Objectives: To determine whether transnasal excision of olfactory epithelium is a safe, effective therapy and to learn more of the pathogenesis of phantosmia by studying the histological features of the excised mucosa.

Design: A retrospective study consisting of a medical record review and telephone survey. Follow-up ranged from 1 to 11 years (average, 5.4 years). Excised tissues were histologically processed and descriptively compared with normal and other abnormal olfactory tissues.

Setting: Tertiary university medical referral centers.

Patients: All patients who presented to the primary author (D.A.L.) from 1988 to 1999 with unremitting phantosmia lasting longer than 4 years.

Intervention: Olfactory testing and transnasal endoscopic excision of olfactory mucosa.

Main Outcome Measures: Tested olfactory function, patients’ perception of phantom odor resolution, and histological findings.

Results: Of 8 patients, 7 have complete and permanent resolution of their phantosmia. Postoperatively, the single nostril olfactory ability in the operated-on nostril is decreased in 2 nostrils, remains unchanged in 7, and is improved in 1. The excised olfactory mucosa generally shows a decreased number of neurons, a greater ratio of immature to mature neurons, and disordered growth of axons with some intraepithelial neuromas.

Conclusions: Surgical excision of olfactory epithelium is an effective and safe method to relieve phantosmia while potentially preserving olfactory ability. The abnormal histological features of the excised olfactory tissue suggest at least some pathological condition in the peripheral olfactory system. This nasal surgery requires intensive olfactory evaluation and follow-up. It is also extremely difficult with significant risks, and therefore should be limited to specialized centers.


Phantosmia is the intermittent or continuous perception of an odor when no odorant stimulus is present. Some individuals with this symptom perceive the odor independent of nasal airflow, and there is no change in the odor perception when nasal airflow is blocked unilaterally or bilaterally. There are other individuals, however, in whom blockage of uninasal airflow eliminates the phantom odor, and they are the subject of the present article. Most commonly, the perceived odor is unpleasant, and is typically described as “burned,” “foul,” “rotten,” “sewage,” or “chemically.” A variety of extrinsic or intrinsic stimuli such as changes in nasal airflow, strong odors, or loud sounds can trigger the odor or it may appear spontaneously. Some patients may have an aura associated with the onset of the phantosmia. When the phantom perception is present, everything the patient eats has this flavor, and foods do not mask the perception. All of these patients with phantosmia have a self-admitted poor quality of life, with each meal having the aroma of foul meat, burned garbage, or feces. It is usual for the patients to have thought about suicide because they had been offered no hope for resolution from other physicians.

The perceived odor usually lasts only a few minutes the first time it is experienced, and it almost always has a spontaneous onset. It then will recur at monthly, then weekly, then daily intervals over a period of 6 months to a year. The duration that the perceived odor is present also increases over the same time, often lasting most of the day after 1 year. For the first year or two, the phantom smell sponta-
PATIENTS AND METHODS

PATIENTS

Eight patients (7 women and 1 man) presenting to the primary author (D.A.L.) from August 1988 to May 1999 with phantosmia lasting longer than 4 years were reviewed. The length of symptoms ranged from 4 to 19 years (average, 8.2 years). Preoperative evaluation included a thorough history, a complete head and neck examination, nasal endoscopy, uninasal smell testing (eg, a 40-odorant scratch-and-sniff Smell Identification Test [SIT] [Sensonic Inc, Haddonfield, NJ]), and computed tomography of the sinuses as well as magnetic resonance imaging or computed tomography scan of the head to rule out intracranial pathological conditions. All these patients were judged to be psychiatrically stable in that they were all employed, displayed no unusual behavior, did not have histories of alcohol or drug abuse, displayed a lively affect, and had logical thought patterns. None of the patients thought the odors were coming from them, or referred to the odor as being human in origin. Most importantly, blocking the involved nostril could always stop the perceived odor.

All patients underwent a sequential uninasal anesthesia of each olfactory cleft, which temporarily eliminated the phantom odor when the involved nostril was selected. This was performed by dripping 1 cm³ of 4% cocaine into the patient’s nostril while their neck was fully extended and they were supine. The level of anesthesia could be judged by the lack of response to olfactory stimuli. Electroencephalograms had been obtained on 3 patients to determine if there was any abnormal brain electrical activity. Positron emission tomography of the brain using fluorodeoxyglucose is an imaging technique that was performed in 3 patients to help understand the disease and to possibly aid in their care.

Follow-up data were obtained through medical record review and telephone interviews. Also, a SIT was mailed to each patient with instructions to perform uninasal smell testing. The telephone interview included questions regarding nasal and sinus status since surgery, perceived olfactory function, and whether they would have the surgery if they had it to do over again. The length of follow-up ranged from 1 to 11 years (average, 5.4 years). A meaningful change in olfactory function was defined as a change of greater than 5 odors on the SIT.

SURGICAL TECHNIQUE

The surgery was performed under general anesthesia using transnasal and transethmoidal endoscopic techniques on only 1 side and was generally the same in each patient. The olfactory mucosa was removed along the length of the cribriform plate, taking care to sharply cut the fila olfactoria as they were identified. The area was then inspected for cerebrospinal fluid leak. A mucoperiosteal graft was placed against the cribriform plate to prevent cerebrospinal fluid rhinorrhea and treat it when it occurred. The patients remained in the hospital overnight on bed rest with the head of the bed elevated. All excised olfactory mucosa was sent for special immunostaining. The surgery that was done in those patients who failed to improve the first time was performed in a similar manner. This operation is difficult because the olfactory nerve tissue is tough in character and difficult to cut sharply because of the angles involved. Care is also needed to operate “gently” to avoid disturbing the neural tissue of the olfactory bulb, and the orbital tissues that are close. Finally, the operation must be done with attention to preserving ventilation, stability, and mucosal coverage of all nasal and ethmoid tissues.

HISTOLOGICAL METHODS

Excised tissue was fixed by immersion in Bouin fluid for 2 to 4 hours and embedded in paraffin. Serial sections were collected throughout the entirety of the tissue, and selected ones were immunostained with antibodies against olfactory marker protein (anti-OMP) (the gift of Frank Mar-golis, PhD, University of Maryland, Baltimore), neurotubulin (antineurotubulin [anti-NT] monoclonal antibody), and growth-associated protein GAP-43 (monoclonal antibody 7B10) (the gift of Karina Meiri, PhD, Upstate Medi-cal University, Syracuse, NY) using standard techniques.

nerously resolves with more than an hour of sleep. Patients often describe stereotypical methods to relieve the unpleasant odor perception, including bending over and holding the ankles while holding the breath, forced crying, intranasal instrumentation, and gagging. All of these manipulations, including sleep, eventually fail to resolve the phantosmia.

Many of the patients stated that their olfactory ability fluctuated, with it being worse when the phantom odor perception was present. Olfactory testing usually reveals a decreased olfactory ability in the involved nostril.

Because phantosmia is a rare and poorly understood disorder, there has been no well-defined treatment. Often, patients are given ineffective therapy, and numerous providers will instruct them to “just live with it.” Because of analogies with psychiatric conditions, some patients are told that they have a mental illness.

A variety of treatments have been proposed both medically and surgically. Medical treatments have included sedatives and antiepileptic drugs. Patients receiving these treatments may not experience relief, or the adverse effects may limit their use. Surgical treatment has included olfactory bulb ablation through a bifrontal craniotomy approach. This procedure results in bilateral permanent anosmia and includes the risks associated with a craniotomy.

Although the pathophysiological mechanisms of phantosmia are poorly understood, there is some evidence to suggest that it is either a peripheral problem in the olfactory mucosa or axons or a central phenomenon with a peripheral stimulus. Thus, resection of the olfactory mucosa could possibly eliminate the phantom odor by eliminating the peripheral disease or input. Previous experience with a single patient has suggested that transnasal endoscopic excision of olfactory epithelium can successfully eliminate phantosmia with preservation or regeneration of olfaction. To determine the safety and efficacy of this procedure and to further explore the pos-
sible histological correlates, we have studied a consecutive series of 8 patients on whom transnasal endoscopic excision was performed.

### RESULTS

As given in the Table, 8 patients underwent 14 procedures. In 4 patients, the excision needed to be repeated because the phantom smell was not eliminated after the first operation; 2 patients underwent bilateral procedures; 1 patient had bilateral disease at presentation, while another subsequently developed disease on the opposite side. Ages ranged from 21 to 35 years in the women, and the only man was aged 54 years. All 8 patients were contacted by telephone, and in response to the question, ‘If you had it to do over again, would you have the surgery?’ all responded affirmatively. Phantom smell persisted in 1 patient. Two patients occasionally believed that the phantom was about to come on (aura), but it never did. Complete resolution of the phantosmia occurred in 7 of the 8 patients.

The intent of the operation is to destroy the olfactory ability, and all patients had no olfactory ability using olfactory testing in the first few weeks after the surgery. Starting about 2 months after the operation, the patient’s olfactory ability usually returned and stabilized. Testing 1 to 11 years postoperatively showed the olfactory ability in the operated-on nostril to be unchanged in 5 of 10, improved in 2 of 10, and decreased in 3 of 10 nostrils compared with preoperative levels. In the nonoperated-on nostril, 3 of 6 remained unchanged, 1 of 6 decreased, and 2 of 6 improved. Two cerebrospinal fluid leaks were noted intraoperatively, and these were successfully treated with the surgical technique. There were no difficulties with visual changes, epiphora, meningitis, or scarring resulting in chronic rhinosinusitis.

Positron emission tomography scanning was done in 3 patients and revealed increased activity in the opposite frontal, insular, and temporal regions, which decreased after excision of the olfactory epithelium from the involved nasal cavity. These changes add evidence to the theory that phantosmia may be a ‘central’ process. This information, however, did not help in the clinical treatment of the patients, thus positron emission tomography scanning was not performed on all patients.

The electroencephalograms did not show seizure activity, thus they were not obtained in most of the patients. Most described olfactory ‘auras’ associated with seizures lasting seconds to minutes, and all of our patients had odor symptoms lasting hours to days. Thus, seizure is unlikely to be the cause of this symptom.

Olfactory epithelium and/or fascicles of the olfactory nerve were identified in the excision specimens from all phantosmic patients. The comparison of staining with anti-OMP and anti-NT on adjacent sections permits the discrimination of mature (anti-OMP-stained) and immature (anti-NT–stained but not stained with anti-OMP) neurons and the classification of axons in the olfactory fascicles by the same criteria. Of the tissue from the patients complaining of phantosmia, 3 features were different compared with biopsy specimens from normosmic volunteers without nasal inflammation undergoing nasal procedures such as septoplasty and transnasal pituitary surgery. First, in each of the phantosmic cases, the epithelium contained a higher proportion of immature than mature neurons in contrast with the predominance of mature neurons in the normosmic biopsy specimens (Figure 1). Second, the epithelium in many of the cases contained intraepithelial neuramas, which are tangles of disordered axons situated superficial to the basal lamina. Invariably, most of the neuramous axons were elaborated by immature olfactory neurons and were labeled by anti-NT but not anti-OMP (Figure 1). These first 2 features were also noted in our previous report on phantosmia.

The last feature has not been described previously. Much of the cross-sectional area of large fascicles of the olfactory nerve lacked axons as evidenced by an absence of immunostaining with anti-NT and anti-OMP. Those axons that were retained in the nerve were predominantly immature in their phenotype, ie, they stained with anti-NT and not anti-OMP (Figure 2). The reduction in axonal staining was true of all phantosmic patients. Examination of fascicles lacking immunopositive fibers in other patients without phantosmia

### Table

<table>
<thead>
<tr>
<th>Patient No. (Test)</th>
<th>Age at Surgery, y</th>
<th>Nostril (No. of Operations)</th>
<th>Most Recent Postoperation Smell Test Score</th>
<th>Preoperation Smell Test Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (OCM)</td>
<td>25</td>
<td>L (1)</td>
<td>R: 63% L: 71%</td>
<td>R: 48% L: 75%</td>
</tr>
<tr>
<td>2 (SIT)</td>
<td>35</td>
<td>L (1)</td>
<td>R: 9 L: 7</td>
<td>R: NA L: NA</td>
</tr>
<tr>
<td>3 (SIT)</td>
<td>21</td>
<td>R (2)</td>
<td>R: 23 L: 26</td>
<td>R: 23 L: 37</td>
</tr>
<tr>
<td>4 (SIT)</td>
<td>26</td>
<td>R (2)</td>
<td>R: 36 L: 40</td>
<td>R: 40 L: 40</td>
</tr>
<tr>
<td>5 (SIT)</td>
<td>34</td>
<td>L (1)</td>
<td>R: 37 L: 36</td>
<td>R: 18 L: 20</td>
</tr>
<tr>
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<td>26</td>
<td>R (1)</td>
<td>R: 32 L: 31</td>
<td>R: 34 L: 36</td>
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<td>26</td>
<td>R (2), L (2)</td>
<td>R: 32 L: 13</td>
<td>R: 30 L: 21</td>
</tr>
<tr>
<td>8 (SIT)</td>
<td>54</td>
<td>L (1), R (2)</td>
<td>R: 12 L: 16</td>
<td>R: 25 L: 27</td>
</tr>
</tbody>
</table>

*On the odorant confusion matrix (OCM) test (Wright,† 1987) greater than 80% correct is considered normosmic, and 10% is chance performance. On the smell identification test (SIT), greater than 35 correct out of 40 indicates a generally useful olfactory system, whereas 10 is chance performance. R indicates right; L, left; and NA, not available.
demonstrates replacement of axons by collagen fibers (J.E.S., unpublished observation, 1992). By extension, we interpret the lack of anti-NT immunostaining in phantosmic patients as an indication that the large fascicles have lost a significant number of axons. In contrast with the loss of staining (and axons) in large fascicles, the staining of smaller subepithelial fascicles was uniform and without interruption (Figure 2). The loss of axons from large fascicles of phantosmic patients contrasts with the greater complement of stained axons, albeit also immature in phentypotpe, in the fascicles of patients who complain of hyposmia of anosmia after head trauma (Figure 2).

**COMMENT**

The pathophysiological mechanisms of this disorder are yet to be determined. The site of the disorder may be anywhere along the olfactory pathway. The histological findings suggest that the growth of olfactory axons is disordered in these patients. The presence of intraepithelial neuromas is not unique to this population and has been observed in patients with idiopathic olfactory loss, congenital anosmia (including Kallmann syndrome), and head trauma among others (J.E.S., unpublished observation, 1992). In experimental animals, in which the timing, primary locus, and nature of the insult is better controlled, the generation of neuromas is indicative of either prior damage to the epithelium that is severe enough to prevent axons from exiting the vicinity of their parent neurons or damage to the olfactory bulb or nerve that causes the axons to grow back into the epithelium at some distal point along their course to the bulb. Thus, neuroma formation by itself does not permit us to distinguish whether the primary lesion underlying the phantosmic symptoms is central or peripheral.

The abnormalities in the large fascicles of the olfactory nerve are more consistent with the suggestion that the locus of damage is in the peripheral olfactory system—either the epithelium per se or along the course from the epithelium to the cribriform plate. The contrast in the status of the fascicles of the olfactory nerve between patients with dysosmia secondary to head trauma and the phantosmic population tends to rule out the notion that damage at the cribriform plate and/or to the olfactory bulb is responsible for the aberrant axonal growth in phantosmic patients.

Given the tentative localization of the lesion, at least 2 alternatives may be offered as explanation for the phantosmia: (1) The phantosmia sensation may arise because neurons located near intraepithelial neuromas have an altered response to olfactory stimuli; in this case, activity may be modulated by ionic shifts occasioned by a large mass of activated axons. (2) Alternatively, ephaptic transmission between axons that are disconnected and others that innervate the bulb might result in disordered signaling in response to a stimulus. Ephaptic activation of neighboring axons is known to mediate altered patterns on activity in other nerves. The histopathological observations suggest that the cross-talk might take place at the transition from small olfactory nerve bundles (which appear in-

**Figure 1.** In the epithelium harvested from phantosmic patients, immature neurons predominate and neuromas have formed. A, Anti-NT–stained section of epithelium from a 35-year-old woman (original magnification ×100). Boxed area is shown in higher power (original magnification ×280) in B. Curved arrows (A, B, and D) indicate intraepithelial neuromas. C, Adjacent section stained with anti-OMP (original magnification ×100). Boxed area is shown in higher power (original magnification ×280) in D. Note that the staining of the neuromas is weaker with anti-OMP. Note also that the fascicles are weakly stained with anti-OMP or not at all (open arrows in A and C) and that the number of OMP-positive neurons is commensurately less than the number of NT-positive/OMP-negative neurons (compare B vs D).
tact) to large fascicles (which lack their normal complement of axons). A more definitive test of that hypothesis awaits 3-dimensional reconstruction of the course of axons from the epithelium to the larger fascicles.

Despite the abnormalities of axon distribution in the periphery, we cannot exclude the hypothesis that altered central processing of the stimulus is primarily responsible for the phantosmic symptoms. The improvement in symptoms after excision of the olfactory mucosa does not exclude that interpretation. For example, decreased olfactory input to the bulb is known to down-regulate dopaminergic periglomerular interneurons, which may affect both the transmission of the signals from the olfactory nerve to bulb and the processing of those signals by the bulb itself. Findings from the positron emission tomographic scan studies are also consistent with this central hypothesis. In any event, disrupting the olfactory input seems to somehow eliminate the phantosmia.

The improvement or maintenance of some of the patients’ olfactory ability was unexpected because the surgery was intended to destroy all olfactory ability. One possible explanation is that some of the olfactory receptor cells were spared during the resection. Another possibility is the regeneration and reconnection of the receptor neurons to the olfactory bulb, something known to occur in mammals, but only suggested in humans.

With regard to the patient whose phantosmia did not resolve, several points can be made. He is somewhat older (54 years) and is the only man in the series. It seems from our clinical experience (and others’) that phantosmias are more common in women; however, the reason for this is unclear. Similarly, the significance of his age is also unknown, although the regenerative potential of his olfactory neurons likely decreases with increasing age.

Finally, his case of phantosmia had a burning component, which is suggestive of a trigeminal nerve involvement. Consistent with this suggestion, his was the only phantom odor in our series that was not masked by food. The fact that we were still able to eliminate the perceived odor with nasal anesthesia even after bilateral surgical olfactory ablation further supports the possibility that this is a trigeminal phantom perception.

In conclusion, our experience in this series indicates that transnasal endoscopic excision of olfactory epithelium is a safe and effective treatment for patients with unremitting phantosmia. In addition, olfactory function is potentially spared. Although the histopathological features are suggestive of an abnormal process occurring in the peripheral olfactory mucosa, the exact mechanism has yet to be determined. The surgery, however, is technically challenging, is associated with major risks, and should be relegated to specialized centers.

Accepted for publication November 15, 2001.

This study was presented at the Association for Chemoreception Sciences Meeting, Sarasota, Fla, April 14-18, 1999.
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REFERENCES


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