome groups, but contained only a few microtubules, and their cell bodies showed only meagre development of membranous

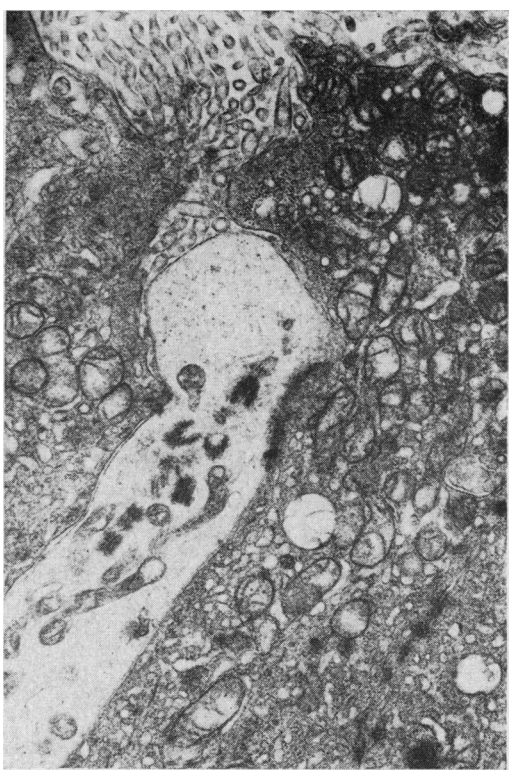

Fig 5 *Electron micrograph of material shown in previous figure (congenital anosmia) showing a pale receptor ending containing centrioles and mitochondria but bearing no cilia. Supporting cells with microvilli are present on either side of the ending.* × *11 250*

organelles such as granular endoplasmic reticulum. Olfactory axons were irregular in shape and disorganized in their arrangement. All of these features are similar to those of early fetal olfactory receptors (*see* Discussion).

Discussion

These are early days in the study of pathological changes in anosmia and our findings may be the first recorded in this way. For this reason they are open to some qualification. Only a small number of patients have been examined and this type of biopsy, like all biopsies cannot guarantee that the area seen is representative.

This accepted, our findings do clarify certain questions. It seems that vasomotor or allergic rhinitis does not damage the olfactory organ and that disuse even for more than a decade will not grossly impair the sense of smell. Treatment therefore remains a possibility.

Chronic infection may damage areas of the olfactory organ and this will be replaced with respiratory epithelium. On the other hand this means that islands of normal epithelium may persist and the possibility of at least partial regeneration is not excluded.

Influenza virus appears to cause the destruction of receptors and supporting cells accompanied by scarring of the adjacent tissues. Although individual 'stem' cells capable of giving rise to new receptors may still exist it seems that their possible attempts at regeneration are not effective perhaps because of the pathological changes of the surrounding tissue.

Our congenital case shows an immaturity of receptor structure similar to that seen in fetal animals before functional contact is made with the cells of the olfactory bulb (Cuschieri & Bannister 1975), and it may be therefore that the abnormality here is one of incorrect or incomplete contact with the central nervous system.

Conclusion: We have shown within the limits imposed by biopsy methods, the different types of cellular structure found in anosmic patients suffering from allergic or vasomotor rhinitis, chronic infective rhinitis, influenzal anosmia and congenital anosmia.

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Aberrations of the Sense of Smell in Head Injury and Cerebral Tumours

This paper considers the differential diagnosis of lesions outside the nasal passages which may cause disorders of the sense of smell; ethmoidal carcinoma and nasal meningocœles are excluded.

As with all neurological conditions, the first essential is to spend the greater part of the time available delving into the history. This is especially important if fits have occurred, for it may then be necessary to interrogate relatives and witnesses. There are many people with a defective sense of smell who only become aware of their disability when it is brought to light by litigation or some other circumstance, such as an escape of gas. The next step is a full neurological examination, with particular reference to tests of intellectual function and signs of a change of personality, or raised intracranial pressure and visual field defects. If it is possible to use the more refined techniques for testing olfaction they will provide more information, but the usual test substances such as camphor, coffee, and asafœtida are generally enough, each nostril being examined separately. Plain X-rays of the skull may show fractures, signs of raised intracranial tension, the presence of calcification, or a hyperostosis associated with a meningioma. However, interpretation is often difficult, and abnormalities are sometimes only found retrospectively.

The electroencephalogram (EEG) may not be particularly helpful because the majority of the lesions we are concerned with are extracerebral, and may cause little disturbance of electrophysiological activity. Lesions causing psychomotor or temporal-lobe epilepsy are of course an exception.

First it is necessary to exclude the possibility of a traumatic origin of hyposmia or anosmia. Olfactory fibres which pass through the cribriform plate may be disrupted by frontal fractures, which are diverted towards this area by an oblique bar of thickened bone which crosses the roof of the orbit (Johnson & Dutt 1947). These injuries are frequently associated with cerebrospinal rhinorrhœa because the dura is torn by an upturned fragment of bone. The brain is trapped in the opening, which communicates with the nasal passages. Repair is effected by placing a sheet of fascia lata over the defect after it has been fully exposed. The olfactory fibres going to the bulb are usually torn on the same side as the defect, and unilateral anosmia may be a help in the often difficult task of locating the source of leakage.