### **REVIEW SERIES**

# Cough $\cdot$ 3: Chronic cough and gastro-oesophageal reflux

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The pathogenesis and clinical features of gastrooesophageal reflux related cough are complex and the diagnostic tests available are of limited reliability. Treatment needs to be tailored to the specific needs of individual patients and other possible causes of chronic cough should be investigated. Treatment should only be considered to have failed when cough persists after administration of proton pump inhibitors at an adequate dosage for a sufficient length of time.

hronic cough, conventionally defined as a cough persisting for more than 8 weeks,<sup>1</sup> represents both a disabling symptom for the patient and a difficult management problem. In most instances, however, clearly defined causes are recognised,<sup>1</sup> of which gastro-oesophageal reflux (GOR) is one of the most common.<sup>1-5</sup> It has been proposed<sup>6</sup> that patients with GOR related cough meet a specific clinical profile: non-smoking patients with a normal chest radiograph and not receiving angiotensin converting enzyme inhibitors. GOR alone or in combination with other factors such as postnasal drip syndrome and/or asthma is the cause of chronic cough in 10–40% of adult patients.<sup>2 5 7 8</sup>

#### PRESENTATION

GOR related cough has two main but not mutually exclusive pathogenetic mechanismsmicroaspiration of gastric contents and a vagally mediated oesophageal-tracheobronchial reflex.9 When aspiration predominates, gastrointestinal symptoms are generally prominent and include heartburn, regurgitation, waterbrash, and sour taste; odynophagia, dyspepsia, night sweats, chest pain, and globus sensation may also be present.<sup>10</sup> At the level of the extrathoracic airway, recurrent aspiration phenomena may lead to pharyngolaryngeal symptoms such as dysphonia, hoarseness, sore throat, as well as gum inflammation and dental erosion.11 Patients with pulmonary aspiration may report a variety of symptoms including chest pain, dyspnoea, sputum production, and wheeze.<sup>12</sup> When GOR related cough is reflex in origin, the gastrointestinal manifestations may be less evident or even absent in up to 75% of cases<sup>13 14</sup>; cough as the sole presenting symptom of GOR has also been reported.7 A negative clinical history does not rule out GOR as the cause of chronic cough<sup>6</sup> since, in some instances, GOR related cough may have no distinctive clinical features.8 However, an association between cough and GOR can be suspected on clinical grounds, most typically

when cough is exacerbated by postural changes (especially stooping) or food intake.

#### Cough duration and descriptors

Symptom duration can be quite variable, ranging from several weeks to years,<sup>8</sup> and not significantly different from that observed when cough is due to other causes such as asthma and postnasal drip.<sup>4</sup> A study of patients with chronic cough showed that none of the cough descriptors such as paroxysmal, honking, propagating, brassy, and barking was consistently associated with GOR related cough.<sup>8</sup>

#### Timing and posture

It is commonly believed that nocturnal cough is typical of GOR, but the consistency of this relation was not confirmed by studies which specifically addressed this possibility: nocturnal episodes of coughing have been found to occur in patients with GOR disease as frequently as in those with other common causes of chronic cough.<sup>8</sup> This finding is in keeping with the notion that GOR events, as detected by prolonged oesophageal pH monitoring, are more frequent when patients are awake and upright.7 Furthermore, transient lower oesophageal relaxation is suppressed during stable sleep,15 and cough of any cause is less likely to occur during sleep since this reflex is inhibited.<sup>16</sup> In our experience, however, some patients with GOR related respiratory symptoms do report an increased occurrence of gastrointestinal symptoms of GOR with or without cough when supine. In such cases, a hypotonic or incompetent lower oesophageal sphincter (LOS) may be suspected.<sup>17</sup> Nocturnal cough has recently been shown to be predictive of proximal GOR in patients with a manometrically incompetent LOS.18

## Association with food intake, drug consumption, and smoking

Foods can aggravate reflux symptoms by a number of mechanisms including gastric distension causing transient lower oesophageal relaxation, food contents directly lowering LOS pressure, and irritant effects on the inflamed oesophageal mucosa.19 Significant exposure of the distal oesophagus to acid and impaired acid clearance can occur after consumption of moderate amounts of alcohol.<sup>20</sup> A number of medications, both prescribed and over the counter, can lower LOS pressure and cause oesophageal mucosal damage. The former group includes theophylline<sup>21</sup> and oral (but not inhaled)  $\beta$ adrenergic agonists,22 while the latter group includes non-steroidal anti-inflammatory drugs and ascorbic acid. Xanthine-containing food may contribute to increase GOR episodes by the same

See end of article for authors' affiliations

Correspondence to: Dr G A Fontana, Dipartimento di Area Critica Medico Chirurgica, Sezione di Medicina Respiratoria, Università di Firenze, Viale G B Morgani, 85 50134 Firenze, Italy; g.fontana@ dac.unifi.it mechanism as that of theophylline. Cigarette smoking contributes to GOR via the pharmacological effect of nicotine which lowers LOS pressure and decreases acid clearance.<sup>23</sup> Patients often report that meals, especially when high in fat content, worsen the gastrointestinal symptoms of GOR.<sup>24</sup> Although an increase in the fat content of meals does not appear to affect oesophageal motility and the number of reflux events in patients with GOR,<sup>25</sup> fatty acids in the intestinal lumen may stimulate afferent nerves implicated in the facilitation of pain pathways.<sup>26</sup>

#### Sputum production

Reflux induced cough is more frequently dry, but sputum production of varying degrees may also be present.<sup>8</sup> Sputum production may be reflex mediated<sup>27</sup> and does not necessarily imply aspiration of gastric contents with subsequent airway infection.

#### **Complications of cough**

Cough is well known to cause several complications involving virtually all body systems,<sup>28</sup> but their prevalence in chronic cough due to GOR remains to be established. However, since such complications are a consequence of the large swings in intrathoracic and abdominal pressure produced by the intense repetitive muscle efforts of coughing, they are unlikely to be related to any specific underlying cause. It has been proposed that the mechanical events of coughing initiate a self-perpetuating positive feedback cycle whereby coughing from any cause may precipitate further reflux.<sup>29</sup> Recent lines of evidence suggest that reflux episodes lead to cough in the majority of cases.<sup>30</sup>

#### DIAGNOSTIC PROCEDURES Manometry

Oesophageal manometry may be used to assess the physiological attributes of the oesophageal body and of the upper and lower oesophageal sphincters. Previous uncontrolled studies in patients with motility disorders have suggested an association between abnormal motility profiles and chronic cough.<sup>31-33</sup> More recently, impaired motility of the oesophageal body has been shown to be important in the development of GOR associated respiratory symptoms. Transient LOS relaxation is the major event leading to reflux,<sup>34</sup> although an important minority of reflux episodes (about 4%) occur because of defective basal LOS pressure.<sup>35</sup>

#### **Barium radiography**

The barium swallow has been used widely in the diagnosis of GOR, and movement of barium from the stomach into the oesophagus is considered diagnostic for GOR.<sup>36</sup> However, free reflux after the barium swallow has been detected in 30% of normal subjects and is absent in up to 60% of patients with GOR.<sup>36</sup> making it a rather insensitive and non-specific method for diagnosing GOR disease with a positive predictive value as low as 30%.<sup>28</sup> It is generally agreed that the major clinical usefulness of barium is for the study of local anatomical complications of GOR disease such as hiatal hernias or strictures.<sup>37</sup> However, in a few patients with chronic cough due to GOR but with a negative oesophageal pH study (see below), the barium swallow may be the only method to suggest GOR as a likely cause of cough.<sup>2</sup>

#### **Bernstein test**

This test aims to evaluate objectively the relationship between acid exposure and symptoms. It is performed by instilling either saline or an acid (0.1 N HCl) solution into the oesophagus, and is considered positive when symptoms are reproduced by acid but not saline instillation. The sensitivity of the test is approximately 80% for GOR,<sup>38</sup> but it is much lower (<30%) when used to reproduce cough in patients with proven GOR related cough.<sup>2</sup> The method may provide evidence of GOR but does not allow a relationship to be established between GOR events and symptom appearance.

#### Endoscopy

Endoscopy is the best single test to document mucosal abnormalities and establish a diagnosis of erosive oesophagitis or Barrett's oesophagus in patients with suspected GOR disease. Macroscopic lesions of the oesophageal mucosa have been detected in up to 60% of patients with heartburn or regurgitation, while the remainder have a normal oesophagus or minimal non-erosive alterations.<sup>39</sup> In patients with GOR related cough the test can confirm the presence of mucosal damage by reflux but, similarly to barium swallow, cannot prove that cough is due to reflux.

#### Pharyngeal pH monitoring

It has recently been proposed that pharyngeal pH monitoring with a pH catheter placed 2 cm above the upper oesophageal sphincter is an accurate method to identify patients in whom abnormal reflux causes airway problems,<sup>40</sup> and that pharyngeal reflux is present in 70% of patients with airway symptoms including cough.<sup>41</sup> At variance with GOR, pharyngeal reflux is uncommon in normal subjects.<sup>41</sup> The clinical usefulness of pharyngeal pH monitoring in the study of GOR related cough remains to be established.

#### 24 hour oesophageal pH monitoring

The bulk of the literature (reviewed by Irwin *et al*<sup>1</sup>) indicates that the most sensitive and specific test for diagnosing cough due to GOR is 24 hour oesophageal pH monitoring. Abnormal pH profiles on oesophageal pH monitoring that may be used in the diagnosis of GOR related cough have been reported.<sup>42 43</sup> The recording of cough events by means of a diary or event marker during oesophageal pH monitoring is also useful, since patients with normal standard reflux parameters may still have acid related cough if a temporal relationship between GOR episodes and cough can be established.<sup>2</sup> Prospective studies in which the causes of chronic cough were determined in  $\sim$ 90% of patients also showed that the positive and negative predictive value of reflux indexes derived from oesophageal pH monitoring were 89% and 100%, respectively.<sup>4</sup> Similar outcomes have recently been obtained by McGarvey et al.42 In contrast, Ours et al31 reported that only 35% of patients with chronic cough and abnormal pH profiles responded favourably to proton pump inhibitor therapy, and concluded that oesophageal pH monitoring is not a reliable predictor of acid related cough. Resistance to acid suppression,35 short treatment duration,45 cough mediated by non-acid reflux events,44 and co-existence of other causes of cough can all account for the discrepancy.

It is now well established that reflux can be acid, non-acid, pure liquid, and a mixture of gas and liquid. Intraoesophageal impedance recording is therefore emerging as a useful tool to diagnose the presence of non-acid reflux in patients whose symptoms persist despite adequate acid suppression.<sup>44-46</sup>

#### **Empirical trial**

When oesophageal pH monitoring is not available or the results obtained with this technique are controversial, an empirical trial of antireflux therapy may represent a useful and reasonable diagnostic alternative. Recent lines of evidence suggest that cough relief following empirical treatment with high doses of proton pump inhibitors identifies patients with GOR related chronic cough in which other common causes have been excluded.<sup>31</sup> If an empirical trial is chosen, treatment must be continued for up to 3–4 months before GOR can reasonably be excluded as a cause of cough.<sup>4 7</sup> Confirmation of GOR, preferably by pH

monitoring, may be useful to increase the patient's compliance with prolonged treatment. When empirical treatment fails, pH monitoring should be performed to identify patients with a poor response to treatment and to verify the adequacy of drug dosing.

#### TREATMENT

Treatment of GOR related cough should be carefully tailored to the specific needs of each patient.<sup>1 47 48</sup> Treatment should be directed to both reduce the number of reflux events and change the chemical characteristics of the refluxing material. Since many factors may combine in the genesis of cough,<sup>1</sup> treatments for other established causes of chronic cough (such as asthma and rhinitis) should be added, especially when the response to antireflux treatment has been partial. Finally, treatment failure does not rule out GOR as the cause of chronic cough.<sup>49</sup> Reassessment of lifestyle measures, drug selection, dosage regimen, and length of treatment should be considered, together with the possibility of cough induced by non-acid reflux.<sup>50</sup> In some patients insensitive to any form of medical treatment,<sup>31</sup> surgery may be the most appropriate therapeutic option.

#### Conservative and lifestyle measures

Sleeping with an elevated head in patients with documented night time reflux episodes, smoking cessation, weight reduction, and a low fat diet (<45 g/day) have all been found to be useful measures.<sup>2</sup> <sup>6</sup> Avoidance of food and beverages with a pH of <5 and/or capable of relaxing the LOS—such as alcohol, chocolate, mint, onions, coffee, tea, cola, citrus fruits—is also highly recommended, and patients should avoid food and beverages 2–3 hours before going to bed.<sup>2</sup> <sup>6</sup>

#### Pharmacological treatment

H<sub>2</sub> receptor antagonists, whose action is based on the reduction of gastric volume and acid secretion, have been widely used in the treatment of GOR related cough. Response rates of 80%, usually in association with conservative measures, have been observed with both cimetidine and ranitidine.1 The positive effect persists 6 weeks after discontinuing treatment. Prokinetic agents such as metoclopramide, cisapride, and domperidone exert their effects mainly by facilitating gastric emptying. They are usually used in association with H<sub>2</sub> antagonists or proton pump inhibitors. When used as monotherapy in children, prokinetic agents have been shown to produce high response rates in the suppression of cough.<sup>1</sup> However, the risk of fatal arrhythmia with cisapride outweighs the benefit for which the drug is prescribed, and this has led to its discontinuation in most countries.<sup>51</sup> Similar adverse effects have been described for domperidone.<sup>52</sup> Proton pump inhibitors, whose effect is based on the inhibition of acid secretion, have recently emerged as the most effective treatment for GOR disease. A recent randomised, double blind, crossover, placebo controlled study showed that omeprazole in a daily dose of 40 mg for 8 weeks produced a significant reduction in GOR induced cough and the effect continued after cessation of treatment.53 In a few patients, however, gastric acidity persisted despite treatment with doses up to 80 mg daily.49

New agents related to  $\gamma$ -aminobutyric acid-B (GABA<sub>B</sub>) agonists have been shown to reduce the rate of transient lower oesophageal relaxation.<sup>54</sup> Baclofen is the most potent inhibitor of transient lower oesophageal relaxation identified to date.<sup>54</sup> Drowsiness, nausea, and lowering of the threshold for seizures are presently the main challenge to the use of baclofen and other GABA<sub>B</sub> agonists for the treatment of GOR related disorders. Notably, intraventricular administration of baclofen inhibits the cough evoked by capsaicin inhalation in cats and guinea pigs,<sup>55</sup> which suggests that this drug or

similar compounds may be particularly suitable for treating GOR related cough.

#### Surgery

Surgery (open or laparoscopic fundoplication) is the treatment of choice in patients with signs of recurrent aspiration. and is indicated also in those patients with GOR related cough which persists after appropriate medical treatment, including high doses of proton pump inhibitors.<sup>56</sup> Notably, it has been reported<sup>6</sup> that, in a selected group of patients with chronic cough that persisted after total or near total acid suppression who met the clinical profile for GOR related cough, the symptoms disappeared or were greatly improved by antireflux surgery. A prospective trial has shown that 51% of patients who had not responded to maximal medical treatment with omeprazole were free of cough and 31% experienced a significant improvement 6 months after fundoplication.<sup>57</sup> In a study of 118 patients with GOR, 53% of whom had additional respiratory symptoms, surgery resulted in relief of respiratory symptoms in 76% of patients. Interestingly, oesophageal dysmotility was significantly more common in patients whose condition failed to improve with surgery.58 Although this finding would suggest that surgical management of GOR should be restricted to patients who have normal oesophageal motility, this possibility has been denied by Fibbe et al<sup>59</sup> who reported similar postoperative outcomes in patients with and without dysmotility.

#### CONCLUSIONS

Given the complex pathogenesis and the protean clinical features of GOR related cough and the limited reliability of the available diagnostic tests, the procedures for assessing and managing the condition need to be more accurately defined. In general, treatment needs to be tailored to meet the specific needs of each patient, and the possible presence of other causes of chronic cough must be ascertained. Failure of treatment should be considered only when cough persists after administration of proton pump inhibitors at an adequate dosage and for a sufficiently long period of time.

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#### REFERENCES

- Irwin RS, Boulet LP, Cloutier MM, et al. Managing cough as a defense mechanism and as a symptom. A consensus panel report of the American College of Chest Physicians. Chest 1998;114(2 Suppl):133–81S.
- Invin RS, French CL, Curley FJ, et al. Chronic cough due to gastroesophageal reflux: clinical, diagnostic, and pathogenetic aspects. Chest 1993;104:1511–7.
- 3 Irwin RS, Corrao WM, Pratter MR. Chronic persistent cough in the adult: the spectrum and frequency of causes and successful outcome of specific therapy. *Am Rev Respir Dis* 1981;**123**:413–7.
- 4 Invin RS, Curley FJ, French CL. Chronic cough. The spectrum and frequency of causes, key components of the diagnostic evaluation, and outcome of specific therapy. Am Rev Respir Dis 1990;141:640–7.
- 5 Irwin RS, Mello CJ. Chronic cough as a symptom of GERD. Contemp Intern Med 1995;7:15–5.
- 6 French CT, Irwin RS, Fletcher KE, et al. Chronic cough due to gastroesophageal reflux disease: failure to resolve despite total/near-total elimination of esophageal acid. Chest 2002;121:1132-40.
  7 Irwin RS, Zawacki JK, Curley FJ, et al. Chronic cough as the sole presenting
- 7 Irwin RS, Zawacki JK, Curley FJ, et al. Chronic cough as the sole presenting manifestation of gastroesophageal reflux. Am Rev Respir Dis 1989;140:1294–300.
- 8 Mello CJ, Irwin RS, Curley FJ. Predictive values of the character, timing, and complications of chronic cough in diagnosing its cause. Arch Intern Med 1996;156:997–1003.
- 9 Sekizawa S, Ishikawa T, Sant'Ambrogio FB, et al. Vagal esophageal receptors in anesthetizect dogs: mechanical and chemical responsiveness. J Appl Physiol 1999;86:1231–5.
- Katz PO, Castell DO. Diagnosis of gastroesophageal reflux disease. In: Stein M, ed. Gastroesophageal reflux disease and airway disease. New York: Marcel Dekker, 1999:55–68.

- 11 Koufman JA. The otolaryngologic manifestations of GERD. In: Stein M, ed. Gastroesophageal reflux disease and airway disease. New York: Marcel Dekker, 1999:69-88.
- Ing AJ. Cough and gastroesophageal reflux. Am J Med 12 1997;103(5A):91s-96s
- Ing AJ, Ngu MC, Breslin AB. Chronic persistent cough and clearance of esophageal acid. Chest 1992;102:1668–71.
   Ing AJ, Ngu MC, Breslin AB. Pathogenesis of chronic persistent cough associated with gastroesophageal reflux. Am J Respir Crit Care Med 1994;149:160–7.
- 15 Dent J, Dodds WJ. Mechanism of gastroesophageal reflux in recumbent asymptomatic human subjects. J Clin Invest 1994;19:100–4.
- 16 Sullivan CE, Kozar LF, Murphy LF, et al. Arousal, ventilatory, and airway responses to bronchopulmonary stimulation in sleeping dogs. J Appl Physiol 1979.47.17-25
- 17 Orlando RC. Overview of the mechanisms of gastroesophageal reflux. Am J Med 2001;111:174–75.
- Tomonaga T, Awad ZT, Filipi CJ, et al. Symptom predictability of reflux-18
- Iomonaga I, Awad ZI, Filipi CJ, et al. Symptom predictability of reflux-induced respiratory disease. Dig Dis Sci 2002;47:9–14.
   Kavuru MS, Richter JE. Medical treatment of gastroesophageal reflux disease and airway disease. In: Stein M, ed. Gastroesophageal reflux disease and airway disease. New York: Marcel Dekker, 1999:179–207.
   Vitale CG, Cheadle WG, Patel B, et al. The effect of alcohol on nocturnal gastroesophageal reflux. JAMA 1987;258:2077–9.
   Ruzkowski CJ, Sanowski RA, Austin J, et al. Effect of theophylline on
- gastroesophageal reflux in patients with asthma. Arch Intern Med 1992;152:783-5.
- 22 Schindlbeck NE, Heinrich C, Huber RM, et al. Effects of albuterol (salbutamol) on esophageal motility and gastroesophageal reflux in healthy volunteers. JAMA 1988;**260**:3156–8.
- Dennish GW, Castell DO. Inhibiting effect of smoking on lower esophageal sphincter. N Engl J Med 1971;284:1136–7. 23
- 24 Nebel OT, Fornes MF, Castell DO. Symptomatic gastroesophageal reflux and Precipitating factors. *Dig Dis* 1976;21:953-6.
  Pehl C, Waizenhoefer A, Wendl B, *et al.* Effect of low and high fat meals on
- 25 lower esophageal sphincter motility and gastroesophageal reflux in healthy subjects. Am J Gastroenterol 1999;**94**:1192–6.
- 26 Holloway RH, Lyrenas E, Ireland A, et al. Effect of intraduodenal fat on lower oesophageal sphincter function and gastro-oesophageal reflux. *Gut* 1997;**40**:449–53.
- 27 German VF, Corrales R, Ueki IF, et al. Reflex stimulation of tracheal mucus gland secretion by gastric irritation in cats. J Appl Physiol 1982;52:1153–5
- 28 Smyrnos NA, Irwin RS, Curley FJ. Chronic cough with a history of excessive mucus production. Chest 1995;108:991-7.
- 29
- 30
- Ing AJ, Ngu MC, Breslin AB. Chronic persistent cough may precipitate gastro-esophageal reflux. Am Rev Respir Dis 1992;145:A11. Avidan B, Sonnenberg A, Schnell TG, et al. Temporal associations between coughing or wheezing and acid reflux in asthmatics. Gut 2001;49:767–72. Ours TM, Kavuru MS, Schilz RJ, et al. A prospective evaluation of esophageal testing and a double-blind, randomized study of omeoprazole in a diagnostic and the area the advertise therapic acute. Am (Contractored) 31 and therapeutic algorithm for chronic cough. Am J Gastroenterol 1999:**94**:3131-8.
- 32 DeMeester TR, Bonavina L, Lascone C, et al. Chronic respiratory symptoms and occult gastro-oesophageal reflux: a prospective clinical trial and results of surgical therapy. Ann Surg 1990;**211**:337–45. **Knight RE**, Wells JR, Parrish RS. Esophageal dysmotility as an important co-factor in extraesophageal manifestations of gastroesophageal reflux
- 33 Laryngoscope 2000;110:1462-6.
- 34 Kahrilas PJ, Clouse RE, Hogan WJ. American Gastroenterological Association technical review on the clinical use of esophageal manometry.
- Gastroenterology 1994;107:1865–84.
   Barret J, Peghini P, Katz P, et al. Ineffective esophageal motility: the most common abnormality in GERD (abstract). Gastroenterology 1997;112:4.
   Richter JE, Castell DO. Gastroesophageal reflux. Pathogenesis, diagnosis,
- and therapy. Ann Intern Med 1982;97:93-103.

- 37 Orlando RC. Reflux esophagitis. In: Yamada T, Alpers DH, Owyang C, et al, eds. Textbook of gastroenterology. 2nd ed. Philadelphia: J B Lippincott, 1995:1214-42.
- Bernstein LM, Baker LA. A clinic test for esophagitis. Gastroenterology 38 1958;34:760-81.
- Winters C Jr, Spurling TJ, Chobanian SJ, et al. Barrett's esophagus. A 30 prevalent, occult complication of gastroesophageal reflux disease Gastroenterology 1987;**92**:118–23.
- 40 Eubanks TR, Omelanczuk PE, Hillel A, et al. Pharyngeal pH measurements in patients with respiratory symptoms before and during proton pump inhibitor therapy. Am J Surg 2001;181:466–70.
- Eubanks TR, Omelanczuk PE, Maronian N, et al. Pharyngeal pH monitoring in 222 patients with suspected laryngeal reflux. J Gastrointest Surg 2001.5.183-91
- 42 McGarvey LPA, Heaney LG, Lawson JT, et al. Evaluation and outcome of patients with chronic non-productive cough using a comprehensive diagnostic rotocol. Thorax 1998;**53**:738–43.
- Johnston BT, McFarland RJ, Collins JSA, et al. The symptom index. A useful marker of gastro-oesophageal reflux disease. Br J Surg 1992;79:1054-5
- 44 Castell DO, Vela M. Combined multichannel intraluminal impedance and pHmetry: an evolving technique to measure type and proximal extent of gastroesophageal reflux. Am J Med 2001;111(Suppl 8A):157–9S.
  45 Vela MF, Camacho-Lobato L, Srinivasan R, et al. Simultaneous
- intraesophageal impedance and pH measurement of acid and nonacid gastroesophageal reflux: effect of omeprazole. *Gastroenterology* 2001;**120**:1599–606.
- Sifrim D, Holloway R, Silny J, *et al.* Acid, nonacid, and gas reflux in patients with gastroesophageal reflux disease during ambulatory 24-hour pH-
- impedance recordings. *Gastroenterology* 2001;120:1588–98.
   47 DeVault KR. Overview of therapy for the extraesophageal manifestations of gastroesophageal reflux disease. Am J Gastroenterol 2000;95(Suppl):S39–44.
- 48 Ing aj, Ngu MC. Cough and gastro-oesophageal reflux. Lancet 1999;353:944-6.
- Leite LP, Johnston BT, Just RJ, et al. Persistent acid secretion during 49 Center LP, Johnston BP, as NJ, et al. resistent acid section adming omeprazole therapy: a study of gstric acid profiles in patients demonstrating failure of omeprazole therapy. Am J Gastroenterol 1996;91:1527–31.
   Irwin RS, Madison MJ. The persistent troublesome cough. Am J Respir Crit Care Med 2002;165:1469–74.
- Wysowski DK, Corken A Gallo-Torres H, et al. Postmarketing reports of QT prolongation and ventricular arrhythmia in association with cisapride and Food and Drug Administration regulatory actions. Am J Gastroenterol 2001;96:1698-703.
- 52 Drolet B, Rousseau G, Daleau P, et al. Domperidone should not be considered a no-risk alternative to cisapride in the treatment of gastrointestinal motility disorders. Circulation 2000;102:1883-5.
- Kiljander TO, Salomaa ERM, Hietanen EK, *et al.* Chronic cough and gastro-oesophageal reflux: a double-blind placebo-controlled study with 53 omeprazole. Eur Respir J 2000;16:633-8.
- Holloway RH. Systemic pharmacomodulation of transient lower esophageal sphincter relaxations. Am J Med 2002;111:178-85S.
- 55 Bolser DC, De Gennaro FC, O'Reilly S, et al. Peripheral and central sites of action of GABA<sub>B</sub> agonists to inhibit the cough reflex in the cat and guinea pig. Br J Pharmacol 1994;113:1344–8.
- 56 Mello CJ. GERD. A major factor in chronic cough. In: Stein M, ed. Gastroesophageal reflux disease and airway disease. New York: Marcel Dekker, 1999:89-113.
- Allen CJ, Anvari M. Gastro-oesophageal reflux related cough and its response to laparoscopic fundoplication. Thorax 1998;53:963-8
- 58 Johnson WE, Hagen JA, DeMeester TR, et al. Outcome of respiratory symptoms after antireflux surgery on patients with gastroesophageal reflux disease. Arch Surg 1996;131:489–92.
  Fibbe C, Layer P, Keller J, et al. Esophageal motility in reflux disease before
- and after fundoplication: a prospective randomized, clinical and manometric study. Gastroenterology 2001;121:5-14.