The etiology of vocal fold nodules in adults
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Introduction
Vocal fold nodules (VFNs) are bilateral epithelial swellings of the anterior third of the true vocal fold and can be found in children, adolescents, and adults working in jobs with high voice demands, predominantly females [1]. Teachers seem to be one of the main groups of professional voice users at high risk for developing VFNs [2].

Many issues contribute to the formation of VFNs and a multidisciplinary approach is paramount to achieve the best possible outcome. Nodules frequently interfere with vocal fold closure and present usually with hoarseness and occasionally with breathiness. They are usually the result of subepithelial scar deposition and, as there is incomplete vocal fold closure, there may be a decrease in range and increase in vocal fatigue, more noticeable in professional voice users. There are many cases, however, of undiagnosed or untreated VFNs, especially in singers, that cause little or no problems at performance [1]. The decision to treat aggressively or conservatively, therefore, should be individualized and based on comprehensive history and physical examination.

The present article reviews the recent literature and emerging science with respect to the etiology of VFNs in adults.

Discussion
Laryngeal function must be coordinated, efficient, and physiologically stable to produce a normal voice. Any imbalance in this delicate system affects vocal quality. Clearly, the interacting processes that give rise to voice disorders are not easily defined and etiological profiles are often difficult to establish, especially when organic factors – acute or chronic – existed prior to or concurrent with the onset of dysphonia. The task of the voice team is to define and sort out pathological processes that precipitate or predispose to a patient’s dysphonia. Taking a history from a dysphonic patient can be a complex and time-consuming process and ideally requires a multidisciplinary approach, including an experienced speech therapist and laryngologist. Attention to detail, in
particular past medical history, is paramount. General health, allergies, smoking, diet, and alcohol are all very important and the question of possible underlying reflux needs special attention. One should remember that it is rare to have only one single finding on laryngoscopy without other synergistic cofactors, hence the need for a detailed medical history. Optimizing the laryngeal environment is one of the primary goals of voice therapy. This may include eliminating phonotraumatic behaviors, optimizing hydration, setting guidelines for voice use, discussing psychosocial contributors, and addressing reflux.

**Phonotrauma and molecular changes in extracellular matrix**

Voice overuse and poor technique (misuse) – especially in professional voice users – are pivotal in the formation of VFNs. Vibration during phonation leads to increased forces and maximum impact stress and trauma at the midmembranous part of the vocal fold, resulting in wound formation followed by healing, remodeling, scarring, and nodule development [3,4]. Several studies over the last two decades have shown that the main focus of injury is at the level of the superficial layer of the lamina propria (SLP) [4,5]. Hyaluronic acid is one of the main contributors to the viscoelasticity of the SLP and when absent may result in scar formation [6]. In a recent animal study, cross-linked hyaluronic acid (hylan B gel) was evaluated as a scaffold for tissue regeneration and mucosal wave restoration in canine vocal folds [7]. Five beagles underwent stroboscopy before ablation of the vocal fold with a laser. Four weeks later, stroboscopy was repeated before and after submucosal injection of hylan B gel into the left vocal fold of four animals and of isotonic saline solution in one animal. Stroboscopy was repeated 12 weeks later, and histologic analysis was performed. Submucosal hylan B gel injection in laser-ablated canine vocal folds restored tissue volume and mucosal waves and facilitated functional tissue regeneration over 12 weeks. The authors concluded that hyaluronic acid may have utility as a soft tissue scaffold for rehabilitation of phonatory function in vocal folds with lamina propria defects [7].

A great deal of information has been acquired recently regarding the function of the extracellular matrix and fibronectin in particular. Immunohistochemical characterization of nodules reveals intense fibronectin staining. Fibronectin is a glycoprotein found in the extracellular matrix of regenerating, healing, and embryonic tissue. Evidence supports the hypothesis that fibronectin participates in many diverse functions that are relevant to vocal fold biology. Courey et al. [5] have shown that fibronectin is increased in the SLP of certain benign vocal fold lesions, including polyps and nodules. Much work remains to be done on a microscopic level before we have a complete understanding of the molecular changes that occur within VFNs and other benign lesions.

**Laryngopharyngeal reflux**

The role of laryngopharyngeal reflux (LPR) in the pathogenesis of benign and malignant laryngeal lesions is probably the most extensively researched laryngology topic of the last decade, with conflicting results. Although there are numerous papers focusing on the relationship of LPR with a group of various otolaryngological symptoms [8,9], there are only a few studies focusing on an isolated symptom or finding alone, such as VFNs, and its possible relationship to reflux. Karkos et al. [10] recruited 25 voice clinic patients with functional dysphonia. Patients with minor degrees of laryngeal inflammation and mild nodule formation – often not clearly distinguished from functional dysphonia – were included. The study failed to demonstrate any relationship between LPR and functional dysphonia. Their findings were consistent with recent randomized data showing that reflux in the upper aerodigestive tract may be somewhat overestimated, and some of the symptoms or signs, originally thought to be reflux-related, could also be self-limiting conditions responding equally to placebo or antireflux therapy [11].

On the other hand, the effect of LPR on the healing of surgically induced laryngeal trauma was recently investigated in a clinical prospective study [12]. Two groups of patients were recruited: the first had benign vocal fold lesions (Reinke’s edema, polyps, and nodules) and no reflux on pH-metry and the second group had benign lesions and reflux. In patients with LPR, proton pump inhibitors (PPIs) were given in half of them, randomly chosen. Fifty LPR-free patients operated for Reinke’s edema or laryngeal polyps during the same time period were used as controls. After 1-year postoperative follow-up, epithelization was complete in all vocal cords of both the control group and the group of patients who had been administered PPIs. Within the group of patients who had not taken PPIs, six patients presented granulation tissue or recurrence of the polyps and in two of them revision surgery was needed. The authors concluded that LPR influences epithelization and recurrence of laryngeal polyps or Reinke’s edema in vocal folds after surgery and that the surgical outcome is superior in patients with LPR who undergo perioperative antireflux treatment.

Any study addressing LPR is bound to be somehow flawed from its very beginning, as there is still no ideal
A recent British study poses the question whether dysphonia due to allergic laryngitis is misdiagnosed as LPR. In their cohort, three times as many patients demonstrated allergy compared with LPR, raising the question of whether some patients with allergic laryngitis are being misdiagnosed with LPR and overtreated with PPIs [17]. Krouse et al. [18] examined the baseline laryngeal effects among individuals with dust mite allergy. Individuals allergic to dust mite perceived significantly greater vocal handicap on the Voice Handicap Index than nonallergic individuals, although no significant differences were noted between groups in laryngeal appearance or function.

**Biomechanical experimental models**

Experimental models to study the biomechanics of the larynx and the relationship between trauma and lesion formation in the vocal folds have been introduced. Jiang et al. [19,20] with a computer model of the vocal fold using finite element technology measured the intraglottal pressure and impact stress and found that the midpoint of the membranous vocal fold received the maximum impact stress during hyperfunctional dysphonia. In normal phonation, mechanical stress was the least at the midpoint and the maximum at tendon attachments. This finding supports a hypothesis that mechanical intraepithelial stress plays an important role in the development of vocal nodules, polyps, and other lesions that are usually ascribed to hyperfunctional dysphonia. Using a self-oscillating model, it was evident that stress was higher on the surface than on the undersurface of the vocal fold [21].

A fluid saturated poroelastic model of the vocal fold with hydrated tissue was introduced recently by the same team [23]. It was found that the liquid in the vocal fold tissue could be accumulated at the anterior–posterior midpoint during phonation, which could cause a pressure increase in the liquid. The authors suggested that the liquid dynamics in the tissue during phonation could be related to the development of some vocal diseases, including VFNs.

**Conclusion**

There is good evidence based on excellent experimental models and clinical studies that phonotrauma is the primary cause for VFN formation. There is also high evidence that the majority of patients with nodules are socially extroverts, aggressive, and impulsive. The synergistic effect of reflux and allergy may be an important part of the multifactorial contributions to vocal fold lesion formation in the vocal folds have been introduced. Jiang et al. [19,20] with a computer model of the vocal fold using finite element technology measured the intraglottal pressure and impact stress and found that the midpoint of the membranous vocal fold received the maximum impact stress during hyperfunctional dysphonia. In normal phonation, mechanical stress was the least at the midpoint and the maximum at tendon attachments. This finding supports a hypothesis that mechanical intraepithelial stress plays an important role in the development of vocal nodules, polyps, and other lesions that are usually ascribed to hyperfunctional dysphonia. Using a self-oscillating model, it was evident that stress was higher on the surface than on the undersurface of the vocal fold [21].

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formation. Basic science research on the molecular characteristics of the lamina propria and advanced experimental models will aid to better understanding, diagnosis, and treatment of these lesions.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

• of special interest

•• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 494).

A recent study proving once again the role of personality traits and extrovert psychological characteristics in patients with nodules.
A recent small but well thought out study on the relationship between allergy and voice and the possible – very contemporary – overdiagnosis and overtreatment of LPR.
22 Czerwonka L, Jiang JJ, Tao C. Vocal nodules and edema may be due to vibration-induced rises in capillary pressure. Laryngoscope 2008; 118:748–752.
A state-of-the-art experimental study using a mathematical blood vessel model showing that intravascular pressure rises significantly during vocal fold vibration and may lead to the type of injury seen in benign vocal fold lesions.