

*Editorial*

## Physiology and treatment of cough

Cough is a powerful physiological mechanism that causes the central airways to be cleared of foreign material and excess secretions. It is characterised by a violent expiration, which provides the high flow rates that are required to shear away mucus and remove foreign particles from the larynx, trachea, and large bronchi. Most sensory stimuli that cause coughing also increase airway secretion, which is beneficial as this provides a vehicle for expulsion of particulate matter.

Cough is a very common presenting symptom in general practice and in the chest clinic. The prevalence of cough in the population depends on the prevalence of smoking and other environmental factors and in different populations has varied from 5% to 40%.<sup>1-7</sup> One indication of the size of the problem is the self prescription of over the counter antitussives, which has been estimated at 75 million doses per annum in the United Kingdom.<sup>8</sup> The most common causes of cough are the virus induced acute upper respiratory tract infections, when the cough is usually non-productive and self limiting. In other patients cough is associated with increased mucus production or a chronic respiratory disease such as asthma; in a proportion of patients, however, no such cause is obvious at presentation and cough may persist for many years. When cough is associated with sputum production, it is likely to be due to the excess secretion in the airway stimulating sensory nerves. In the absence of abnormal sputum production there is likely to be some other reason for the cough. The likely explanation would be an increased sensitivity of the cough reflex,<sup>9,10</sup> which would lead to the abnormal response of the patient to "natural" inhaled stimuli. In this review we will discuss the physiology of cough, the mechanism of abnormal cough, the clinical investigation of unexplained cough, and the limitations of treatment for non-productive cough.

### Physiology

Cough usually results from the stimulation of sensory nerves in the airways. The nerves that initiate cough are predominantly in the upper airway, for it is here that the greatest protection against the ingress of foreign material is required. We have considered sensory innervation of the airway in the larynx and pharynx and in the rest of the tracheobronchial tree. Table 1 lists the various sensory nerves and their anatomical location and physiology.

### LARYNX AND PHARYNX

The larynx, being the sentinel of the lung, possesses abundant sensory innervation, which a mere biscuit crumb can activate to produce violent coughing. Most of the sensory traffic from the larynx is conveyed in the superior laryngeal nerves.<sup>11</sup> Single fibre recordings show that three types of receptors in the larynx are activated by different events of the breathing cycle. Pressure receptors respond to changes in translaryngeal pressure; "drive" receptors are stimulated by passive or active motion of the larynx; and cold/flow receptors respond to a decrease in laryngeal

temperature.<sup>12,13</sup> It is unlikely, however, that either laryngeal cold/flow, pressure, or drive receptors contribute to coughing because changes in their activity are happening throughout the respiratory cycle and cough does not occur. Afferent activity may also be elicited from the larynx by mechanical and chemical irritants. Cough is probably caused by the stimulation of the irregularly firing irritant receptors, as described in cats.<sup>14</sup>

The role that laryngeal C fibre endings play in the initiation of cough is not clear. The evidence for their role is based largely on experiments where capsaicin has been used to produce cough. As inhaled capsaicin, which causes violent coughing when inhaled, has been regarded as a specific stimulant of non-myelinated nerve endings, the conclusion has been reached that stimulation of laryngeal C fibres causes cough.<sup>15,16</sup> Unfortunately, capsaicin shows limited specificity for non-myelinated nerve endings, so the conclusion is unsound.

### THE TRACHEOBRONCHIAL TREE

The vagus nerves are known to carry the sensory information from the lung which initiates the cough reflex,<sup>17</sup> as cough from stimulation of one side of the bronchial tree is abolished by ipsilateral vagotomy.<sup>18</sup> The lung has three types of sensory nerves: slowly adapting stretch receptors, rapidly adapting stretch receptors (or "irritant receptors"), and C fibre endings. The latter are subdivided into pulmonary C fibre endings and bronchial C fibre endings, depending on the source of their blood supply.<sup>19</sup>

#### *Slowly adapting stretch receptors*

The slowly adapting stretch receptors increase their activity during inspiration, and there is convincing evidence that they are responsible for the termination of inspiration and prolongation of expiration on lung inflation, which in anaesthetised animals provides the dominant mechanism for regulating the depth and rate of breathing.<sup>20</sup> The receptors are located in the membranous posterior wall of conducting airways within the smooth muscle<sup>21</sup> and, as their name implies, adapt very slowly to changes in the length of this muscle. It has been proposed that the sensory input to the cough centres from the pulmonary stretch receptors is important for the act of coughing. This view has been supported by animal experiments in which the stretch receptors have been destroyed by sulphur dioxide. These animals do not cough when the trachea is stimulated mechanically.<sup>22</sup>

#### *Rapidly adapting stretch receptors or "irritant" receptors*

The rapidly adapting stretch receptors are situated within the mucosal surface of the proximal tracheobronchial tree and their sensory information is conducted in the vagus nerves by myelinated nerves. The receptors are found around the whole circumference of the conducting airways and their density is greatest at bifurcations.<sup>23</sup> The receptors discharge sporadically during normal respiration but there may be bursts of activity during the inspiratory phase.<sup>24</sup> There is some evidence that the rapidly adapting stretch

Table 1 Sensory nerves in the lung associated with cough

Site	Receptor type	Location	Natural stimuli that cause cough	Experimental stimuli that cause cough	Effect of stimulation
Larynx	(i) Myelinated irregularly firing irritant receptors	Laryngeal folds	Particulate matter (mechanical stimulation). Cigarette smoke. Cold air	Capsaicin?	Cough
	(ii) Non myelinated C fibre endings	Laryngeal folds	Particulate matter (mechanical stimulation). Chemicals?	Capsaicin. Nebulised distilled water	Cough
Lung	(i) Myelinated (a) Rapidly adapting stretch receptors	Mucosal surface of the proximal tracheo-bronchial tree	Particulate matter (mechanical stimulation). Noxious gases. Cigarette smoke	Nebulised distilled water? PGE <sub>2</sub>	Cough
	(b) Slowly adapting stretch receptors	Membranous posterior wall of conducting airways in smooth muscle	Inhalation	Veratrum alkaloids	Facilitates reflex activity of expiratory muscles
	(ii) Non-myelinated (a) Pulmonary C fibre endings	Peripheral airways supplied with blood from the pulmonary circulation	Lung inflammation. Noxious gases	Lobeline. PGE <sub>2</sub> . Bradykinin	Cough or cough suppression?
	(b) Bronchial C fibre endings	Airways supplied with blood from the bronchial circulation	Lung inflammation. Noxious gases	Lobeline. PGE <sub>2</sub> . Bradykinin	Cough or cough suppression?

receptors have different functions, depending on their location—those in the trachea and proximal bronchi causing cough and those deeper in the lung causing augmented breaths, hyperpnoea, and possibly cough.<sup>23</sup>

Historically, the rapidly adapting stretch receptors have been regarded as the receptors most likely to be the cause of coughing from within the lung and the evidence for this is as follows:

1 The rapidly adapting stretch receptors respond to the lightest of mechanical stimuli.<sup>21</sup>

2 The receptors are located in the places where sensory nerves responsible for clearing mucus and expelling foreign material would be expected to be placed—that is, in the mucosal surface of the major airways with a high concentration at bifurcations, where particulate matter is most likely to become impacted.<sup>23</sup>

3 In some viral respiratory infections the cough reflex is heightened.<sup>25</sup> The responsiveness of the rapidly adapting receptors is increased during lung infection in the dog.<sup>26</sup>

4 The receptors respond to irritants that are known to cause cough in man—for example, prostaglandin (PG) E<sub>2</sub>,<sup>27</sup> and cigarette smoke.<sup>28</sup> Stimulation of rapidly adapting stretch receptors with chemicals may be direct or indirect. Any substance that deforms the bronchial smooth muscle will stimulate the rapidly adapting stretch receptors and therefore may cause cough. There are also chemicals that do not change the state of the bronchial smooth muscle but stimulate the rapidly adapting stretch receptors, and may also precipitate cough.

5 Blocking myelinated fibres in the vagus has in some studies inhibited the cough reflex.<sup>29</sup>

There is some evidence, however, that the rapidly adapting stretch receptors may not play as big a part in the genesis of cough as has been previously thought. Firstly, there is not a good correlation between the presence of intraepithelial nerves and the presence of the cough reflex in different species. For example, the ferret has no intraepithelial nerves but coughs when its bronchi are mechanically stimulated<sup>30</sup> and the rat, which has intraepithelial nerves in the trachea, has no cough reflex when the lung is stimulated.<sup>31</sup> Secondly, in man the stimuli most frequently used to induce cough are citric acid,<sup>32</sup> nebulised distilled water (fog),<sup>8</sup> and capsaicin.<sup>15</sup> Capsaicin and fog probably cause cough by stimulation of receptors in the larynx. Citric acid may initiate cough by the stimulation of rapidly adapting stretch receptors as inhalation is associated with a “burning” sensation in the chest.<sup>32</sup>

Experiments with dogs have failed to show that citric acid can stimulate the rapidly adapting stretch receptors (personal observation).

#### C FIBRE ENDINGS

Most of the sensory fibres originating from the lung and travelling in the vagus are non-myelinated.<sup>33</sup> The C fibre endings in the lung are relatively insensitive to mechanical stimulation and, unlike the myelinated nerve endings, they are found throughout the lung.<sup>16</sup> There is strong evidence that C fibre endings supply afferent information when cough is produced by chemical stimulation. The injection of lobeline causes cough and a retrosternal sensation in man as it passes through the pulmonary circulation.<sup>34</sup> Paintal has proposed that the cough caused by lobeline administration results from the stimulation of C fibre endings in the lung, though there is no electrophysiological evidence for this view.<sup>35</sup> In man inhalation of bradykinin causes coughing and a sensation of rawness in the airways.<sup>36</sup> Administration of bradykinin aerosols to dogs causes substantial stimulation of C fibre endings but has no effect on other vagal afferents in the lower respiratory tract.

Prostaglandin E<sub>2</sub> inhalation in man causes coughing and heightens the cough reflex.<sup>37,38</sup> In the dog administration of aerosols of 0.1 mg/ml PGE<sub>2</sub> stimulate airway C fibres.<sup>39</sup> Sulphur dioxide causes cough when given to conscious dogs through a tracheostomy and stimulates the C fibres in bronchi and extrapulmonary airways, but has little effect on irritant receptors when inhaled in similar concentrations by anaesthetised dogs.<sup>40</sup>

#### CONCLUSIONS

Cough caused by mechanical irritation results from stimulation of myelinated or non-myelinated sensory nerves in the larynx or the rapidly adapting stretch receptors in the lung, or both. Cough caused by direct chemical stimulation results from activation of receptors in the larynx (myelinated or non-myelinated) or activation of C fibre endings in the lung, or both.

#### Diagnosis of persistent cough

##### HISTORY

A careful clinical history in one series was shown to aid the diagnosis of cough in 80% of patients.<sup>41</sup> This figure will vary, depending on the duration of cough and the local referral pattern. Evidence of an association between cough and respiratory infection, bronchial disease, rhinitis, post-nasal drip, oesophageal reflux, and angiotensin converting

enzyme inhibitor treatment must be sought. When these conditions are treated conventionally the cough may be relieved. The patient should also be questioned about the factors that precipitate attacks of coughing during daily life, as it may prove possible to help the patient symptomatically if the symptoms are predictable even if the underlying cause is not found or treatable. Such treatment would include avoidance of the factor concerned and the use of short lived antitussive agents, such as demulcents and local anaesthetics.

#### INVESTIGATION

A chest radiograph is mandatory for patients with persistent cough and radiography of the sinuses and upper tract should be performed if the patient's history suggests a postnasal drip or oesophageal reflux. Upper gastrointestinal endoscopy and 24 hour oesophageal pH monitoring may aid the diagnosis.<sup>42</sup> Irvin<sup>42</sup> has suggested that oesophageal reflux is underdiagnosed in patients with cough and therapeutic trials of an H<sub>2</sub> receptor antagonist may be helpful if pH probes are not available. Bronchoscopy should be performed if there is a specific indication; "blind" bronchoscopy has a low diagnostic yield, however, in patients with isolated cough.<sup>43</sup> Spirometry before and after a bronchodilator and a histamine challenge should be performed if spirometric values are normal as a proportion of patients have asthma<sup>3</sup> and hence a treatable cause for their cough. Objective testing of the sensitivity of the cough reflex may prove helpful; sensitivity is increased in a high proportion of patients with dry, non-productive cough.<sup>9,10</sup> An abnormal cough reflex and normal spirometric values and chest radiograph would make further investigation unnecessary.

#### COUGH REFLEX TESTING

Many agents when inhaled cause coughing. One such agent, capsaicin, the hot extract of red pepper, when inhaled in very low doses causes reproducible dose related coughing.<sup>15</sup> Capsaicin is used to study cough because it can be administered easily to patients with a single breath, dosimeter controlled nebuliser or the hand held Devilbiss nebuliser. We use concentrations ranging from 1 to 500 μM capsaicin in 90% saline obtained from a stock solution of 1 mM in ethanol, and count the number of coughs after each dose. In our experience normal people do not usually cough with a concentration below 10 μM and often not until 30 μM, the mean for the concentration causing two or more coughs being 12.5 (95% confidence interval 6–19) μM.<sup>9</sup> Patients with a dry cough, however, whether related to angiotensin converting enzyme inhibitor treatment<sup>9,44</sup> or to other causes,<sup>10,25</sup> cough with lower doses (as low as 1 μM). Patients who cough at concentrations of capsaicin below 10 μM can therefore be regarded as having increased sensitivity of their cough reflex.

#### PHYSIOLOGY OF THE ABNORMAL COUGH REFLEX

The reason for the abnormal cough response in patients is uncertain. It is not merely a reflection of bronchial hyperreactivity as asthma in itself does not alter the cough reflex<sup>10</sup> and most of our patients with an increased cough reflex have a normal histamine response and no other symptoms of asthma. Asthmatic patients, however, clearly do cough and in the patients we studied this was associated with either mucus production or, more commonly, an increased cough reflex. The patients with an increased cough reflex tended to have asthma that was less well controlled and it is likely that the increased cough reflex is due to the asthmatic inflammation. On the assumption that the central nervous connections have not changed, the sensory information originating from the lung or larynx is

likely to be increased in these patients. Dogs infected with *Bordetella bronchiseptica* (kennel cough) have been shown to have rapidly adapting stretch receptors that are more responsive to histamine.<sup>26</sup> Viral infection in man may increase the cough response<sup>25</sup> by several means. Firstly, the infection may physically or functionally strip away the epithelium<sup>8</sup> and thus expose the sensory nerves, making them more responsive to both mechanical and chemical stimuli. Secondly, the inflammation associated with a lung infection may produce mediators (prostanoids) that sensitise the sensory nerve endings.<sup>38</sup> An interesting comparison can be made between cough and pain. It is generally accepted that pain receptors can be up regulated by local "sensitising agents" to produce hyperalgesia. A similar up regulation may occur in the lung and be responsible for the abnormal cough reflex. In angiotensin converting enzyme inhibitor cough this seems to be the cause as the cough is reduced by an oral non-steroidal anti-inflammatory drug, sulindac.<sup>45</sup>

#### Management of cough

Management strategies depend on whether the cough is mainly productive or non-productive. The treatment of productive cough secondary to conditions such as chronic obstructive airways disease, cystic fibrosis, and bronchiectasis will depend on manipulation of mucus secretion (except during exacerbations), which so far does not appear to be possible in man. During exacerbations the increased cough and mucus production should respond to appropriate treatment of the infection and inflammation. The use of cough suppressants in these patients in theory could lead to retention of mucus and deterioration in the patient's underlying disease.

The treatment of non-productive cough presents different problems. Should an underlying cause for the cough be identified, the treatment of that condition may lead to the relief of the patient's symptoms. This is most usually seen when the cough is associated with asthma, where appropriate and adequate treatment will greatly reduce cough.<sup>46</sup> Other conditions, such as carcinoma and interstitial lung disease, may be less amenable to treatment. Patients who have cough associated with postnasal drip or oesophageal reflux should respond to treatment of the underlying cause, but despite optimistic reports<sup>41</sup> adequate symptomatic relief of these conditions does not always reduce the cough in our experience. This appears to be because some patients have an abnormally sensitive cough reflex and coincidental postnasal drip or oesophageal reflux. The remaining group contains most of the patients with non-productive cough, including those with virus induced cough and chronic cough associated with an increased sensitivity of the cough reflex. In these patients the aim is for the patient either to avoid stimuli that cause coughing—that is, smoky rooms, cold air, exercise, pungent chemicals, etc—or to use drugs that suppress coughing. Patients with cough associated with angiotensin converting enzyme inhibitor will respond to stopping treatment; if this is undesirable then reducing the dose of the drug or adding sulindac treatment is worth trying.

#### THE PHARMACOLOGY OF COUGH SUPPRESSION

When cough is associated with the excessive production of mucus within the lung, suppression of the cough reflex is undesirable as mucus retention may occur. When cough is unproductive and a nuisance, preventing rest and sleep, suppression may be desirable. Complete suppression of the cough reflex is dangerous as the lung is then deprived of an essential defence mechanism. An ideal drug would reduce the increased sensitivity of the reflex to normal either by

altering the disease process or by reducing the response of the sensory nerves in the lung. The most obvious neurones to direct such activity against would be the rapidly adapting stretch receptors. The only effective peripherally acting cough suppressant are demulcents and local anaesthetics. Drugs that affect cough can also do so indirectly. For example, drugs that cause bronchodilatation could reduce the initiation of coughing without having any significant central effects. The most frequently used pharmacological cough suppressants, however, act in the midbrain and have many undesirable side effects. The older reports on antitussive agents have been reviewed by Eddy *et al*<sup>47 48</sup> and by Salem and Aviado,<sup>49</sup> who highlighted the paucity of objective effects of antitussive agents in clinical practice.

The commonly used antitussive agents, their pharmacology, and their relative effectiveness are shown in table 2.

#### Demulcents

Many proprietary cough preparations contain mainly sugar. These preparations are purchased in multi-million pound quantities each year. They have been shown to reduce cough in normal individuals in response to challenge with citric acid<sup>50</sup> and capsaicin for a short time (under 10 minutes in 10 volunteers; personal observation). The mechanism by which they do this is unknown; little research has been done to investigate their mode of action. There are three possibilities:

1 The sugar content of the cough mixture encourages saliva production and swallowing; the act of swallowing may interfere with the cough reflex.

2 The sugar solution may coat sensory nerve endings in the epipharynx and cause their stimulation; this stimulation may suppress cough by a "gating" process. A similar phenomenon has been described in cats, where stimulation of pulmonary C fibre endings by phenyldiguanide and capsaicin suppressed the cough reflex.<sup>51</sup>

3 The sugar solution may act as a protective barrier to sensory receptors that can either produce cough or heighten the cough reflex. These receptors must obviously be accessible to solutions that are swallowed, and have yet to be defined.

#### Opiates

The opiates are the oldest and the most studied of all cough suppressants, and are the standard by which all other cough suppressants are measured. There is no doubt that systemic morphine (0.12 mg/kg)<sup>47 52</sup> can suppress cough but this dose is far higher than that found in the proprietary cough mixtures. The *British National Formulary* lists seven opiate analogues as antitussives and the most commonly used contain codeine 15 mg/5 ml, pholcodeine 5 mg/5 ml, and dextromethorphan 13.5 mg/5 ml. There is little evidence in favour of using one drug in preference to another, all having a similar side effect profile at effective antitussive doses. The reason for any efficacy of proprietary cough mixtures containing opiates probably lies in the

sugar solution in which they are prepared as only limited pharmacological activity has been detected at these doses against either clinical cough or artificially induced cough.<sup>47 49</sup> The opiates exert their pharmacological action via  $\mu$  opioid receptors, though the site of the receptors concerned in the cough reflex is not clear. The most likely possibilities are:

1 They act on the sensory nerve endings responsible for initiating cough. The Wellcome compound 443C, which suppresses cough in animals, acts on  $\mu$  receptors on sensory receptors in the lung,<sup>53</sup> having poor penetration of the blood-brain barrier.

2 They act within the central nervous system. This may be by a direct action on the cough centre in the medulla or by an action on the brainstem respiratory centres. When high doses of opiates are required to suppress cough respiration is depressed and this may decrease peripheral sensory stimulation and therefore coughing.

3  $\mu$  receptor stimulation may reduce mucus production or increase mucociliary clearance and so reduce the need for cough.

#### Local anaesthetics

Local anaesthetics prevent sensory nerve traffic in both myelinated and non-myelinated nerves and are the most consistently effective antitussive agents.<sup>54</sup> As they can remove all the protective reflexes of the lung and may precipitate bronchoconstriction they must be used with extreme care. Interestingly, inhalation of lignocaine reduces cough at doses that do not affect reflex bronchoconstriction.<sup>55</sup> This suggests that C fibres are important in the genesis of cough, as local anaesthetics inhibit sensory transmission in non-myelinated nerves at lower concentrations than myelinated nerves. The *British National Formulary* lists several local anaesthetic lozenges and sprays for the symptoms of the common cold. Unfortunately these sprays are not designed to deliver the agent to the larynx and they are therefore ineffective as antitussives. The use of inhaled local anaesthetics is empirical and confined to patients without asthma. We give increasing doses of lignocaine from a portable nebuliser (Portaneb), starting at 10 mg, by nebuliser until a shift in the cough dose-response relation is observed. The patient is then instructed to take this dose from a portable nebuliser, having first been warned of the possible risks. The maximum dose depends on the patient's response; if lignocaine at the maximum practicable dose of 40 mg is of little value, then bupivacaine up to 8 mg may be used with caution. This helps some desperate patients but it may need to be used frequently as the effect tends to be short lived. The effect may be sufficient to prevent predictable causes of coughing, such as cold air exposure.

#### Expectorants

Some agents included in over the counter cough preparations are claimed to be expectorants. These include

Table 2 Pharmacology of cough suppressants

Cough suppressant	Site of action	Mode of action	Clinical effectiveness*
Demulcents	Epipharynx	Unknown (i) Increased swallowing (ii) Stimulation of sensory nerves in epipharynx (iii) Protection of sensory nerves in epipharynx	+
Opiates	Central nervous system or peripheral nerves	Stimulation of $\mu$ receptors	++ only at high doses
Local anaesthetics	Peripheral nerves	Suppression of sensory nerve activity	+++
Expectorants	Lung or epipharynx	Direct action on mucus producing cells or indirect action on sensory nerves that can promote mucus production	0
Bronchodilators	Bronchial smooth muscle	Bronchodilatation	++ where cause of cough is bronchoconstriction

\*Measured on the scale + to +++.

ammonium chloride, ipecacuanha, and squill. Few have been studied in detail. One agent, guaiphenesin, has been shown to be ineffective in patients with spontaneous cough and in suppressing citric acid induced cough,<sup>56</sup> though patients reported a reduction in sputum thickness. Other drugs, such as ipecacuanha, may cause coughing by stimulating the chemotactic trigger zone in the midbrain. It may be possible to alter the rheological properties of mucus to aid clearance by altering the secretion rate or by physicochemical actions. It has not proved possible to show clinically important effects on cough from oral agents such as *N*-acetylcysteine.<sup>57</sup> The use of these agents in the presence of an increased cough reflex would be expected to increase the frequency of coughing as more mucus would be present to stimulate the abnormally sensitive reflex.

#### *Antiasthma treatment*

Inhaled bronchodilators such as beta<sub>2</sub> agonists and antimuscarinic drugs may have a role as antitussive agents in patients with no airway obstruction. They have been shown to reduce citric acid induced cough,<sup>58</sup> low chloride ion induced cough,<sup>59</sup> and cough due to bronchoscopy.<sup>60</sup>

How may bronchodilators alter the sensitivity of the cough reflex? It has been postulated that they reduce the input from stretch receptors by causing bronchodilatation even in normal airways and that this could lead to a reduction of the cough reflex. They may alter mucociliary clearance, and in the case of an inhaled tussive challenge they would alter the distribution of the tussive agent within the airway. A beta<sub>2</sub> agonist could also have a direct effect on sensory nerves, which may possess inhibitory beta<sub>2</sub> receptors, or on epithelium to alter the penetration of the tussive agent to the nerves. So far, however, no study has shown them to be effective in patients with cough in the absence of airflow obstruction, and in our experience they have little role in the treatment of non-asthmatic cough.

Sodium cromoglycate and nedocromil sodium have also been shown to reduce cough in asthmatic subjects<sup>61</sup> and to reduce cough in response to some<sup>62</sup> but not all<sup>63</sup> stimuli in volunteers. As yet no studies have been reported in non-asthmatic patients with cough. A recent report<sup>64</sup> showed no benefit from the inhaled corticosteroid beclomethasone on cough in non-asthmatic patients.

The use of any antiasthmatic drug for cough cannot be recommended in the absence of asthma.

#### *Antihistamines*

There is some historical evidence that antihistamines can be antitussive.<sup>48</sup> They reduce postnasal drip, however, and this could lead to an indirect antitussive action. No direct antitussive effect of antihistamine has been shown.

#### *Proprietary combinations*

The *British National Formulary* lists 36 mixtures for treatment of cough. These contain opiates, decongestants (vasoconstrictors), sedative antihistamines, putative expectorants, aromatics, and demulcents. All are likely to have some effect because they are demulcents, and those that are sedative will be effective at night. The decongestants may help postnasal drip, which is a cause of coughing. The combination of an expectorant with an opiate is illogical. The only recommendations that can be made are that a demulcent alone is likely to be as effective as and safer than one combined with other drugs for the daytime symptoms; a mixture containing a sedative may help at night but should be used only for short lived symptoms.

#### **Conclusions**

The control of acute virus induced cough and chronic

cough associated with mucus hypersecretion or hyperreactivity of the cough reflex with no treatable disease remains difficult. The reduction of the abnormal cough response to a normal one is an attractive proposition, but in practice is difficult to achieve. In acute cough demulcents are of some practical help. All antitussive doses of opiates will have some sedative and addictive effects. The use of high doses that will undoubtedly reduce the cough response can be recommended therefore only in patients with terminal disease; the use of lower doses or safer analogues should be used only for a short time and usually only at night. Inhaled local anaesthetics may be used in patients whose life is severely disturbed by cough, but there are practical problems. Standard nebuliser systems are not truly portable and the duration of effect of the local anaesthesia is short (about 30 minutes) for doses that can be used without compromising the patient's safety. The use of such drugs is therefore best reserved for the truly desperate and in circumstances where the occurrence of cough can be predicted.

There is plenty of scope for improvement of the treatment of cough. In the short term development of efficient ways of applying local anaesthetics to the airways may produce effective treatment. New drugs are required that reduce the severity of the cough reflex while avoiding the problems of current treatment.

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