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Laryngopharyngeal Reflux

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Editorial Board

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Editorial

Laryngopharyngeal Reflux

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Laryngopharyngeal reflux (LPR) is here to stay. Despite advances in the role of pepsin, better drugs, and less invasive tests, diagnosis is still difficult and is still in many places—based on empiric treatment rather than robust evidence.

In this special issue on LPR, we attempt to review some hot topics regarding this entity which still puzzles otolaryngologists all over the world.

The issue of chronic cough, postnasal drip, and reflux is quite a controversial topic and remains a therapeutic challenge. Chronic cough can be associated with many diseases that often overlap more than one medical specialty. A detailed assessment of the patient with chronic cough relies on a multidisciplinary approach and close cooperation between pulmonary medicine, gastroenterology, and otolaryngology. Gastroesophageal reflux (GERD) and postnasal drip syndrome account for a significant number of cases of chronic nonproductive cough seen in otolaryngology practice. Each may, alone or in combination, contribute to cough even when clinically silent and failure to recognise their contribution may lead to unsuccessful treatment. Many of these patients are notoriously difficult to diagnose and treat but the literature suggests that a systematic and thorough approach in a multidisciplinary setting can lead to successful diagnosis and treatment in the majority of patients.

The role of surgery in management of LPR is also a matter of debate in the literature. Results of laparoscopic fundoplication for the treatment of classic GERD are well established. In theory, surgery for persistent LPR after failure of medical treatment should be equally as effective, if we agree on the notion that LPR and GERD share common pathophysiology. Many studies have demonstrated symptomatic improvement after surgical fundoplication. However, current knowledge does not allow this conclusion. Large multicenter, randomized control trials are needed, focusing on diagnostic tools to improve selection criteria, presenting standard endpoints and long-term follow-up.

Eosinophilic esophagitis (EE) is a great reflux mimic and often presents with dysphagia, recurrent food bolus obstruction and GERD-like symptoms. Despite higher awareness, the literature suggests that EE remains a commonly misdiagnosed condition especially in the otolaryngology community. The treatment though differs than the LPR treatment and EE should be part of the differential diagnosis when faced with "difficult to treat LPR or GERD". The introduction of Transnasal Esophagoscopy in the ENT office over the last decade has meant that increasingly more laryngologists become accustomed in recognising esophageal pathology including EE.

The presence of specific endoscopic laryngeal findings in patients with suspected LPR has been well documented in the literature. Because the first-line therapy for LPR is considered to be proton pump inhibitors, there are many studies comparing the endoscopic laryngeal findings before and after acid suppression therapy.

Finally, the role of pepsin and the fact that LPR is much more dependent on pepsin-mediated damage in the laryngeal and airway mucosa than on acid have been well

described over the last few years. The crucial role of pepsin in LPR may, in turn, stimulate the development of drugs which specifically target this molecule. This may radically enhance our knowledge and management of this condition.

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Review Article

Chronic Cough, Reflux, Postnasal Drip Syndrome, and the Otolaryngologist

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Objectives. Chronic cough is a multifactorial symptom that requires multidisciplinary approach. Over the last years, general practitioners refer increasingly more chronic cough patients directly to the otolaryngologist. The aim of this paper is to highlight the issues in diagnosis and management of chronic cough patients from the otolaryngologist perspective. *Design*. Literature review. *Results*. Gastroesophageal reflux and postnasal drip syndrome remain one of the most common causes of chronic cough. Better diagnostic modalities, noninvasive tests, and high technology radiological and endoscopic innovations have made diagnosis of these difficult-to-treat patients relatively easier. Multidisciplinary assessment has also meant that at least some of these cases can be dealt with confidently in one stop clinics. *Conclusions*. As the number of referrals of chronic cough patients to an Ear Nose Throat Clinic increases, the otolaryngologist plays a pivotal role in managing these difficult cases.

1. Introduction

Chronic cough is a persistent and frustrating symptom for many adults and children and a frequent reason for primary or secondary care visits or referrals. This condition generates significant healthcare and economic cost and is associated with a spectrum of disorders across multiple medical specialties and can provide significant challenges for the involved physician or surgeon. Chronic cough is associated with deterioration in the quality of patients' lives. Associated symptoms and negative outcomes with this condition include loss of sleep, exhaustion, irritability, urinary incontinence, cough syncope, social disability, and inability to perform daily activities. Many patients experience chronic cough secondary to another medical condition, such as COPD, asthma, rhinosinusitis, Gastroesophageal reflux syndrome (GERD), postnasal drip syndrome (PNDS), or unknown etiology. GERD is thought to be the most common cause of chronic cough in a nonsmoker nonasthmatic individual.

Thorough assessment of a patient with a chronic cough relies on a multidisciplinary approach. The otolaryngologist should be familiar with the diagnostic algorithm of chronic cough patients and should work closely with the gastroenterologist and the pulmonologist, ideally in "cough clinics," to confidently diagnose and treat these patients.

1.1. Reflux and Chronic Cough. Chronic nonspecific cough, defined as a nonproductive cough in the absence of identifiable respiratory disease or known cause [1] persisting for more than three to eight weeks [2], poses a significant burden to healthcare costs and considerably impairs quality of life. Gastroesophageal reflux disease (GERD) represents one of the three main causes of chronic cough (along with asthma and upper airways cough/postnasal drip syndrome), implicated in up to 41% of chronic cough patients [3]. The clinical features of GERD-related cough include heartburn, regurgitation, and/or worsening of cough after foods or medications known to decrease lower esophageal sphincter-pressure, with extraesophageal manifestations such as hoarseness, wheezing, sore throat, chest pain, and globus also described.

Whilst classic GERD symptoms are present in 6–10% of chronic cough patients, GERD is clinically silent in up to

75% of patients with GERD-related cough [4]. Diagnosis of GERD is frequently based on the clinical responses of cough to antireflux therapy rather than on objective assessments of GERD *per se*. Furthermore, an increased understanding of the pathophysiology of GERD and in particular the specific phenomenon of laryngopharyngeal reflux (LPR), has highlighted the complexity of this condition, with the need for individual patients assessment and tailoring of therapy becoming apparent.

Coughing may be provoked by reflux via a number of mechanisms. The regurgitation of gastric contents into the laryngopharynx can cause mechanical or pH-sensitive stimulation, with chronic inflammation leading to the sensitisation of peripheral nerves mediating cough [5]. This may have an acid or nonacid (namely, bile and pepsin) basis. Adhami et al. [6] demonstrated that bile can injure the laryngeal epithelium but only in an acidic environment, and furthermore, Sasaki et al. [7] were able to demonstrate histological laryngeal injury in a rat model following bile exposure in neutral environments. Pepsin, the principal proteolytic enzyme of the stomach, is predominantly active in acidic pH and has been shown to cause laryngeal injury in this state [6]; however proteolytic activity is still present up to pH 7 and can be reactivated [8]. Johnston et al. [8] found the presence of pepsin in the larynx of patients with the clinical diagnosis of LPR but not in controls and in these same patients, pepsin was absent in their esophageal epithelium [9]. It has been suggested that coughing can also be induced by "micro" or "silent" aspiration, caused by the direct activation of tracheo-bronchial receptors by reflux entering the airway. Distal esophageal reflux may also induce coughing through vagal stimulation known as the oesophago-bronchial reflex [10], Ing et al. [11], demonstrating that infusing acid into the oesophagus of chronic cough patients increases coughing. Additionally whilst infusion of acid (compared to saline) into the oesophagus of those GERD patients without chronic cough had no effect, a sensitised cough reflex to capsaicin was seen in those GERD patients with chronic cough [12].

An alternative pathophysiology is that coughing can in fact be the causation in reflux: increased intra-abdominal pressure during strenuous coughing episodes negatively impacting the lower esophageal sphincter, possibly by way of a positive feedback loop [13].

As discussed above, reflux associated cough can be a laryngopharyngeal or distal esophageal phenomena. LPR has distinct features, as first identified by Koufman and colleagues. In a combined reported series of 899 patients, throat clearing was a complaint of 87% of LPR patients versus 3% of those with GERD, while only 20% of LPR patients complained of heartburn versus 83% in the GERD group [5]. Differences in body mass index (BMI) between GERD and LPR patients have also been highlighted; in a retrospective study of 500 patients attending for pH probe studies, the mean BMI of isolated LPR patients was 25.9 compared to 28.3 for those with GERD [14].

Identifying GERD as the cause of a chronic cough can be challenging. Esophageal pH testing can demonstrate an increased number of reflux events, prolonged exposure of the esophageal mucosa to reflux, or more convincingly a significant temporal association between reflux events and cough. Although esophageal pH testing has a sensitivity of approximately 90% for the evaluation of chronic cough, specificity ranges from 66% to 100% [15, 16]. Additional diagnostic tests include inhaled tussigenic challenges, endoscopy, examining bronchoalveolar lavage fluid, and/or sputum for lipid laden macrophages, barium swallow, Bernstein test, radioisotope scintiscan, and radionucleotide emptying studies with solids [17]. Examination of the larynx may reveal evidence of LPR: key examination findings being vocal cord oedema and erythema as well as medial vocal cord erythema [18, 19]. Findings should, however, be taken in context: Hicks and colleagues finding that almost 80% of study participants had a least one reflux-attributable finding on laryngoscopy when 100 healthy volunteers were examined [20].

1.2. Treatment of GERD-Associated Cough. Patient counselling is essential in reducing GERD and related LPR. Dietary advice includes the avoidance of a high-fat diet and losing weight if obese, avoiding eating two hours before bedtime and refraining from caffeine, carbonated drinks, alcohol, and citrus products [21]. Patients should also be asked to refrain from smoking and elevate the head of the bed by 15 cm. Some medications are associated with increase GERD, namely, anticholinergics, beta-agonists, bisphosphonates, calcium-channel blocker, corticosteroids, benzodiazepines, oestrogens, opiates, progesterone, prostaglandins, and theophylline [17]. Other recommendations include nasal continuous positive airway pressure if obstructive sleep apnoea is present [22] and avoiding exercise that may increase intra-abdominal pressure [23].

Proton pump inhibitors (PPIs) have commonly been the mainstay empirical treatment for GERD-related cough. Given the difficulty in clearly diagnosing this condition, Irwin [21] has described the clinical profile of such patients in whom empirical therapy should be considered; those not exposed to environmental irritants, not a present smoker, not on an ACE inhibitor, with a normal/stable chest radiograph, and in whom symptomatic asthma, upper airways cough syndrome, and nonasthmatic eosinophilic bronchitis has been ruled out. The use of empirical therapy has, however, been questioned. In a meta-analysis of 5 randomised controlled trials on GERD treatment for cough in adults and children without primary lung disease, Chang et al. [24] found that there was no difference in cough resolution for patients who received a placebo versus a PPI (OR 0.24 (95% CI 0.04 to 1.27). There was, however, a significant difference in secondary outcomes of mean cough score (mean difference of −0.51 (−1.02 to 0.01)) and change in cough score (−0.29 (−0.62 to 0.04)) at the end of the trial. This led the authors to conclude that the use of PPI had "some effect in some adults." More recently, a Cochrane Database Systematic review by Chang and colleagues [2] including 9 randomised controlled trials of PPIs for adults with chronic cough found that using intention-to-treat, pooled data from studies resulted in no significant difference between treatment and placebo in total resolution of cough (OR 0.46; 95% CI 0.19 to 1.15 no overall significant improvement in cough outcomes (end of trial or

change in cough scores). There was, however, a significant improvement in cough scores at end of intervention (two to three months) in those receiving PPI (standardised mean difference −0.41; 95% CI −0.75 to −0.07) using generic inverse variance analysis on cross-over trials. The authors were unable to conclude definitely that GERD treatment with PPIs is universally beneficial for cough associated with GERD. Despite the current lack of evidence for definite treatment of empiric treatment, published guidelines from the ACCP [21] and BTS [25] suggest that PPI therapy should be commenced, for example, omeprazole 20–40 mg twice daily or equivalent taken before meals for at least 8 weeks [25].

Of particular interest in nonacidic refux, medications such as Gaviscon or Gaviscon Advance, which act by forming a raft or physical barrier to reflux present a supplementary or even alternative treatment option. McGlashan et al. [26] conducted a randomised controlled trial of Gaviscon Advance in 49 patients with a diagnosis LPR (based on the reflux symptom index (RSI) and the reflux findings score (RFS)). Patients were assessed pretreatment and at 2, 4, and 6 months after treatment. Significant differences in the mean (SD) between treatment and control were observed for RSI at the 2-month (11.2 (7.0) versus 16.8 (6.4), $P = 0.005$) and 6-month (11.2 (8.1) versus 18.3 (9.4), $P = 0.008$) assessments and for RFS at the 6-month (7.1 (2.8) versus 9.5 (3.4), $P = 0.005$) assessment. The details of the cough component of the RSI were not, however, detailed further in the report.

Gastroesophageal dysmotility has been implicated in the pathophysiology of GERD via abnormalities of delayed gastric emptying and reduced pressure or inappropriate transient relaxation of the lower esophageal sphincter [27]. Several prokinetic agents (e.g., bethanechol, metoclopramide, domperidone, cisapride, and macrolides such as erythromycin) can stimulate gastrointestinal motility and have, therefore, been proposed as useful adjuncts to antireflux medication. The evidence base for this lies only in unblinded, uncontrolled studies, where, when in combination PPIs for treating GERD-associated cough, cough or hoarseness improved by 70% to 100% [10, 28–31]. In the recent Cochrane review, Chang et al. [2] found insufficient data to evaluate the evidence for the use of prokinetic agents in chronic cough. However, interestingly in 56 patients diagnosed with GERD-related cough, 24 responded to a PPI alone; however, 18 of the remaining patients improved with the addition of metoclopramide or cisapride [32]. These drugs, however, may have significant side-effects: erythromycin, for example, often causes nausea and abdominal pain and cisapride was withdrawn from the US market due to safety concerns.

Although surgery is more traditionally used to treat the more typical reflux symptoms, it may be of some value in the management of reflux-related cough. Studies relating to the outcomes of surgical treatment of GERD are, however, of questionable value as they suffer from lack of controls and blinding, use differing postoperative evaluation criteria, and are typically based on a highly selective group of patients. Kaufman and colleagues [33] reported their long-term (mean 53 months) outcomes of 128 patients treated with laparoscopic antireflux surgery. Cough and hoarseness was improved in 65% to 75% of cases compared to heartburn and regurgitation in over 90% of subjects. In their review of treatment options for GERD-related cough, Chandra and Harding [17] summarised the finding of 9 prospective studies of surgical management, reporting that 586 of 689 surgically treated patients had a "significant cough response."

GERD remains one of the leading causes of chronic cough; however, the difficulty in diagnosing this condition, especially as "classic" reflux symptoms are often absent means that it can be overlooked. The mainstay of treatment, for now, remains as lifestyle modification, dietary advice, and medical therapy. The role of traditional empirical treatment with PPIs is questionable, with evidence from randomised trials implying that there is some benefit in the right patient group. Identifying this patient group is, therefore, imperative: careful clinical history taking and laryngeal evaluation along with objective reflux assessment being key. The use of alginate preparations seems to be quite popular in the last few years, although evidence is currently lacking. Surgical management, although not as useful for cough symptomatology as for classic symptoms also has a role in patients resistant to medical therapy.

2. Postnasal Drip Syndrome (or Upper Airway Cough Syndrome)

Postnasal drip (PND) or catarrh is the drainage of secretions from the nose or paranasal sinuses into the pharynx. Clinically, the diagnosis of PND syndrome (PNDS) is very vague, made on history and examination and relies on the reporting of the patient of this sensation of something "dripping down the throat," rhinorrhoea and constant throat clearing [34]. Nasendoscopy revealing rhinitis and mucopurulent secretions is suggestive, although not diagnostic. The issues when attempting to diagnose PNDS, is that there are no objective sensitive or specific tests and no way to quantify the amount of catarrh or to prove that it is directly responsible for causing cough. PNDS is associated with very nonspecific symptoms and a definitive diagnosis of PND-induced cough cannot be made from the history and examination findings alone.

The differential diagnosis of PNDS-induced cough includes all other causes of rhinitis including, allergic rhinitis, perennial nonallergic rhinitis, bacterial sinusitis, allergic fungal sinusitis, rhinitis due to anatomic sinonasal abnormalities, rhinitis due to physical or chemical irritants, occupational rhinitis, rhinitis medicamentosa, and rhinitis of pregnancy.

Another issue when attempting to diagnose PNDS-induced cough is that GERD is often associated with a high prevalence of upper respiratory symptoms and therefore can either coexist or mimic PNDS [35]. The introduction of the-more widely accepted in Americas-term of "Upper Airway Cough Syndrome" (UACS) was made based on the need to answer the question whether "the conditions listed above actually produce cough through a final common pathway of PND or whether, in fact, in some circumstances they cause irritation or inflammation of upper airway structures that directly stimulate cough receptors and produce cough independently of or in addition to any associated PND" [35].

It is obvious that because there are no objective tests for diagnosing PND, treatment is often based on the specific disease that is present. For example, avoidance of specific allergens after allergy testing has been done, nasal steroid treatment and antihistamines, treatment of concomitant infection, and correction of any associated sinonasal anatomical abnormalities can have an indirect effect on the management of PND-induced cough.

The American College of Chest Physicians recommends an empiric trial of therapy for UACS because improvement or resolution of cough in response to specific treatment is the pivotal factor in confirming the diagnosis of UACS as a cause of cough. That should especially be the case if no specific cause can be elicited from the history and examination [36].

A usual empiric therapy involves a first generation antihistamine/decongestant. If a patient has resolution or partial resolution of cough, then UACS is considered to have been a cause of cough and antihistamine therapy is continued. Marked improvement or resolution of cough may take several weeks and occasionally as long as a few months [37].

If there is no response with a first-generation antihistamine, then the patient should undergo sinus imaging. Chronic sinusitis causes a productive cough or can be clinically silent, in that the cough can be nonproductive, and none of the typical findings associated with acute sinusitis may be present [36, 38].

Allergy skin testing, measurement of serum Ig levels to see whether (acquired) hypogammaglobulinemia is present, evaluation of the patient's home and workplace if there is a potential environmental cause for persistent upper airway symptom are all reasonable diagnostic strategies especially if there is lack of response to sinusitis treatment. If nasendoscopy reveals nasal polyps, in the absence of any contraindication, the patient should undergo a standard aspirin challenge. If the results of the challenge are positive, the patient should undergo desensitization, followed by the consideration of chronic aspirin therapy unless it is contraindicated.

3. Conclusions

Chronic cough can be associated with many diseases that often overlap more than one medical specialty. A detailed assessment of the patient with chronic cough relies on a multidisciplinary approach and close cooperation between pulmonary medicine, gastroenterology, and otolaryngology. Gastrooesophageal reflux and postnasal drip syndrome account for a significant number of cases of chronic nonproductive cough seen in otolaryngology practice. Each may, alone or in combinationcontribute to cough even when clinically silent, and failure to recognise their contribution may lead to unsuccessful treatment. Many of these patients are notoriously difficult to diagnose and treat but the literature suggests that a systematic and thorough approach in a multidisciplinary setting can lead to successful diagnosis and treatment in the majority of patients.

Conflict of Interests

The authors declare no conflict of interests.

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Review Article

Impact of Laparoscopic Fundoplication for the Treatment of Laryngopharyngeal Reflux: Review of the Literature

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Laryngopharyngeal reflux (LPR) is part of the so-called extraesophageal manifestations of gastroesophageal reflux disease (GERD). It is presented by unspecific symptoms and signs and is believed to be caused by the reflux of gastric content to the proximal esophagus and larynx. However, evidence considering the role of the antireflux surgery for LPR has failed to demonstrate results comparable to those for GERD. The aim of this paper is to review the current literature regarding the impact of laparoscopic fundoplication for the treatment of LPR.

1. Introduction

Gastroesophageal reflux disease (GERD) is defined as a condition that develops when the reflux of stomach contents into the esophagus causes troublesome symptoms and/or complications and represents the failure of the antireflux barrier [1]. It has long been recognized as a significant public health concern, since heartburn afflicts nearly two-thirds of US adults at some point in their lives and accounts for a great number of physician office visits every year [2]. While most GERD patients suffer from typical esophageal manifestations, such as heartburn and regurgitation, there is a subset of patients who experience the so-called laryngeal symptoms, which may be caused by laryngopharyngeal reflux (LPR) [3]. Table 1 displays the most frequent symptoms associated with LPR, which are unspecific and can be found in other otolaryngologic disorders [4].

Despite the advances in medical management for GERD, the surgical treatment has been studied more methodically since the introduction of laparoscopic Nissen fundoplication [5], and increasing numbers of patients have opted for the surgical treatment since the advent of this minimally invasive technique. However, most of the studies regarding the surgical treatment for LPR symptoms have failed to show results as good as those for GERD symptoms [6]. Interestingly, the efficacy of medical treatment for LPR is also not comparable to that for GERD [7].

Although LPR and GERD have different clinical presentation and response to management, accumulating evidence shows the correlation between the pathophysiology of both entities, which is the reflux of the gastric content to esophagus or proximally, to the larynx [8]. Perry et al. 2008 [9] showed that, in the upright position, LPR patients have the same degree of gastric cardia dilation that is found in patients with typical GERD symptoms and those with a mixed presentation, suggesting that the same pathophysiologic disturbance that predisposes typical GERD patients to reflux is present in patients with symptoms of LPR. Furthermore, acid reflux is thought to lead to not only

Table 1: Laryngopharyngeal reflux symptoms.

Dysphonia
Swallowing difficulty (pseudodysphagia)
Globus
Throat clearing
Cough
Choking
Post nasal drip
Laryngospasm
Sore throat

laryngeal alterations associated with LPR, but also the direct contact of the laryngeal epithelium with gastric refluxate containing pepsin, bile acids, and other components, which are not prevented by the proton pump inhibitors (PPIs) [8]. Taking together, this evidence suggests that the antireflux surgery should have good results in LPR patients as well, since it provides an effective barrier to gastroesophageal reflux and eliminates both acid and nonacid reflux.

The aim of this paper is to present the current evidence regarding the impact of laparoscopic fundoplication (LF) for the treatment of LPR.

2. Materials and Methods

A Medline, PubMed, and Cochrane database search was done to find articles in the English language on surgery for LPR in adults. The following keywords were used: "surgery/fundoplication and extraesophageal manifestations of gastroesophageal reflux," "surgery/fundoplication and laryngopharyngeal reflux," and "surgery/fundoplication and atypical symptoms of gastroesophageal reflux." Related articles and links were searched. Additional articles were identified by a manual search of the references from the key articles. only articles regarding antireflux surgery specifically for the treatment of LPR and not including lower respiratory or other extraesophageal symptoms of GERD were selected.

3. Results

A total of five studies were selected. There were no randomized clinical trials and only one study had a control group. The inclusion criteria, preoperative evaluation, and endpoints are not standardized, making the data too heterogeneous.

Westcott et al. 2004 [10] studied 41 patients submitted to LF due to LPR symptoms. After a mean follow-up time of 14 months, he observed 84% improvement in reflux symptom index (RSI). From the preoperative evaluation, the factors significantly associated with poor outcome after surgery were structural changes seen in laryngoscopy (i.e., vocal-cord scarring, paresis, granuloma, and carcinoma or subglottic stenosis) and no improvement with PPIs treatment.

Swoger et al. 2006 [11] conducted a controlled study with 25 patients presenting LPR symptoms that did not respond to aggressive PPI treatment (omeprazole 40 mg twice daily or lansoprazole 60 mg twice daily for 4 months). From this group, patients who decided to submit to LF ($n = 10$) were compared to the ones who decided to keep on medical management (control group $n = 15$). No significant improvement in symptom scale was observed in both groups, despite a significant improvement in pH and laryngoscopy scores after surgery. Some patients have demonstrated improvement in symptoms by treating additional pathologies such as allergy or asthma.

Catania et al. 2007 [12] studied 58 patients submitted to LF for laryngopharyngeal reflux, for a mean followup of 15.4 months. Since the first month after surgery, he observed 97% improvement in symptoms (decrease >5 points in RIS) and 65% of total response (patients experiencing no symptoms). These results were maintained on late follow-up evaluation. Also, there was a significant increase in quality-of- life index used measured by laryngopharyngeal reflux-health-related quality-of-life index.

Sala et al. 2008 [13] evaluated vocal and laryngeal symptoms in 22 patients submitted to LF for LPR, after a 3 months course of medical treatment. Vocal and laryngeal symptoms significantly improved after 3 months of medical treatment and kept improving after surgery, showing a statistically significant difference between pre-and postsurgical treatment too. However, voice quality and laryngeal findings only showed a significant improvement after surgery.

Wassenaar et al. 2011 [14] introduced a new approach to preoperative evaluation. While most of the studies use classical evaluation with dual-probe 24 h-esophageal pHmetry, upper endoscopy, laryngoscopy, in this study, patients were additionally evaluated with laryngeal pepsin measured by western blotting in sputum and posterior laryngeal biopsies. All but one patient with LPR symptoms were positive for pepsin in laryngeal biopsy before surgery. Also, sputum was collected preoperatively in 5 patients and 4 of these were positive for pepsin, in correlation with correspondent biopsy. Seven patients were submitted to LF, and 2 were submitted to endoscopic fundoplication (EsophyX, EndoGastric Solutions, Redmond, Wash). From these 2 patients, 1 had to be submitted to LF for failure of the endoscopic treatment. Eight patients had symptom improvement (6 good improvement and 2 mild), and 1 had no improvement. From the 8 patients who experienced improvement, 7 were negative for pepsin in postoperative sputum analyses, and 1 had a consistent decrease in pepsin (from +++ preoperatively to + after surgery). The only one patient who did not experience improvement was negative for pepsin in preoperative biopsies and sputum.

4. Discussion

Literature review demonstrated additional studies regarding surgical treatment for LPR, but including patients with other extraesophageal symptoms, such as lower respiratory symptoms [15, 16]. We decided to exclude those studies from this paper in order to achieve a more specific analysis, since even the studies directed to LPR present critically heterogeneous evidence. Whereas most studies had shown some degree of symptomatic improvement after surgical

fundoplication, further conclusions are challenging, due to the weak evidence grade of the studies.

A possible explanation to the difficulty of the studies in proving the efficacy of LF for LPR is that, in most of the studies, the diagnosis of LPR is focused on traditional measures of gastroesophageal reflux (esophagoscopy or pH monitoring), identification of injury by laryngoscopy, pharyngeal pH monitoring, or empiric treatment of symptoms by PPIs, which have demonstrated not to be reliable diagnostic tools [6]. LPR presents with a spectrum of symptoms and signs that are very unspecific and most of the times not associated to classical GERD symptoms [17]. Therefore, any advance in preoperative evaluation that could lead to a more specific characterization of the LPR and the correlation of the symptoms with the gastric reflux will help to study the effect of the restoration of the antireflux barrier in those patients.

Recent studies have focused on more specific methods for diagnosis and prediction of response to treatment in LPR patients [18]. Although not controlled and with a small number of patients, the study by Wassenaar et al. 2011 [14] probably brought a more specific marker for LPR, with a good correlation between symptoms and reflux, which marked even the efficacy of LF. Pepsin in sputum and/or in laryngeal biopsies must now be studied in large randomized controlled trials.

Another important factor to be taken into account is the body mass index (BMI) of subjects submitted to surgery. From the studies presented above, only one has provided the BMI of the patients [14]. Several studies have proposed a causative role for obesity on GERD [19, 20], but the correlation between obesity and LPR is still poorly understood [21, 22]. Additionally, long-term control of GERD by LF in obese patients seems to be worse than in normal weight subjects [23]. Therefore, patients BMI must be well characterized in any study regarding the efficacy of LF.

5. Conclusion

Results of LF for the treatment of GERD are well established [24], and, in theory, both GERD and LPR share a similar pathophysiology. Consequently, well-indicated antireflux surgery should be as effective for LPR as for GERD. Many studies have demonstrated symptomatic improvement after surgical fundoplication. However, the current knowledge presented by the literature does not allow this conclusion. Large multicenter, randomized control trials are needed, focusing on diagnostic tools to improve selection criteria, presenting standard end-points and long-term followup.

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Review Article

Eosinophilic Esophagitis for the Otolaryngologist

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Objectives. This paper focuses on current diagnostic and treatment options for Eosinophilic Esophagitis (EE). *Study Design*. literature review. *Results*. EE can be suspected on history and endoscopy although definitive diagnosis is strictly based on histopathology. It is a relatively new entity and is often misdiagnosed as gastroesophageal reflux (GERD). Eosinophilic infiltration of the esophageal mucosa is responsible for esophageal symptoms which can range from mild to debilitating dysphagia and food impaction, when untreated. In fact recurrent foreign body and food impaction can often be blamed for undiagnosed EE. There seems to be a strong familial component and association with allergy. The introduction of transnasal esophagoscopy in adult laryngology has enabled otolaryngologists to readily diagnose EE and promoted awareness of this often difficult to recognize entity. *Conclusions*. Despite higher awareness, the literature suggests that EE remains a commonly misdiagnosed condition especially in the otolaryngology community. Genetic studies are required to unfold the true familial and genetic component of this fascinating entity.

1. Introduction

Eosinophilic esophagitis (EE) previously known as idiopathic eosinophilic oesophagitis, atopic oesophagitis, and allergic oesophagitis is a clinicopathological entity that is being diagnosed with increasing frequency. According to the latest consensus EE represents a chronic immune/antigen-mediated esophageal disease characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation [1]. This disease is isolated to the esophagus and has to be distinguished of any moderate eosinophilic infiltration associated to a generalized eosinophilic infiltration of a gut mucosa (gastroenteritis and colitis) [1]. The diagnostic criteria of EE include esophageal and/or upper gastrointestinal tract symptoms accompanied by ≥ 15 intraepithelial eosinophils/high power field (HPF) in 1 or more biopsy specimens without pathologic gastroesophageal reflux disease (GERD), as shown by normal pH monitoring of the distal esophagus or the lack of response to high-dose proton pump inhibitor (PPI) medication [2].

2. Epidemiology

EE was thought to be a rare condition; however a sharp rise in its prevalence is recognized in most countries. This could be due to a combination of a true escalation in its incidence, combined with an increasing recognition, awareness, and testing amongst gastroenterologists, otolaryngologists, and pathologists. This notion is supported by the fact that there are numerous reports of patients with multiple oesophageal rings with intraepithelial eosinophils that had been ascribed to acid reflux, but who did not respond to standard acid suppression therapy. In retrospect, these patients may have had EE [3–5].

The literature reveals an increase in frequency in both pediatric [6] and adult [7] populations. One particular north American study showed that the incidence of EE has increased dramatically from 0.35 per 100 000 between 1991 and 1995 to 9.45 per 100000 between 2001 and 2005 making the prevalence of EE 55.0 per 100,000 people [8].

EE affects both sexes and all age groups with the typical patient being an atopic male presenting in childhood or the 3rd or 4th decades of life [1]. The age at diagnosis can vary though. The disease affects 8 children and one adult, and most pediatric cases appear in the first three years [1, 3]. Moreover, children with eosinophilic esophagitis have a higher frequency of atopic symptoms and peripheral eosinophilia than do adults [7]. The male-to-female prevalence ratio has been reported as 3 : 1 with cases extensively reported

in patients of different ethnic origins [3]. Familial trends have been reported [9–12] with the majority of cases to date reported from North America and Europe and to a lesser extent Asia, Australia, and South America. No cases have been reported from Africa [10].

3. Etiology

There are a number of factors that are believed to play a role in the origin of EE. These are genetics, allergy, seasonal variation, and GERD.

There is more literature to support a genetic basis for EE. Studies have validated the expression of a unique EE transcriptome and validated that it differentiates EE from GERD, with eotaxin-3 being abundantly overexpressed in patients with EE [1, 13]. IL-13 has been found to be specifically upregulated in the esophagi of patients with EE and might function as a master regulator of the EE transcriptome [14]. Rothenberg et al. have identified the first genome-wide susceptibility locus at 5q22 [15]. Sherrill et al. have reported that polymorphisms in the thymic stromal lymphopoietin (TSLP) gene are risk factors for EE independent of underlying allergy phenotypes [16]. They state there is a gender-specific association between single-nucleotide polymorphisms (SNPs) in TSLP as well as a nonsynonymous SNP in the TSLP receptor which suggests a mechanism for the male predilection of the EoE [16]. Another SNP in the promoter of the TGF-β1 gene has been linked to reduced esophageal remodeling following topical steroid treatment. Familiar cases have also been reported [17].

More studies are supporting the concept that EE is an antigen-driven allergic condition, with a varying percentage of pediatric and adult patients having at least one more "allergic" disease. It is reported that 50%–60% of patients with EE have a prior history of atopy [1, 8, 18]. The majority of patients have evidence of or a familiar history of allergic rhinitis, asthma, eczema, or hypersensitivity to foods or aeroallergens. The latter two are based on skin prick testing and IgE test results. Moawad et al. demonstrated a seasonal variation in the diagnosis of EE which correlated with higher pollen count [19]. However, EE was still present during periods of lower atmospheric pollen concentrations and in patients without a history of atopic disease, pointing towards a possible multifactorial pathogenesis. In the pediatric literature, food allergies have been implicated in the pathogenesis of EE [19, 20].

Allergens induce T-helper-2 (Th2) cells to produce interleukin (IL)-13, which can cause esophageal cells to overexpress eotaxin-3 and fibroblasts. Activated Th2 cells also produce IL-5, which regulates eosinophil numbers and their response to eotaxin-3. In addition to eosinophils, mast cells and lymphocytes (including B cells) accumulate in the esophagus to contribute to the local inflammatory responses observed in patients with EE. The resulting injury leads to esophageal remodelling with wall thickening and fibrosis [9]. The cytotoxic role of eosinophils in EE is directly related to the observed histopathological changes with destruction of the most superficial epithelial layers and the regenerative response from the basal layers of the epithelium [21, 22].

The exact role of GERD in the development of EE is unclear; however the latest updated consensus recommendations states esophageal pH monitoring is useful to establish whether GERD is present in EE or not [1].

4. Clinical Presentation

Clinical manifestations in children are less specific, whereas in adults they are more predictable. Feeding difficulties are the manifestation in infants and toddlers, whereas vomiting and/or pain may be present in school-aged children. Dysphagia is the main symptom in adolescents [1, 5]. Other symptoms include a failure to thrive, heartburn, and isolated nausea [9]. To date, no pathognomonic features have been identified. Atopy is a common association in pediatric and adult patients with evidence of another allergic disease (allergic rhinitis, asthma, eczema, or hypersensitivity to foods or aeroallergens) in more than half the cases. Family history of atopy is frequent, with one study reporting a rate of 74% [9, 23].

The most common presenting symptom in adults is solid food dysphagia. Others include food impaction (which may or may not require endoscopic intervention), chest and upper abdominal discomfort/pain, and resistant reflux symptoms (despite a trial of acid suppression). One study showed that more than half of patients with esophageal food impaction, based on clinicopathologic features are likely to have EE [24].

There is a subset of patients who have symptoms of EE, have had GERD diagnostically excluded but still demonstrate a clinicopathologic response to PPIs. Terms used to describe these patients include PPI-responsive esophageal eosinophilia. The definition and diagnostic guidelines of EE include the term immune/antigen driven; however, studies and clinical experience have identified a potential anti-inflammatory or "barrier healing" role for proton pump inhibition in patients with esophageal eosinophilia [1].

5. Diagnosis

Esophagoscopy with biopsy is the ideal investigation for the diagnosis of EE. There are various endoscopic findings, however none pathognomonic for EE. These include mucosal fragility (59% of cases), esophageal "trachealization" (multiple concentric rings resembling the trachea) in 49%, strictures in 40% of cases, furrows, white plaques, or papules in 16% (aggregates of eosinophilic microabscesses), irregular mucosa, reddish changes in esophageal mucosal pattern, esophageal tears, and a narrow caliber in 5% [10]. Many of these features, including longitudinal furrows, are subtle and can be missed. Between 9% and 32% of patients with symptoms suggesting eosinophilic esophagitis have normal endoscopic findings, and studies have shown patients can have histologically proven EE yet normal macroscopic appearance on endoscopy [25].

Radiological investigations are not recommended except in selected cases in order to elicit anatomical abnormalities/variations.

Histology is essential in making the diagnosis of EE. The latest consensus recommends that 2 to 4 mucosal biopsy specimens of the proximal and distal esophagus should be obtained, as various studies have shown the eosinophilic infiltration is similar in these sections of the esophagus. In children and, when indicated in adults, biopsy specimens of the gastric antrum and duodenum should be obtained once to exclude other potential causes of esophageal eosinophilia [1]. No prospective studies have determined a threshold number of esophageal eosinophils that can establish a diagnosis of EE with high specificity and sensitivity and consistently allow differentiation of EE from other causes of esophageal eosinophilia. It is recommended that, until more studies are performed, all histologic features including eosinophil microabscess formation, superficial layering of eosinophils, extracellular eosinophil granules, basal cell hyperplasia, dilated intercellular spaces, rete peg elongation, subepithelial lamina propria fibrosis, and increases in other cell types be noted in pathology reports [1].

One-third to one-half of patients have peripheral eosinophilia, and up to 55% have increased serum levels of immunoglobulin E (IgE), therefore the search for specific IgEs is strongly advised [20]. Although peripheral eosinophilia can correlate with tissue eosinophilia in some patients with EE, changes in the former need to be considered with caution [1]. Because of the association with allergic diseases, a complete evaluation of aeroallergen and immediate type food allergy is warranted.

6. Treatment

Management of patients EE remains controversial. EE is a chronic disease and its activity may fluctuate independently of any therapeutic intervention, and, although it affects quality of life, it does not seem to limit life expectancy or be associated with malignant or premalignant conditions. Several treatment modalities have been tested. We focus on medical, dietary, and surgical interventions according to the 2011 recommendation [1], which have recently replaced the 2007 recommendations.

Surgical intervention is usually reserved for the complications of EE, namely, stenosis of the esophagus. Esophageal dilation with either Savary dilators or unsedated transnasal balloon techniques is associated with an 83% symptom response rate and a low complication rate of 5% [26]. Other smaller studies report excellent symptomatic relief, for both adults and children [27, 28]. Although dilation does not improve the underlying inflammatory process and will probably need to be repeated, perhaps it is an adequate strategy for the healthy, young to middle-aged men commonly affected by the disease, who might prefer it to regular medications or diet [29]. Although complications are more frequent than those associated with dilation for other benign conditions [30], the risk of perforation appears to have been exaggerated—a systematic review of 18 studies [31] identified 1 perforation in 671 dilations (0.1% risk).

Medical treatment for EE needs to be both effective and safe, considering the fact that EE is a chronic disease requiring prolonged courses of therapy for remission. Medications used include corticosteroids, cromolyn sodium, proton-pump inhibitors (PPIs), leukotriene receptor antagonists, immunosuppressive agents, and monoclonal antibodies.

PPIs are used both for diagnostic and therapeutic purposes. Acid suppression is important to rule out secondary esophageal eosinophilia due to GERD, although some authors feel EE's contribution to refractory GERD is not significant [32]. A high PPI dose of 20–40 mg twice daily is recommended for 8 to 12 weeks in adults (1 mg/kg twice daily in children with the adult dose as maximum). PPI therapy alone is not effective for patients with EE; however it might alleviate symptoms related to secondary GERD [1]. It has been suggested that PPI-responsive esophageal eosinophilia is a different clinical entity. A small randomized controlled trial comparing PPIs versus topical corticosteroids failed to show a difference between the groups [33].

Topical corticosteroids are effective in children and adults, inducing remission in most cases. A number of randomized controlled trials have evaluated this in recent years: a 15-day course of treatment with budesonide (viscous suspension, 1 mg twice daily for adults, 0.5 mg twice daily for children under 10 years old) is well tolerated and highly effective in inducing a histologic and clinical remission [1]. Fluticasone (440–880 mg twice daily for adults, 88–440 mg twice to 4 times daily for children, puffed and swallowed through a metered-dose inhaler) has also been used in adults and children and was favoured before 2007 [33]. There is no significant evidence that either treatment is superior to the other [1]. Systemic corticoids are not recommended due to their adverse effects (up to 40%) as other treatments are almost equally effective [33]. For severe urgent cases requiring hospitalization, Prednisone 1-2 mg/kg should be considered [1].

Other treatment modalities [1, 33] include

(a) cromolyn sodium, which was shown to be ineffective and is not recommended,

(b) leukotriene receptor antagonists, of which montelukast might have a role in maintaining remission in children but was proven inefficient in adults and is not recommended,

(c) immune suppressants, such as azathioprine or 6-mercaptopurine, which were shown to be ineffective and is not recommended

(d) monoclonal antibodies, such as Mepolizumab, a humanized monoclonal antibody against interleukin-5 (IL-5) which is not effective in adults and although it promotes a histologic response it is not clinically effective in children, Omalizumab (a monoclonal anti-IgE antibody) which is not effective [34], and Infliximab (a chimeric monoclonal anti tumor necrosis factor-α antibody) which is not effective.

Diet modification (elimination of specific foods guided by skin prick and atopy patch testing) is effective in over 75% of patients and should be attempted in children. In adults results are mixed, possibly because of poor compliance [1]. Elemental diet is not a real option in adults and elimination diets (directed, or empirical of milk, egg, soy, peanut,

tree nut, wheat, shellfish, and fish) do not achieve consistent results.

7. Conclusions

Despite higher awareness, the literature suggests that EE remains a commonly misdiagnosed condition especially in the otolaryngology community. The introduction of Transnasal Esophagoscopy in the ENT office over the last decade has meant that increasingly more and more laryngologists become accustomed in recognising esophageal pathology including EE.

Genetic studies are required to unfold the true familial and genetic component of this fascinating entity.

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Research Article

Endoscopic Laryngeal Findings in Japanese Patients with Laryngopharyngeal Reflux Symptoms

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Objective. To know the characteristics of endoscopic laryngeal and pharyngeal abnormalities in Japanese patients with laryngopharyngeal reflux symptoms (LPRS). *Methods*. A total of 146 endoscopic images of the larynx and pharynx (60 pairs for the rabeprazole group and 13 pairs for the control group) were presented to 15 otolaryngologists blinded to patient information and were scored according to several variables potentially associated with laryngopharyngeal reflux. The median value of the 15 scores for each item from each image was obtained. The mean pretreatment scores of each item and total score were assessed in both rabeprazole and control groups. In the rabeprazole group, the endoscopic findings before and after the 4-week treatment with rabeprazole were compared. Changes between corresponding duration in the control group were also evaluated. *Results*. The median and mean pretreatment total score was 3 and 3.02, respectively, from the 73 patients with LPRS. No significant differences were observed before and after treatment in either the rabeprazole or control groups for any item or total score. In 24 patients with a high pretreatment score (total score ≥ 4) from the rabeprazole group, significant decreases in scores for "thick endolaryngeal mucous" (0.54 to 0.17, $P = 0.017$) and total (4.77 to 3.58, $P = 0.0003$) were observed after the 4-week treatment.

1. Introduction

Gastroesophageal reflux is a recognized cause of ENT symptoms [1]. Laryngopharyngeal symptoms and signs were referred to as laryngopharyngeal reflux (LPR) [2]. The laryngopharyngeal findings attributed to gastroesophageal reflux have been reported in the posterior pharyngeal wall, true vocal folds, and arytenoid medial wall [3]. However, accurate assessment of signs in the larynx and pharynx is likely to be difficult because these signs observed during a laryngoscopic examination cannot be reliably determined from clinician to clinician [4]. The sensitivity and specificity of laryngopharyngeal findings, therefore, remain uncertain, challenging the diagnostic accuracy of LPR. In this study, we conducted a multicenter clinical trial to explore the presence of endoscopic laryngeal findings in Japanese patients with laryngopharyngeal reflux symptoms (LPRSs). Because the first-line therapy for LPRS is considered to be proton pump inhibitor (PPI) [2], we also compared the endoscopic laryngeal findings before and after a 4-week acid suppression therapy.

2. Methods

Subjects consisted of outpatients visiting the otolaryngology departments of participating institutions between October 2007 and May 2008 who had at least one LPRS such as lump in the throat, throat pain, irritation in the throat, chronic

Table 1: Score for endoscopic laryngeal findings used in this study.

Findings	Score				
Infraglottic edema with pseudosulcus formation	0	1	2	3	NE
Laryngeal mucosa ledema	0	1	2	3	NE
Posterior commissure hypertrophy	0	1	2	3	NE
Granulation formulation	0	1	2	3	NE
Thick endolaryngeal mucous	0	1	2	3	NE
Redness in the intra-arythenoid medial wall	0	1	2	3	NE
Mucous pooling in the pyriform sinus	0	1	2	3	NE

NE: not evaluable.

Table 2: Mean scores for pretreatment endoscopic findings (n = 73).

Endoscopic findings	Total (n = 73)	RPZ (n = 60)	Control (n = 13)	P-value
Infraglottic edema with pseudosulcus formation	0.39	0.40	0.35	0.776
Laryngeal mucosa edema	0.52	0.50	0.62	0.471
Posterior commissure hypertrophy	0.83	0.88	0.62	0.106
Granulation formulation	0.15	0.17	0.08	0.362
Thick endolaryngeal mucous	0.22	0.23	0.15	0.523
Redness in the intra-arythenoid medial wall	0.49	0.53	0.31	0.153
Mucous pooling in the pyriform sinus	0.43	0.43	0.42	0.968
Total	3.02	3.13	2.54	0.258

cough, and hoarseness and whose consent could be obtained. A total of 255 endoscopic laryngeal images were presented to 15 otolaryngologists listed in the appendix with the subjects' names and their before and after therapy status blinded. The 15 otolaryngologists individually scored on a four-point scale as 0 (none), 1 (mild), 2 (moderate), and 3 (severe) or NE (not evaluable) for findings potentially associated with LPR, as shown in Table 1. First 5 of 7 items are derived from the Reflux Finding Score proposed by Belafsky et al. [5] and the other 2 were from the report by Vaezi et al. [3].

Of the 255 images, 109 were excluded (95, patient overlap; 14, number of NE items > 3), and the remaining 146 images were used for further analysis. The median value of the 15 scores for each item from each subject was obtained. The mean pretreatment scores of each item and total scores were assessed. Examples for the images with high (total score: 7) and low (total score: 0) median scores were shown in Figures 1(a) and 1(b), respectively. To 60 patients who were considered for indication of acid suppression therapy based on their symptoms, 10 mg/day of rabeprazole (RPZ) for 4 weeks was administered and the endoscopic findings before and after the 4-week treatment with RPZ were compared.

Table 3: Endoscopic findings before and after 4 weeks in the control group (n = 13).

Endoscopic findings	Initial	4 weeks later	P-value
Infraglottic edema with pseudosulcus formation	0.35	0.46	0.570
Laryngeal mucosa edema	0.62	0.77	0.337
Posterior commissure hypertrophy	0.62	0.62	1.000
Granulation formulation	0.08	0.08	1.000
Thick endolaryngeal mucous	0.15	0.31	0.337
Redness in the intra-arythenoid medial wall	0.31	0.15	0.337
Mucous pooling in the pyriform sinus	0.42	0.50	0.838
Total	2.54	3.00	0.239

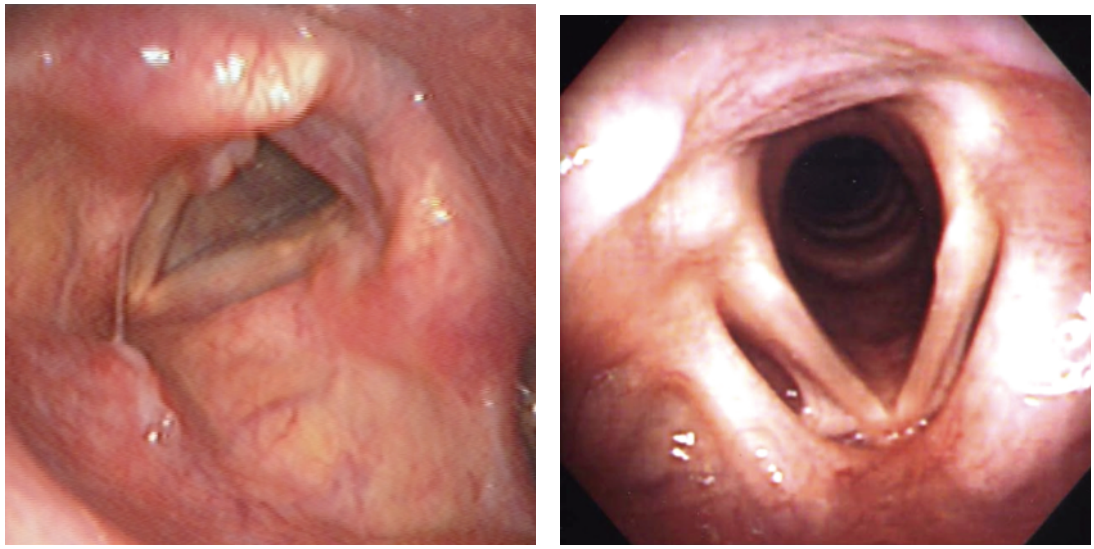
Table 4: Pre- and posttreatment endoscopic findings in the RPZ group (n = 60).

Endoscopic findings	Pretreatment	Post-treatment	P-value
Infraglottic edema with pseudosulcus formation	0.40	0.33	0.419
Laryngeal mucosa edema	0.50	0.59	0.268
Posterior commissure hypertrophy	0.88	0.98	0.147
Granulation formulation	0.17	0.18	0.709
Thick endolaryngeal mucous	0.23	0.15	0.279
Redness in the intra-arythenoid medial wall	0.53	0.62	0.273
Mucous pooling in the pyriform sinus	0.43	0.37	0.279
Total	3.13	3.20	0.779

Changes between corresponding duration in 13 patients, who had at least one LPRS and had not received acid suppression therapy, were also evaluated. Double-sided paired or unpaired t-tests were used to test the significance of differences.

3. Results

The pretreatment total score for all 73 subjects ranged from 0 to 7 (median score 3, mean score 3.02). No significant differences were observed between the groups for any item or total score (RPZ group: 3.12; control group: 2.54, Table 2). Further, no significant differences were observed before and after treatment in either the RPZ or control groups for any item or total score (Tables 3 and 4). In 24 patients with a high



(a) (b)

Figure 1: Examples for endoscopic laryngeal images with (a) a high score (total score: 7) and (b) a lowest score (total score: 0).

Table 5: Pre- and post-treatment endoscopic findings in patients with a total score ≥ 4 from the RPZ group ($n = 24$).

Endoscopic findings	Pretreatment	Post-treatment	P-value
Infraglottic edema with pseudosulcus formation	0.58	0.38	0.203
Laryngeal mucosa edema	0.79	0.65	0.307
Posterior commissure hypertrophy	1.10	0.96	0.166
Granulation formulation	0.29	0.29	1.000
Thick endolaryngeal mucous	0.54	0.17	0.017
Redness in the intra-arythenoid medial wall	0.83	0.73	0.396
Mucous pooling in the pyriform sinus	0.63	0.42	0.135
Total	4.77	3.58	0.0003

pretreatment score (total score ≥ 4) from the RPZ group, significant decreases in scores for "thick endolaryngeal mucous" (0.54 to 0.17, $P = 0.017$) and total (4.77 to 3.58, $P = 0.0003$) were observed after the 4-week treatment (Table 5).

4. Discussion

The precise laryngoscopic diagnosis of LPR is likely to be difficult because the examination of abnormalities in the larynx and the pharynx could be highly subjective [4]. Even with using gastrointestinal endoscopy which provides clear images with higher resolution than laryngoscopy, diagnostic value was limited when evaluating these laryngopharyngeal lesions in patients with gastroesophageal reflux [6]. Some authors emphasize these findings in the larynx and pharynx as being specific for acid-related problems, others argue that these may be secondary to other factors such as smoking, allergies, asthma, viral illness, and voice abuse [3, 7, 8].

During our daily practice in the ENT clinics, we noticed that most of Japanese patients who complain a typical constellation of LPRS do not necessarily exhibit such laryngopharyngeal abnormal findings. We also noticed that minimal changes of these findings are very difficult to be documented objectively. These small abnormalities cannot be revealed due to the consideration to examiner bias [4, 6]. We performed this study to ensure objectivity to some extent of the examination of abnormalities in the larynx and pharynx in this patient population. We presumed that the median value of 15 otolaryngologists was the most appropriate value of each finding of the laryngopharyngeal abnormality. We then found a low pretreatment score among the Japanese patients with LPRS, suggesting that most of them had only mild laryngeal signs. When limited to the patients with a high endoscopic laryngeal score, a significant decrease in total score was observed after acid-suppression therapy.

There are some limitations in this study. Among them, the major one would be the length and the dose of PPI treatment. These could be a possible reason for causing no significant difference before and after the RPZ treatment. The 4 weeks of acid suppression with RPZ with a dose of 10 mg/day may not be long or strong enough to see objective improvement. Ford proposed an empirical therapeutic trial using double-dose, twice-daily PPI for three months [2], suggesting that both the length and the dose of PPI treatment in this study were not enough to observe significant changes in the laryngopharyngeal findings.

Currently, only the patients with obvious laryngopharyngeal abnormalities were recruited to the prospective, randomized, double-blind and placebo-controlled studies on

the effect of PPI on symptom improvement [9, 10]. In Lam's report, there were no significant differences in laryngopharyngeal findings between the PPI and placebo groups, suggesting that the improvement in laryngeal signs might not lead to significant improvement in patient symptoms. In other words, laryngeal signs may not correlate faithfully with actual improvement in LPRS. It may be possible to postulate that the effect of PPI is not limited to the patients with obvious laryngopharyngeal abnormalities. The correlation between laryngopharyngeal symptoms and signs would need further studies. Because the precise diagnosis of LPR is still difficult, it is of critical importance to identify morphologic or physiologic features more specific for LPR.

5. Conclusions

The low pretreatment total score of the Japanese patients with LPRS suggested that most of them had only mild objective laryngeal signs. In LPRS patients with a high endoscopic laryngeal score, a significant decrease in total score was observed after acid suppression therapy.

Appendix

Fifteen otolaryngologists who evaluated endoscopic laryngeal images: Nobuhiko Oridate, Yasushi Mesuda, Masanobu Suzuki (Hokkaido University Hospital), Tomoko Shintani, Etsuko Kanaizumi (Sapporo Medical University Hospital), Aya Maruko (Jusendo Hospital), Yusuke Watanabe (International University of Health and Welfare Mita Hospital), Ryoji Tokashiki (Tokyo Medical University Hospital), Yuki Hamashima, Masanori Yoshioka (Nagoya City University Hospital), Kiyoto Hosokawa (Kansai Rousai Hospital), Aki Taguchi (Ehime University Hospital), Rieko Gotoh, Kanako Indoh (Kagawa University Hospital), and Misako Yamamoto (Sanuki Municipal Hospital).

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Review Article

Reflux Revisited: Advancing the Role of Pepsin

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Gastroesophageal reflux disease is mediated principally by acid. Today, we recognise reflux reaches beyond the esophagus, where pepsin, not acid, causes damage. Extraesophageal reflux occurs both as liquid and probably aerosol, the latter with a further reach. Pepsin is stable up to pH 7 and regains activity after reacidification. The enzyme adheres to laryngeal cells, depletes its defences, and causes further damage internally after its endocytosis. Extraesophageal reflux can today be detected by recognising pharyngeal acidification using a miniaturised pH probe and by the identification of pepsin in saliva and in exhaled breath condensate by a rapid, sensitive, and specific immunoassay. Proton pump inhibitors do not help the majority with extraesophageal reflux but specifically formulated alginates, which sieve pepsin, give benefit. These new insights may lead to the development of novel drugs that dramatically reduce pepsinogen secretion, block the effects of adherent pepsin, and give corresponding clinical benefit.

"*For now we see through a glass, darkly.*"—First epistle, Chapter 13, Corinthians

1. Introduction

This quotation from the Bible, often used in drama and thrillers, symbolises "that the clarity of a situation is often obscured". It is in our view an apt description of the syndrome we today recognise as extraesophageal reflux (EER). The inspired insight in the 1990s that the symptoms and findings might constitute a distinct entity [1] was followed by growing awareness in the last decade that the underlying cause was gastroesophageal reflux. Hence, the Montreal classification included several extraesophageal features within the spectrum of gastroesophageal reflux disease (GERD), the association considered "established" for laryngeal symptoms, cough, and asthma (and "proposed" for recurrent otitis media, idiopathic pulmonary fibrosis, pharyngitis, and sinusitis) [2]. This was a remarkable foresight, for at the time, the data on which we today regard for EER was still emerging. Today, however, there is strong evidence that laryngeal damage from EER is mediated by pepsin. This decade may see these discoveries lead to clearer understanding of the disease process and consequently lead to the development of effective therapy.

The earlier confusion surrounding the entity of EER and the story now unfolding is reminiscent of the early 1980s when an unusual organism came to be identified in the stomach, particularly in those with peptic ulcer. Looking back, it may seem self-evident that *Helicobacter pylori* (*H. pylori*) was closely related to the development of duodenal ulcer (DU)—but it certainly did not seem so at the time.

1.1. Acid—and Beyond. GERD has, with good reason, been widely regarded as the consequence of excessive reflux from the stomach into the lower esophagus, the *acid* component of the refluxate damaging the esophageal mucosa. This link is made indelible in the clinician's mind by the rapid and sometimes dramatic relief proton pump inhibitors (PPIs) give, through profound acid suppression. Today, we are increasingly aware reflux can reach much further, extending beyond the upper esophagus into the pharynx, larynx,

airways, and middle ear, and may damage these structures [3, 4].

The benefits of the PPIs are striking in patients with *typical* GERD, that is, those with lower esophageal symptoms, principally retrosternal burning ("heartburn"), and regurgitation (the two together commonly referred to as the "classical symptoms" of reflux) with or without erosive esophageal changes. This is reflected by numerous clinical trials and reinforced by worldwide experience [5, 6]. In contrast, PPIs generally give little benefit when symptoms arise from refluxate-damaged organs further away, indicating that unlike in the esophagus, acid may not be the damaging agent. In EER, the damaging agent we suggest is pepsin (and perhaps bile acids).

Pepsin is produced only in the stomach; hence evidence of its presence in these organs signifies refluxate has reached them. The enzyme has recently been identified within the laryngeal epithelium, in the saliva of patients with suspected reflux laryngitis, and in the exhaled breath of those with airways and lung disease, where reflux is thought to have played a part. Pepsin has also been found in the middle ear in otitis media effusions (where bile acids, too, have recently been identified).

"Host factors" too are presumably involved which influence who develops disease and how severe it becomes. These factors may also have a bearing whether the disorder manifests with typical reflux symptoms arising from the esophagus or as EER. Many with EER have little or no retrosternal burning or regurgitation; this is surprising, for to reach the extraesophageal areas, the refluxate would first have to travel through the esophagus. Refluxate is liquid, but there is growing awareness that it may also be an aerosol. Firm evidence is, however, yet to emerge. Nevertheless, an aerosol remains an "attractive" possibility for it would account for observations as yet unexplained. For example, intuitively, it would seem that the concentration of hydrogen ions would be less in an aerosol (compared to that in liquid refluxate), perhaps below a threshold to trigger esophageal symptoms.

The concept of pepsin and bile acids playing a role in reflux disease developed many years ago but has been often overlooked in recent times, as the very success of PPIs increasingly focused attention on acid (to the exclusion of other factors) but also in part because the relevant literature is not usually referred to by gastroenterologists.

2. Aim

The *aim* of this paper is, therefore, to draw the key evidence together and to raise awareness of EER amongst gastroenterologists, who today are increasingly invited by ENT and respiratory specialists to help investigate patients in whom this condition is suspected. Bile acids are mentioned but the focus is on pepsin; GERD is often referred to but mainly to compare and contrast with EER, the main thrust.

We have broadly adhered to the philosophy of the Montreal classification of GERD, [2] departing only when it does not sufficiently accommodate more recent findings and evolving concepts of pathophysiology. Thus, a degree of reflux into the lower esophagus and without any symptoms is regarded as physiological gastroesophageal reflux (GER). Gastroesophageal reflux disease (GERD) is the term applied when reflux is accompanied by typical symptoms, with or without erosive mucosal damage. At this stage, the total duration of esophageal acid exposure is considerably longer than in physiological reflux. Whilst extraesophageal reflux disease is increasingly recognised, relatively little is known if "physiological" extraesophageal reflux (EER) occurs.

3. History

3.1. GERD: A New Concept Emerges. In 1934, Asher Winkelstein first raised the possibility that the symptoms in five of his patients might have arisen from peptic esophagitis, a condition resulting "from the irritant action on the mucosa of hydrochloric acid and pepsin" [7–9]. From the late 1950s, elegant experimental studies have demonstrated the complex interrelationship between bile acids, pepsin and hydrochloric acid (HCl) interacting and leading to esophageal damage.

3.2. Shifting Perceptions. The role of these nonacid factors, however, appeared to diminish in the clinician's perception when the histamine H_2 receptor antagonists (H_2RA) emerged in 1976. These were the first drugs to powerfully reduce acid secretion and proved highly effective in controlling peptic ulcer, thus demonstrating the central role of acid in the disease process. By extension, it seemed likely to also be of use in GERD, but the clinical benefits proved to be only modest. Acid inhibition, powerful with the H_2RA, was profound with the new class of drugs, the proton pump inhibitors (PPIs), which became available in 1989. These drugs proved markedly superior to H_2RA in the treatment of GERD, which reinforced the growing perception that it was the *acid* component of refluxed gastric contents that was the cause of esophageal damage.

3.3. Pepsin and Bile Acids: At the Beginning

3.3.1. Pepsin. The elegant experimental studies of Goldberg et al. [10] clearly demonstrated pepsin can damage the esophagus. Cat esophagi were infused for an hour with HCl, the pH ranging from 1 to 2.3. Acid at pH 1 proved very damaging, whereas at pH 2.3 was without effect; adding pepsin to each of these infusates caused no further damage. In the intermediate acidity range of pH 1.6 and 2.0, however, the damage was proportional to the amount of pepsin added (25 and 50 μg/mL). Blocking the enzyme effect by first premixing with amylopectin sulphate (a synthetic pepsin inhibitor) protected the esophagus, thereby confirming that pepsin can, in the appropriate circumstances, cause damage.

HCl at pH 1 is probably not encountered in the gastric lumen (other than in exceptional circumstances), for the secreted acid is rapidly diluted. A pH of 1.6–3 is common, however, and it is in this range when gastric refluxate containing acid and pepsin is most damaging to the esophageal mucosa. Pepsinogen arises from the gastric peptic cells (also called the chief cells) which share space in the same glands as the acid-secreting parietal cells: the two secretions are independently controlled but almost always occur together.

Reflux, therefore, irrespective of its pH, always contains pepsin (see below).

3.3.2. Bile Acids. Experimental studies in the 1980s demonstrated the role of bile acids in damaging the esophageal mucosa. In a series of studies by Harmon and colleagues [11] and by Schweitzer et al. [12], varying concentrations of taurine-conjugated and unconjugated bile salts were infused into rabbit esophagi at pH 2, 5 and 7. Significant disruption of the esophageal mucosal barrier occurred at bile acid concentrations similar to those in the stomach of patients with esophagitis [13]. The evidence, however, suggested that such disruption was probably not the direct effect of bile acids solubilising the cell membrane phospholipids. Instead, bile acids enter the epithelial cells and disrupt cellular machinery from within, hence interfere with the cell barrier function. Such entry is determined by the physicochemical properties of the bile acids. Taurine-conjugates have a pKa of ~2 that is, half the molecules are in solution at pH 2 and, being charged, cannot penetrate the lipid bilayer of the cell membrane. As the pH progressively rises, more bile acids come out of solution and by pH 7 are insoluble, lose their charge and as a result can now enter the epithelial cells.

These experimental studies have particular clinical relevance, for bile is present in esophageal refluxate [14–16] and is most frequently noted in patients with severe esophagitis or complicated Barrett's esophagus [17, 18] in whom it is present at high concentrations [19].

3.4. Conceptualizing the Mechanism of Damage. Putting these observations together, one can conceptualise circumstances where pepsin in the refluxate disrupts the esophageal mucosal barrier by acting on the epithelial cell surface, whilst bile acids achieve the same effect by diffusing into the cell and damaging from within.

These seemingly complex mechanisms contrast sharply from the "corrosive" action of acid, an effect "simpler" to picture. Gastric acid consists of H^+ and Cl^- ions in water. When in high concentrations, intuitively, the fluid is more "corrosive"; hence, the longer the time in contact with the esophagus, the greater the likelihood it will damage the mucosa. Conversely, lower concentrations are less damaging. Importantly, the basic constituents of acid are unchanged, only its concentration.

4. Pepsin: Nature, Activation, Acidity, and Enzyme Activity: Clinical Significance

4.1. Nature and Activation. Pepsin is an ancient molecule and present in all vertebrates studied, such as fishes and mammals. The stomach is largely devoid of live organisms (with the exception of *H. pylori*), a state widely believed to result from the presence of gastric acid, which acts as a "bulk steriliser". A second important action of acid is the activation of pepsinogen. This releases pepsin which initiates digestion through proteolysis, an action which also probably helps keep the stomach free of most bacteria [20].

The peptic chief cells produce and store pepsinogen, the precursor of the active enzyme. Pepsin, an aspartic proteinase, is a large bilobed molecule and concave on one surface, the concavity occupied by the detachable pro-part. When in contact with acid, the pro-part detaches exposing the concavity, the active site for enzyme action. The enzyme attaches to its substrate at this point and cleaves it. Acid (pH < 6) is required to convert inert pepsinogen to active pepsin but once converted, the pepsin continues the autocatalytic process sustaining the cascade in the absence of acid [3].

4.2. Pepsin: Isoenzymes. Pepsin has traditionally been studied by gel electrophoresis of gastric juice and tissue homogenates, which typically shows eight zones of lysis to which various names and designations have been applied based on their electrophoretic mobility [21, 26]. The pattern reflects the fact that pepsin is not a single molecule but encompasses a family of isoenzymes which structurally are similar. Today, the pepsin isoenzymes in gastric juice can be separated by high-performance anion exchange chromatography (HPAEC) using chloride counter ion gradient elution (Figure 1). Each pepsin isoenzyme has its own "optimal pH level" when its action is at a maximum, thus ensuring digestion across a wide range of gastric pH (see Table 1).

4.3. Pepsin: pH and Stability. The activity and stability of the enzyme is closely related to the prevailing pH of its environment, a relationship investigated over the last 40 years using different sources of pepsin, various substrates, and changing analytical methods. The results were broadly similar, and differences were attributed to the experimental conditions. Recent studies reexamining the pH-pepsin relationship in conditions of low acidity have given important new insights into enzyme stability and activity which have major clinical significance (and are discussed in detail further on).

Individual pepsin isoenzymes were noted to be stable for 24 hours even at body temperature but were ultimately degraded by autocatalysis if stored at its pH optima. In contrast, a mixture of isoenzymes, as would be found in gastric secretion, proved to be more stable [22]. For example, purified porcine pepsin was irreversibly denatured at pH 7.1, whereas peptic activity of human gastric juice persisted until exposed to pH 7.8. [27]. A "dormant" phase was observed between pH 6 and 8 when the enzyme was inactive but intact, hence it could be activated on return to pH <6 [28].

4.4. Pepsin: pH and Enzyme Activity: The Traditional View. It has long been known that pepsin is at its most active at pH 2 to 3, and activity is declining as acidity diminishes [29]. Emerging evidence has shown that refluxate reaching the extraesophageal areas is characterised by low acidity or none at all in those on high-dose PPI treatment. Such conditions have been widely regarded to destroy pepsin or to render it inactive, hence the scepticism that pepsin played a significant role in damaging extra-esophageal tissues. Recently, however, important new information challenges such beliefs.

4.5. Pepsin: pH and Enzyme Activity: The Emerging Evidence. This interrelation has recently been reassessed, now using pepsin isoenzyme 3B purified from human gastric juice [30]. It is the largest fraction of pepsin and accounts for 70% of the total enzyme effect (Table 1), for which it serves

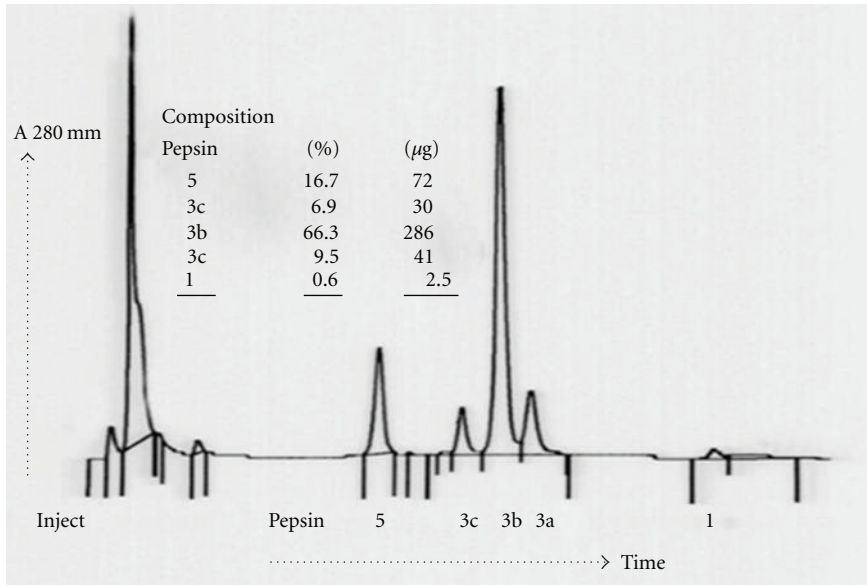

Figure 1: Example of pepsin profile from human gastric juice purified by HPAEC.

Table 1: The active pepsin isoenzymes in man.

Pepsin isoenzyme	Proportion of total pepsin	Substrate: pH optimum range	Molecular weight (Da)	Comments
1	<5%	Haemoglobin: 1.9 Collagen: 3.0 Mucin: 2.0	43810	The proportion of pepsin 1 rises to 23% in DU Mucolytic pepsin Complexed with carbohydrate
2	<1%	Haemoglobin: 2.1	39950	
3	80%	Haemoglobin: 2.4–3.1	37150	Pepsin 3 is a complex of isoenzymes. The assay measures their combined effects.
3A 3B 3C	6% 70% 4-5%	Haemoglobin: 3.2		3A is structurally similar to 3B but is phosphorylated
5 (Gastricsin)	6-7%	Haemoglobin: 2.0–3.6 (maximum at 3.2) Mucin: 3.5–5	31620	Stable up to pH 7.3

"Pepsin 4" is a complex of pepsin and an inhibiting peptide, hence, it does not appear in the list of active pepsin isoenzymes.
"Pepsin 6" is the remnant of a zymogen, in all probability pepsinogen, hence it too does not feature in the isoenzyme list.
"Zone 7" was found to be a cathepsin.
References [21–25].

as a good marker. The assay conditions were designed to resemble those that might be expected in the human larynx in laryngopharyngeal reflux (LPR), namely, little or no acidity (pH 6.8), when pepsin would be inactive unless reactivated by subsequent acidic reflux. The enzymatic activity was measured by the rate of hydrolysis of a synthetic peptide substrate. The isoenzyme activity was at ~80% of its maximum when measured at pH 1.5 and reached its peak at pH 2. Thereafter, it declined to ~45% at pH 4.5, ~40% at pH 5, fell to ~10% at pH 6, and ceased altogether by pH 6.5. The stability of the isoenzyme was then explored having first incubated it at 37°C for 24 hours at various pH levels, ranging from 2 to 8, and assaying at pH 3.0. The enzyme stored at pH 7.0 was inactive but stable, evidenced by the observation that ~80% of its activity was recovered when reassayed at pH 3.0.

4.6. PPI Treatment: Effect on Pepsin Concentration. Numerous studies in man have examined the effect of PPIs on gastric acid secretion but only few on pepsin. An example is a study on the effect of high-dose omeprazole (60 mg daily for nine days) in eight healthy volunteers in whom the volume of gastric secretion and output of acid and pepsin was measured [31]. Acid secretion fell markedly from a mean of 5.4 to 0.3 mmol/h, and the volume decreased substantially from 132 to 36 mL/h. The mean pepsin output, however,

fell only modestly, from 126 to 101 mg/h, but because of the reduced volume, its *concentration* rose from 90 mg to 290 mg per 100 mL.

This study, like most others on gastric secretion, relied on the measurement of stomach contents aspirated through a nasogastric tube. A novel noninvasive approach was recently used to measure gastric volume by magnetic resonance imaging [32]. Unlike the study cited earlier [31], the reduction in the volume of gastric secretion on PPI was only 12%, hence the concentration of pepsin would have increased only slightly. The clinical significance of these contrasting findings is discussed further on.

4.7. PPI Treatment: pH, Pepsin Activity, and H. Pylori. The PPIs commonly used today (e.g., omeprazole) on conventional dosing (single 20 mg dose in the morning) can elevate gastric pH to ≥6 but only for short periods; for much of the time, the pH is around 4 to 5 [6] and falls at night when acid secretion breaks through. Thus, for the majority of 24 hours, pepsin in gastric juice is still active or dormant but stable, hence capable of reactivation when acidity returns.

High-dose PPI treatment (e.g., omeprazole 40 mg twice daily) has a greater effect and is longer lasting, and the newer PPIs (e.g., tenatoprazole) [33] may enhance this. These conditions may keep pepsin inactive, but it seems unlikely that the pH will be elevated to levels which will result in any substantial degradation of the enzyme.

The presence of *H. pylori* increases the effect of PPI, a feature sometimes overlooked yet likely to have a bearing on the efficacy of PPI therapy in the uninfected or in those in whom the organism has been eradicated. Several studies confirm this, an example being the seminal investigation carried out in DU patients [34]. Here, the median 24-hour intragastric pH when PPIs were not used was similar before and after *H. pylori* eradication, 1.0 and 1.1, respectively. On omeprazole 20 mg, however, there was a major difference in pH, 5.5 before eradication but only 3.0 after it. The significance is that whilst the majority of DU patients are infected with *H. pylori*, its prevalence is much lower in GERD patients (and similar to that in the general population), hence theoretically, PPIs might have a lesser effect.

4.8. PPIs, Pepsin, and Reflux: Clinical Significance. PPI therapy suppresses acid profoundly, has a variable effect on the volume of secretion (as indicated earlier) which is difficult to explain, but does *not* reduce the frequency of reflux episodes [35]. When volume is reduced only slightly [32], much fluid remains in the stomach and is available to reflux, carrying pepsin to the extraesophageal areas. When volume is reduced substantially, the concentration of pepsin rises [31] but reflux continues [35], although less is available to reflux, what reaches the extraesophageal areas is rich in pepsin, hence is damaging.

4.9. Pepsin, pH, and Cell Damage. Pepsin is refluxed to the extraesophageal areas where it adheres to the epithelium [36]. If activated by acid in the refluxate, it damages the cells but even in the absence of acid the enzyme has the capacity to damage, for, though dormant, it is stable. Two mechanisms operate. The first is by its reactivation when exposed to acid in subsequent reflux episodes. The second mechanism is independent of such reflux reacidification: it is taken up within epithelial cells by endocytosis and activated from within [37]. This remarkable observation, based on laryngeal cell studies, is a recent discovery with far reaching consequences (and is discussed further on). The significance is that refluxate always contains pepsin; even if devoid of acid (as might happen on high dose PPI treatment), the enzyme will still be damaging if reflux reaches the extraesophageal areas.

4.10. PPIs and Pepsin: Potential Clinical Relevance. Based on older studies, pepsin is commonly assumed to become inactive at pH ≥4 and to be denatured at pH ≥5.5, hence the widespread perception that PPI treatment renders the enzyme inactive by elevating the gastric pH. This view, we suggest, now needs to be readjusted taking into consideration the new evidence which clearly shows the enzyme retains much of its activity at pH ≥4, is still intact up to nearly pH 8, can be reactivated when exposed to acid once again but can damage cells even in the absence of acid.

In clinical practice, PPIs will continue to be used in EER, frequently in high dose, for they help some who in addition to EER symptoms also have features of classical GERD as well as the few who do not [38]. From the evidence above, however, it seems unlikely that profound acid suppression with PPIs as the sole treatment strategy will give results comparable to those with typical esophageal symptoms (heartburn and regurgitation) with or without erosive esophagitis.

5. The Effect of Pepsin on Epithelial Cells

In laboratory studies, pepsin swiftly breaks down protein, the basis of its chemical assay. Its effect on extraesophageal tissues is in contrast subtle and perhaps sustained, depletes the cells of its defences and threatens its viability. These changes have been demonstrated in ongoing clinical and laboratory studies by Johnston and colleagues who explored the effects of human pepsin 3B (purified from gastric juice) on laryngeal epithelium using *ex vivo* systems and cell culture studies [36, 37, 39, 40].

5.1. Pepsin: Entry into Epithelial Cells. Based on esophageal and laryngeal biopsies from LPR patients and from control subjects, and employing a variety of analytical methods, they made three major observations: pepsin adhered to epithelial cells, was endocytosed, and caused internal cell derangements.

Pepsin was found adherent to the surface of laryngeal epithelial cells obtained from LPR patients but not to those from control subjects [36]; the absence in the latter group is to be expected, for significant reflux had already been excluded by esophageal physiology studies. The enzyme was *not* found adherent to the esophageal epithelium (in LPR patients); this is surprising bearing in mind that to reach the larynx the refluxate has first to travel along the length of the esophagus. When active, the adherent enzyme damages the

intercellular junctions and depletes proteins within the cell involved in its defence (and is discussed further on).

Inactive pepsin is taken up within the cells by endocytosis through a competitive receptor-mediated mechanism and is found in vesicles located in the region of the Golgi system [37]. Such endocytosis, the second observation, is surprising, for it seems unlikely that receptors specific for pepsin exist in laryngeal tissues. Presumably, such receptors serve some other purpose but when exposed to pepsin, they "shuttle" the enzyme into the cells.

When cells were exposed to human pepsin 3B at pH 7.4, a level at which the enzyme is *inactive*, several major changes, nonetheless, occurred affecting the inner cell structure and function [39], the third major observation. The Golgi system has a pH of ~5.5, together with its associated endosomes these process large molecules such as proteins and receptors through its slightly acidic environment. The inference is that the changes observed (see below) result from reactivation of the dormant enzyme within the cell.

The cells swelled and structural damage to the mitochondria and to the Golgi system became visible on electron microscopy within an hour and increased by 12 hours. The early damage was accompanied by increased expression of seven genes involved in cell stress and toxicity including certain heat shock proteins (as a family, the production of heat shock proteins is activated when the cell is stressed and its survival threatened) and the late changes by the decreased expression of another 18 such stress genes. The investigators also used in parallel a cell toxicity assay which measures mitochondrial activity in living cells. There was a significant increase in toxicity after pepsin exposure at pH 7.4 which correlated well with the mitochondrial changes noted on electron microscopy.

The evidence strongly argues for the following chain of events: inactive pepsin is endocytosed, is activated within the cells, and causes cell damage; this induces oxidative stress and the accumulation of free oxygen radicals which, in turn, damage mitochondria and may lead to cell death. In the experimental system used, the cells were exposed only once to pepsin, thus mimicking what might happen with an isolated episode of LPR. Though damaged, the cells were still viable at 12 hours but with repeated exposure, as would be expected in chronic LPR, the damaged cells may not survive [39].

5.2. Pepsin: Depletion of Cell Defences. The effect of pepsin was explored using a pig laryngeal epithelial cell model. Human pepsin 3B markedly depleted cell defences only when the enzyme was made active by the presence of acid (pH 4). In contrast, acid on its own had no effect, nor did the enzyme when rendered inactive by raising pH to 7.4 or when its activity was blocked with its inhibitor, pepstatin [30].

In a series of studies, the specific cell defence changes noted were depletion of the carbonic anhydrase isoenzyme CA3 and the stress protein Sep 70, reduction of E-cadherin, and the alteration of the subtype profile of protective mucin produced [30, 36, 40, 41].

The isoenzyme CA3 is widely expressed in tissues, including the basal layers of both esophageal and laryngeal epithelium. It mediates the rapid two-way conversion of CO_2 and water to carbonic acid, bicarbonate, and H^+, hence plays a key role in the regulation of cell pH. When the esophageal epithelium is exposed to acid, the isoenzyme is also expressed in the more superficial cells, thus offering greater protection to the epithelium nearest the refluxed acid. In contrast, its production remains limited to the basal layers in the laryngeal epithelium.

Sep 70, like most other stress proteins, is a molecular chaperone which regulates the correct folding and unfolding of intracellular proteins during their passage through the cell. E-cadherin is crucial for maintaining adhesion between cells, and thereby mucosal integrity and its barrier function. There are several subtypes of mucin, some more prominent in specific tissues than others: collectively, they afford protection. In chronic LPR, MUC-2, -3, and -5AC are amongst the defensive mucins depleted, and *in vitro* studies confirm pepsin interferes with their production [42].

5.3. Tissue Damage in GER and EER: A Comparison. The intensity of damage of the esophageal mucosa by acid reflux (pH < 4) is proportional to the duration of contact. A degree of reflux occurs in health, particularly after meals, but peristalsis rapidly returns the refluxate to the stomach; any residue is neutralised by bicarbonate secreted in saliva and by the esophageal mucus glands.

In striking contrast, the larynx and extraesophageal structures have no mechanism for bulk removal of damaging agents, hence they must rely on intracellular defences; but as indicated earlier, such cell defences are much depleted after exposure to reflux. Hence, even slight exposure to reflux can cause disproportionate damage.

5.4. The Significance of Dilated Intercellular Spaces in the Squamous Epithelium. Acid injury to the esophageal squamous epithelium results in the dilatation of the intercellular spaces, which almost double in width; these changes are visible only by electron microscopy. The phenomenon is now well established in patients with both erosive and nonerosive reflux disease [43, 44]. It was recently also observed in healthy volunteers in whom the lower esophagus was infused with only weak levels of acid (pH 5.5) that the changes are no greater when strong acid (pH 2) with added pepsin (±bile acid) was infused. The changes were widespread and occurred not only at the site of infusion, but also well away from it [45].

Such dilatation has been reproduced experimentally in rabbit epithelium exposed to acid at pH 1.1 or at pH 2 but with added pepsin [44]. These tissues had reduced electrical resistance mainly due to "leakiness" of the paracellular pathways, the "leak" in proportion to the size of dextran particles which could enter the damaged tissue. The significance is that the "leak" is physical not virtual.

These studies clearly show the sensitivity of the esophageal epithelium to even low concentrations of acid. Its *possible* relevance to EER comes from the observation that dilatation of intercellular spaces has also been noted in the laryngeal epithelium in patients with LPR [36, 46], which, unlike that in the esophagus, has not attracted

attention. Whilst there is little acid in refluxate reaching the extraesophageal areas, it does contain pepsin, which may potentially gain entry into the dilated spaces in the laryngeal epithelium.

The nerve endings in the esophageal epithelium (in monkeys) are located in the intercellular spaces and are superficial, appearing at a depth of only three cell layers, a major finding [43]. These sensory nerves are thought to be chemosensitive and respond to even low levels of acid, pH 5.2 to 6.9, chronic irritation leading to secondary hypersensitisation which perpetuates symptoms. The larynx, too, is richly innervated and is exquisitely sensitive. A similar train of events may, theoretically, occur in the larynx, which prolongs the symptoms even when the stimulus is much reduced.

5.5. Summary. In summary, esophageal mucosal damage is mediated principally by acid, and laryngeal epithelial (and *possibly* other extraesophageal epithelium) damage by pepsin (and presumably other agents). The environmental pH in the larynx and hypopharynx is ~5.5 to 6, a level at which pepsin is only slightly active or dormant. Even when inactive, pepsin damages cells after it is endocytosed and reacidified within them. The enzyme adheres to the laryngeal epithelium and when inactive is stable and can be reactivated by acidic reflux even when the episodes are infrequent. These advances in our understanding perhaps explain the apparent paradox noted in classical observations comparing EER and GER. As little as three EER episodes per week can damage the larynx, it was noted, whereas up to 50 GER episodes of acidic reflux (pH < 4) per day can be seen in the asymptomatic individual [1, 47].

6. The Reach and the Nature of Reflux

6.1. Introduction. Reflux into the esophagus is usually imagined as fluid welling up from the stomach and/or spurting in jets which sometimes reach high, a plausible interpretation of pHmetry and impedance study results, the mental image reinforced by artistic impressions in advertisements. For gastroesophageal reflux to cause disease beyond the esophagus, however, the refluxate must self-evidently reach these areas.

Reflux into the extraesophageal areas is not a new concept. Almost two decades ago, Koufman [1] speculated on its possibility as an explanation for chronic laryngeal symptoms seen in several patients but supporting evidence was to emerge only several years later as technology advanced. The presence of refluxed material in the extraesophageal areas *suggests* it may play a role in causing symptoms from the larynx and airways, but the growing evidence that pepsin can cause damage makes the case more compelling.

These insights spurred the development of new technology to detect reflux in the extraesophageal areas. In the course of these investigations, two findings emerged almost as a "byproduct" (hence seemed to attract little notice) which are likely to change the concept of EER disease. First, the refluxate loses much of its acidity as it travels upwards (presumably by neutralisation with bicarbonate in saliva and from the esophageal mucosal glands) [48, 49]. Second, refluxate can be both liquid and aerosol [49–51].

6.2. How Far Up the Esophagus Does Reflux Reach? Standard pHmetry readily detects acid (defined as pH < 4) refluxed into the lower esophagus by its single sensor stationed 5 cm above the lower esophageal sphincter (LES). Dual pHmetry, in which the second sensor is stationed in the vicinity of the upper esophageal sphincter (UES), confirmed proximal reflux does occur [52]. By this time, there was also growing interest in whether refluxate containing lesser concentrations of acid was potentially damaging. The newly developed method of combined impedance pHmetry provided the means to detect liquid reflux independent of its pH and to determine how far proximally such refluxate reaches. The principle is that fluid is a better electrical conductor than air, hence impedance (resistance) falls, the higher the acid concentration, the greater the fall. The catheter has two pH electrodes, as with dual channel pHmetry (see below), and six *pairs* of impedance (resistance) sensors, each pair comprising two sensors separated by a tiny gap. Just a film of fluid is sufficient to bridge this gap and complete the circuit. In the absence of any fluid, the sensors are exposed to air and record high impedance.

The pH electrodes are stationed 5 cm and 20 cm above the LES, whilst the impedance sensors extend from above to below the pH electrodes. The resistance sensor detecting change furthermost from the LES indicates the proximal reach of reflux. These studies have clearly demonstrated refluxate frequently rises to the proximal esophagus, the significance being it is in a position to reach extraesophageal areas [53–56]. Investigations in untreated GERD patients showed 63% of reflux episodes were acidic (and 72% of symptom episodes were associated with acid reflux). In contrast, 80% of reflux episodes on PPI were weakly acid or weakly alkaline (and most symptoms were associated with refluxate of this nature) [57].

6.3. Acid Reflux into the Pharynx. A recent advance is the development of a nasopharyngeal probe bearing a specially constructed pH sensor at its end (available as the Dx-pH probe http://www.restech-corp.com/). The sensor is stationed in the mid-pharynx (i.e., away from the upper esophageal sphincter), where it is kept moistened with each exhaled breath. The environmental pH detected with this method is ~5.5; set against this relatively high pH, reflux containing even only little acid is readily detected [50].

6.4. Reflux into the Oropharynx and Airways: The Presence of Pepsin. Pepsin has recently been detected in the saliva of patients with suspected EER using a highly sensitive immunoassay which utilises two unique monoclonal antibodies against human pepsin 3 [58]. The same immunoassay has detected pepsin in the exhaled breath in patients with chronic cough thought to be due to EER. The breath sample is captured, kept cold, and the immunoassay carried out on the condensate which forms [51].

6.5. The Acidity of Refluxate: Its Relevance to EER Disease. Refluxate detected in impedance studies is arbitrarily divided as acid (pH < 4), weakly acid (pH 4–7), and nonacidic (pH > 7) [59]. Reflux at pH <4 is widely regarded as being damaging to the esophagus because of its high acidity, hence pH 4–7 is less injurious, and pH >7 probably without effect. The real significance of refluxate containing low or no acid, however, is that it always contains pepsin, which potentially can be carried to the extraesophageal areas, where it damages the epithelium.

As indicated earlier, esophageal damage in typical GERD is dominated by acid; in contrast, EER disease is mediated principally by pepsin. This perhaps explains why PPIs fail to rapidly improve EER disease, unlike their effect in classical GERD.

6.6. The Physical Form of Refluxate: Liquid and Aerosol . The concept that reflux may also be an aerosol has only recently emerged, at this stage more plausible (albeit persuasive) than proven. It arises from detecting acid in the pharynx and pepsin in the saliva but particularly in the exhaled breath (see below). Their presence, so far away from the stomach, is more plausibly explained if they were airborne, that is, carried in an aerosol, rather than in a column of liquid rising from the stomach.

Refluxate as an aerosol has several implications. First, as indicated above, it more plausibly explains the presence of refluxate deep in the lungs [60, 61] and in the middle ear in otitis media effusions [62] (where recently bile acids too have been identified) [63]. Second, liquid refluxate probably has higher concentrations of acid and pepsin, but an aerosol is more likely to carry these damaging agents further into the extraesophageal areas. Third, their presence confirms that refluxate has reached. When in excess, and in the appropriate clinical circumstances, the findings are arguably potentially diagnostic of EER. Finally, it draws attention to a major unmet therapeutic need, namely, the development of new approaches to more effectively decrease pepsin in refluxate.

6.7. GER and EER and the Role of the Sphincters: Speculation. The esophageal lumen is occupied by mucosal folds and air, both swallowed and refluxed. Impaired LES function results in excessive reflux, and presumably liquid refluxate rises in the lumen along the mucosal folds. We suggest that the air in the esophagus provides the medium through which an aerosol ascends.

The LES in health allows air from the stomach to be vented whilst minimising the escape of liquids and semisolids; such separation is less efficient in GERD, where the sphincter function is impaired. The role of the UES in reflux is less well understood, but we speculate that like the LES, it too in health can distinguish liquid from gas, holding back the former and allowing the latter to be vented. We think, however, it would be difficult to distinguish between types of gas, air that contains aerosol refluxate from air that does not. Hence, both are vented and refluxate reaches the extraesophageal areas.

7. Detecting Extraesophageal Reflux

7.1. Diagnosis: A Note. Whilst it is beyond the scope of this paper to consider the issues surrounding the diagnosis of EER in any detail, we would like to highlight the following.

7.2. Clinical Manifestations of EER. Today, EER is increasingly considered as a potential cause of symptoms in adults with chronic problems arising from the larynx, throat, and airways. Changes are often seen in the larynx, but there is no feature characteristic of damage by EER. Furthermore, EER when present may be one of several contributory factors, for example, smoking.

7.3. Technology Currently Available. Impedance pHmetry clearly identifies liquid reflux and indicates how far proximally it reaches. Here, it is assumed that liquid is poised to penetrate into the extraesophageal areas hence EER can be *inferred*. Conventionally, one looks to correlation between proximal reflux episodes and symptoms as evidence of a causative link; but bearing in mind that even infrequent episodes of EER can be damaging, the absence of such correlation does not necessarily exclude reflux-related damage.

Impedance pHmetry (MIIpH) has given us remarkable insights into the pathophysiology of gastroesophageal reflux; it readily detects liquid refluxate irrespective of its pH (hence, it is particularly useful when investigating patients already on PPI) and can determine how often and how far up the esophagus the refluxate reaches—but not beyond it (as yet), nor can it, as currently configured, identify aerosol reflux. To detect EER, therefore, we suggest its role is more supportive than diagnostic.

7.4. Emerging Technologies: Acid and Pepsin in the Pharynx, Saliva and Breath. Aerosol acid reflux into the pharynx can today be detected by the Dx-pH nasopharyngeal probe (ResTech). Diagnostic criteria have been developed, and a pH level <5.5 is regarded as abnormal [50].

Pepsin immunoassay now makes it possible to detect minute amounts of the enzyme in saliva and in exhaled breath. It has recently been adapted as a lateral flow-based test (Peptest^{TM}, RD BioMed Ltd., UK), easy to use, with a detection lower limit of 16 ng/mL, and with results available within minutes. The sensitivity is only slightly lower than with conventional ELISA, which is laborious and more timen consuming. The test is noninvasive and will prove more acceptable to patients, particularly if serial assays are clinically required. Determining its clinical usefulness in diagnosis and in monitoring treatment will, however, require more extensive studies.

Venting air is normal and with it a tiny amount of aerosolised gastric content is likely to escape, hence the asymptomatic *may* have pepsin detectable in the saliva. How should such a finding be interpreted? Lessons learnt two decades ago of the diagnosis of GER by pHmetry give guidance. Some reflux of acid into the esophagus is physiological and not associated with any symptoms; that is, it is the norm. Symptoms (with or without erosive esophageal damage) develop only when reflux is excessive. Thus, the difference between health and disease is a quantitative one, that is,

the *degree* of acid reflux. The same model may apply to detecting pepsin in the saliva. The test is quantitative; we *may,* therefore, find that as with GER it is the quantity of pepsin in extraesophageal areas that correlates best with disease (as opposed to the presence of a tiny amount).

8. Medical Therapy

8.1. The Place of PPIs. PPIs, dramatically effective in typical reflux, are rather less so in EER. Several clinical trials and meta-analyses have failed to show clear benefit in LPR [64] other than one single study that observed a benefit of twice daily PPI for LPR symptoms and signs [65]. Patients with asthma when considered as a group showed no discernible benefit with PPIs; the subset with GER symptoms, however, were helped [66] but, interestingly, not those with pHmetry-proven reflux alone (in the absence of GER symptoms) [67]. Patients with chronic cough in whom EER was suspected also did not benefit [68, 69].

Tenatoprazole, a new PPI with a much longer half-life than those currently available, correspondingly suppresses acid for a longer period in the 24 hours [33]. Other PPIs and potassium-competitive acid blockers are in development [5, 6]. These may prove helpful in patients with typical reflux when currently available PPIs give insufficient response; but for the reasons stated earlier, they are unlikely to make much difference in EER.

Nevertheless, the occasional patient does show improvement, generally partial, with PPIs. In the absence of really effective treatment, such anecdotes encourage continued widespread use of profound acid inhibition.

8.2. Antipepsins. Drugs with antipepsin activity have been used in several clinical studies in patients with peptic ulcer but were found not to be effective. Examples are amylopectin sulphate [70–72] and pepstatin [73].

8.3. Alginates: "Sieving Pepsin" from Gastric Secretion. Alginates, widely available for almost 40 years, have recently been shown to have a powerful effect on pepsin and bile in refluxate *in vitro* [74] and potentially offer an effective treatment [75].

Recent *in vitro* studies confirm that Gaviscon Advance (GA), a specific alginate formulation, removes ~90% of pepsin and bile in the first "reflux episode", declining to about 50% by the tenth. Their rate of depletion was similar, suggesting a common mechanism, most probably selective binding [74].

8.4. Alginates: Effectiveness in EER? Only a few studies have as yet been done, mainly in LPR, and give encouraging results.

8.4.1. LPR. A UK study assessed the benefit of adding GA to standard vocal hygiene advice (control group) [75] and a USA investigation on the outcome of adding GA to preexisting PPI therapy [76]. In both, a dose of 10 mL × 4 daily was used; this is the recommended dose when the drug is used for dyspepsia and is generally used only for short periods (4 to 8 weeks) but for the trials treatment was given for six months.

Allocation to treatment in the UK study was randomised and blinded. The outcome was assessed by those unaware of the patients' treatment group. Two scoring instruments were used, both validated and semiquantitative. The reflux symptom index (RSI) measures the symptom burden and the reflux finding score (RFS) the degree of change observed on endoscopic examination.

The baseline scores were similar in both groups. RSI improved significantly in the group compared to baseline both at 2 and 6 months, but the improvement was much greater for those on GA. Treatment with GA gave a significant improvement in RSI compared to the control group at 2 and 6 months. The RFS did not change in the control group but improved significantly in the GA-treated group but only at six months; this suggests that endoscopic improvement lags behind symptom relief [75].

The USA study [76] used both RSI and RSF and, in addition, a voice-related quality of life index (QLI). Both treatment groups had similar RSI symptom scores at the start (comparable to that in the UK study) and similar degree of improvement at two months. Thereafter, however, there was no further symptom improvement in those on PPI alone, whereas the group on PPI + GA continued to make gains, the differences being significant at 4 and 6 months. This change in symptom intensity was also reflected in the RFS and QLI.

8.4.2. Chronic Cough. EER is often suspected in patients with chronic cough. It is, therefore, surprising that no major study has explored the value of using GA in this group.

8.5. Alginates: Reengineering the Polymer? Alginates are hydrocolloids of vegetable origin and are a structural component of marine brown algae to which it gives strength and flexibility. These hydrocolloids are polymers and have the property of forming gels, films, thickeners, and stabilisers. The polymer is composed of two monomers, mannuronate and guluronate, and differences in the properties of alginates are determined by their ratio. Added calcium binds to specific sites and stiffens the overall structure.

The remarkable properties of these natural polymers can, we suggest, be enhanced by modern polymer chemistry, making it possible to develop derivatives with more powerful and specific actions.

8.6. Focusing on Pepsin at Source and at Target. The treatment of EER today is as we were circa 1970 for the treatment of peptic ulcer: the need to reduce acid secretion powerfully was increasingly recognized, but the only drugs then available were antacids (the use of anticholinergics, which also reduced acid secretion, restricted by their side effects). Today, we increasingly recognise the importance of pepsin; alginates help—but effective treatment will probably require substantial if not profound suppression of pepsin secretion (as was achieved for acid with the H_2RAs initially and then with PPIs).

Pepsinogen is secreted by the gastric peptic cells. A great deal is known about the intricate physiology of acid secretion from the parietal cells but not nearly as much on the regulation of pepsinogen secretion. To powerfully

reduce the secretion of this proenzyme at the cellular level requires deeper understanding of mechanisms and probably the development of specific inhibitors: this, we suggest, is an avenue for the future.

Minimising or halting the damage caused when the enzyme is adherent to the extraesophageal epithelium and positioned to be endocytosed requires a different strategy [37, 39]. Hence, the development of an irreversible pepsin inhibitor has recently been mooted.

We speculate that these two strategies, if and when developed, are likely to be used together in troublesome EER disease, the irreversible inhibitor against pepsin already adherent, and a secretion inhibitor to markedly reduce pepsinogen secretion and hence pepsin at source, thereby preventing further damage.

8.7. Surgery. Antireflux surgery for GERD gives very good results in the majority of patients who are carefully selected for this operation, and extensive clinical and trial experience has defined its role in patient management. Because gastroesophageal reflux is at the root of both GERD and EER, it is tempting to presume antireflux operation will also give similar benefit in extraesophageal reflux. There are indeed anecdotal instances where operation has helped individual patients but as yet this cannot be generalized, for there are substantial differences between the two conditions.

There are as yet no specific selection criteria with which to identify those with EER who are likely to benefit from surgery. The development of such criteria for GERD and the optimisation of antireflux surgery developed over the last two decades of the 20th century. It is likely to take several years for a similar position to be reached for the surgical treatment of EER.

9. Conclusion

Knowledge of GERD emerged in the last third of the 20th century, as growth accelerating after the development of PPIs, which triggered many studies on the pathophysiology and dominated treatment. Knowledge of EER, a part of the reflux spectrum but with distinct characteristics, is still emerging and, like GERD, may prove to be a worldwide problem.

The presence of excessive acid in the esophagus is crucial for the development of GERD symptoms and mucosal damage, hence the benefit of PPIs which selectively and profoundly inhibit it. When extended to EER, however, the results are poor. Emerging knowledge now provides a persuasive explanation: EER is much more dependent on pepsin-mediated damage in the laryngeal and airway mucosa than with acid.

It was the recognition that acid might play a major role in peptic ulcer which led to the development of the H_2RA and subsequently to PPIs, the real power of which was to be found in GERD, where profound acid reduction is important. We believe the recognition now of the crucial role of pepsin in EER may, in turn, stimulate the development of drugs which specifically target this molecule. This may radically enhance our knowledge and management of this condition.

Abbreviations

DU: Duodenal ulcer
EER: Extraesophageal reflux
GA: Gaviscon Advance
GERD: Gastroesophageal reflux disease
H_2RA: Histamine H_2 receptor antagonists
HCl: Hydrochloric acid
H. pylori: *Helicobacter pylori*
LES: Lower esophageal sphincter
LPR: Laryngopharyngeal reflux
PPI: Proton pump inhibitor
QLI: Quality of life index
RFS: Reflux finding score
RSI: Reflux symptom index
UES: Upper esophageal sphincter.

Conflict of Interest

K. D. Bardhan has received a small unrestricted educational grant from Reckitt Benckiser towards his research programme. V. Strugala and P. W. Dettmar act as consultants for Reckitt Benckiser. The authors confirm that this paper was developed independently and they have maintained full editorial ownership.

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