

Pathophysiology and clinical presentations of cough

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The human cough reflex is still poorly understood, although it is known to occur independently of bronchoconstriction. Sensitization of the cough reflex is a unifying hypothesis for chronic dry cough in several conditions, including gastroesophageal acid reflux, angiotensin-converting enzyme inhibitor cough, and cough-variant asthma. The most common cause of chronic dry cough is a group of related conditions of chronic rhinitis, sinusitis, and postnasal drip. In these cases the cough reflex may be sensitized through an action of inflammatory mediators from the nasal mucosa on the airways or a reflex sensitization of airway sensory nerves. The association of cough with gastroesophageal reflux may occur through a local esophageal-tracheobronchial reflex. Angiotensin-converting enzyme inhibitor cough is a side effect of treatment in about 10% of patients; it probably results from inhibition of the degradation of kinins, particularly bradykinin, in the airway. Why some patients with asthma have cough as the principal feature of their disease is unclear. Tachykinins are probably involved in the mechanism of sensitization of the cough reflex, and the development of neuropeptide antagonists may open new research opportunities. A study that used ambulatory recording of cough in a group of subjects with asthma confirmed the presence of significant cough, the frequency of which did not correlate with lung function or diurnal variation in peak flow. This finding highlights the problem of cough in patients with asthma, a problem that probably has been underestimated in the past. (J Allergy Clin Immunol 1996;98:S91-7.)

Key words: Angiotensin-converting enzyme inhibitor cough, asthma, cough, gastroesophageal acid reflux, postnasal drip

Although chronic cough is one of the most common symptoms seen in ambulatory practice,¹⁻³ it remains poorly understood and has been aptly described as the "Cinderella" of respiratory symptoms.⁴ Research into cough has been difficult because, unlike bronchoconstriction, the cough reflex is blunted in anesthetized animals. Consequently, understanding of the human cough reflex is still unclear. Significant advances in the field include the observation that the cough reflex is independent of bronchoconstriction⁵; and the observation that it is sensitized in several associated conditions (e.g., gastroesophageal acid reflux [GER], angiotensin converting enzyme inhibitor [ACEI] cough, and cough-variant asthma)⁶; and the development

Abbreviations used

ACEI: Angiotensin-converting enzyme inhibitor
GER: Gastroesophageal acid reflux

of a 24-hour portable ambulatory cough recorder to study cough patterns objectively outside the laboratory.⁷

The pathophysiologic basis of the cough reflex has been better characterized by the use of inhalational challenge tests in human subjects with chemicals such as capsaicin, chloride-deficient solutions, citric acid, nonisoosmolar solutions, and prostaglandins. That substances with a variety of chemical characteristics can stimulate the cough reflex in human beings (Table I) and in animals underlines the heterogeneity of the reflex. Clearly, different mechanisms are operative singly or multiply in patients with cough of various causes. In chronic bronchitis and bronchiectasis, in which the

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TABLE I. Agents that induce cough in human beings

Chemical irritants	Osmotic/chloride-deficient solutions	Inflammatory mediators	Mechanical agents
Capsaicin	Hypertonic saline solution	Histamine	Instrumentation
Citric acid	Distilled water	Prostaglandin E ₂	Lactose
Acetic Acid	Sugar solutions	Prostaglandin F _{2α}	Aerosols
Tartaric acid	Urea solutions		Dust
Acetylcholine			Bronchoconstriction
Nicotine			
Metabisulfite			
Sulfur dioxide			

Data from Fuller RW. Cough. In: Crystal RG, West JB, Barnes PJ, editors. *The lung: scientific foundations*. New York: Raven Press, 1991:1861-7.

stimulus to cough is chronic mucus hypersecretion, the reflex has not been shown to be enhanced.⁴

The rational clinical approach to the management of chronic cough is to search for an underlying cause and to treat the cause. In the majority of patients this approach is successful.^{2,8} Indeed, in patients with a chronic dry cough the sensitivity of the reflex to capsaicin challenge has been shown to decrease with successful treatment of the underlying cause of the cough,⁹ confirming sensitization of the cough reflex as a unifying hypothesis for chronic dry cough in a variety of conditions. There is a subgroup of patients in whom the etiologic basis of the cough remains obscure and in whom the cough is troublesome and serves no useful purpose.^{9,10} In this case antitussive medication is indicated; however, except for opiates in sedative doses, there are no suitable antitussive agents currently available. This problem is a result of the lack of research in this area, in contrast to the attention given to research in airway hyperresponsiveness (the equivalent of the sensitized cough reflex). With the synthesis of neuropeptide antagonists that can be used safely in human beings, the development of newer and specific antitussive agents will become possible.¹¹

The mechanism by which the human cough reflex becomes sensitized is unclear and is a challenge to researchers in the field. The neurophysiologic features of the cough reflex in humans is difficult to analyze.¹² The afferent pathway for the cough reflex is carried in the vagus and superior laryngeal nerves.⁵ There is no consensus about the identity of the airway irritant receptors and their afferent fibers in human beings, but most of the afferent fibers described in animal models probably are involved: they are the rapidly adapting receptors with thin myelinated Aδ fibers and the bronchial C fiber receptors with nonmyelinated fibers.⁵ A recent study showed that bilateral block of the superior laryngeal nerves in

healthy subjects (which would interrupt all afferent supply from the larynx) does not alter the threshold to citric acid-induced cough; this finding may imply that the larynx is not an important or exclusive tussigenic zone, at least to citric acid stimulus in conditions of health.¹³ Considerable controversy still exists as to whether the bronchial C fibers, like their pulmonary counterparts, are inhibitory.¹²

Knowledge of the central pathways of the cough reflex is fragmentary. The afferent nerves travel to the dorsal medulla, where there is considerable cortical modulation of the reflex. Central modulation of the cough reflex is probably important in sensitization of the cough reflex but is difficult to study. In addition to opiates, serotonergic agents have been shown to protect against induced cough in animals and in human beings.^{14,15} There is a need for studies in human beings on the role, if any, of putative central neurotransmitters in the process of sensitization of the cough reflex.

Investigation of the pathophysiologic basis of the cough reflex in patients with defined causes of chronic dry cough provides insight into the modulation of this powerful defensive reflex in health and disease. The clinical presentations of chronic dry cough with particular reference to current knowledge of the pathophysiologic mechanisms are discussed in the following section.

CLINICAL PRESENTATIONS OF CHRONIC DRY COUGH

The cough reflex can be initiated at numerous anatomic sites, and it is therefore not surprising that chronic cough may have a variety of causes. Irrespective of the site of the pathologic disorder, patients with a chronic dry cough invariably have a persistent tickle or irritation in the throat, a condition described as sensory hyperalgesia, which is akin to sensory hyperalgesia of the skin.¹⁶ Two and

sometimes three conditions may occur together in the same patient, thus complicating the clinical picture.^{1, 10}

ACEI cough

ACEI cough remains a clinical enigma. It occurs in 0% to 39% of patients treated with ACEIs, but its average incidence is about 10%.¹⁷ Women are more likely to have this side effect, which may occur any time from a few days to several months after initiation of treatment with this class of drugs. Likewise, the side effect disappears rapidly after withdrawal of the drug. Patients in whom a cough develops demonstrate a sensitized cough reflex in response to capsaicin inhalation challenge.¹⁸ The claim that some newer ACEIs cause less cough¹⁹ is probably the result of data from smaller numbers of patients treated with these new agents. A recent study suggests that the cough may be dose related because reduction in the dose of enalapril resulted in a reduction in coughing.²⁰ Another study claims that continuation of ACEI administration in patients with cough can result in spontaneous improvement.²¹

Several hypotheses have been proposed to explain ACEI cough. It is now known that losartan, a specific angiotensin II receptor antagonist, does not cause cough as frequently in patients with ACEI cough.²² The most logical and popular hypothesis is that the degradation of kinins, particularly bradykinin, in the airway is inhibited. The response of ACEI cough to inhaled cromolyn sodium in some patients supports this hypothesis because cromolyn sodium has been shown to be an effective tachykinin antagonist.²³ Bradykinin inhalation causes cough in human subjects²⁴ but does not potentiate capsaicin-induced cough,²⁵ and bradykinin-induced cough has been shown to be increased in patients with ACEI cough compared with those without ACEI cough.²⁶ In guinea pigs, bradykinin or ACE I administration increases citric acid-induced cough.^{26a} It can also cause cough by stimulation of prostaglandin synthesis, and prostaglandin E₂ has been shown to cause cough and potentiate capsaicin-induced cough.²⁷ Furthermore, cyclooxygenase inhibitors inhibits the cough in some patients.²⁸ Substance P is another tachykinin that may participate in the ACEI cough mechanism. Currently there is no evidence that it causes cough in human beings, and it has failed to induce cough in patients with ACEI cough. However, experiments in animals suggest that it may be an important stimulant of cough-sensitive nerve fibers in the airway,²⁹ and ACEI may also inhibit its

degradation. Finally, too, a genetic predisposition has been proposed on the basis of similarity in the frequency of polymorphism in the gene for angiotensin-converting enzyme and ACEI cough.³⁰

The development of ACEI cough suggests an important role for tachykinins in the human cough reflex. Currently, few tachykinin antagonists can be used safely in human beings to test this hypothesis. More detailed investigations into ACEI cough in animal models and human subjects are required.

Cough in asthma

A chronic dry cough may occur with asthma in three clinical settings. Asthma may present with cough as the predominant symptom, a condition that can be called "cough-predominant" asthma, when the diagnosis of asthma is usually obvious from clinical features such as shortness of breath, wheeze, and reversible airflow limitation. Alternatively, it may manifest as "cough-variant" asthma, which does have the typical manifestations of asthma.^{31, 32} The diagnosis in this latter group is made only by demonstration of airway hyperresponsiveness to methacholine or histamine challenge and an excellent response to treatment with bronchodilators and corticosteroids. In a significant proportion of patients with cough-variant asthma, the classic symptoms and signs of asthma eventually develop, and in some cases the cough resolves without further treatment.³³ The third presentation of cough with asthma is a chronic dry cough that persists despite optimal asthma control. In some of these patients there may be another cause of the cough, such as rhinitis or postnasal drip. We have identified a few cases in which patients with classic asthma have refractory cough despite adequate asthma control, exclusion of other causes, intensive investigation, and empirical treatments for common causes.

Patients with asthma without a chronic cough have a normal cough response to challenge with capsaicin and chloride-deficient solutions, whereas patients with asthma with cough have a sensitized cough reflex.^{4, 34} Twenty-four-hour ambulatory cough recording in 21 patients in stable condition who had asthma with a chronic cough confirmed the presence of significant cough, the frequency of which did not correlate with FEV₁ or diurnal variation in peak expiratory flow.⁷ This observation highlights the problem of cough in patients with asthma, a problem that probably has been underestimated in the past, as well as the need for more specific antitussive agents in the treatment of asthma. At least one study³⁵ has shown that nedocromil sodium reduces the fre-

quency of cough in these patients. Additional trials of this drug for treatment of cough in asthma are necessary.

The mechanism for the cough in asthma has not been elucidated. Why some patients with asthma have cough as the sole or main feature of their disease is unclear. There is no systematic study of the cough reflex in patients with cough-variant asthma, presumably because of the excellent response to bronchodilator treatment. Whether there is a qualitative or quantitative difference in the cough receptors in these patients is not known. The cough-receptor sensitivity to inhaled tartaric acid in asthma does not appear to correlate with bronchial responsiveness to methacholine.³⁶ Muscarinic receptor stimulation, β_2 -receptor stimulation, or bronchodilation has been found to have no effect on the sensitivity of the cough reflex to inhaled capsaicin and tartaric acid in normal subjects.³⁷ Inhaled furosemide has been shown to inhibit the cough response to chloride-deficient solutions in healthy subjects but not in subjects with mild asthma.³⁸ This finding suggests an abnormality in the cough receptor in the asthmatic airway or an abnormality in the epithelial chloride channel, where furosemide is thought to exert its action.³⁹

The repertoire of inflammatory cascades that have been described in asthma indicates that several mechanisms must operate to cause cough in this condition. As in ACEI cough, tachykinins appear to be the most likely candidates. Patients with cough-variant asthma are an ideal group for systematic study of the cough reflex in asthma.

Cough in chronic rhinitis, sinusitis, or postnasal drip

The related conditions of chronic rhinitis, sinusitis, and postnasal drip are considered the most common causes of a chronic dry cough.^{2,8} If the cause of the cough is not obvious after a detailed clinical evaluation and simple spirometry, empirical treatment for postnasal drip syndrome is recommended² before further investigations are undertaken.

In its obvious form, postnasal drip presents with symptoms of secretions in the back of the throat and frequent throat clearing. In one study this presentation was associated with chronic cough and reversible large-airway obstruction typical of an extrathoracic obstruction on the flow-volume loop.⁴⁰ Two of three patients in this study ($n = 9$) who underwent indirect laryngoscopy had vocal cord edema. The pathophysiologic basis of the cough in this group of patients was obviously

stimulation of laryngeal cough receptors by nasal or sinus secretions.

The nasal mucosa is able to mount a similar inflammatory response to the pulmonary airways. The sensory nerves contain neuropeptides and classical neurotransmitters⁴¹ that could stimulate the airway sensory nerves to sensitize the cough reflex and produce cough, but currently there is no direct evidence of such an influence on the cough reflex. We found that the cough reflex to inhaled capsaicin and chloride-deficient solutions was enhanced in our patients with symptoms of rhinitis and postnasal drip in association with a chronic dry cough.

Frequently the obvious symptoms of a postnasal drip are absent, but the patient may have symptoms and signs of chronic rhinitis or sinusitis. Clinical examination of the pharynx may occasionally reveal secretions emanating from the posterior nasal passages or a cobblestone appearance of the mucosa. A significant proportion of patients respond to empirical treatment with nasal steroids, decongestants, antihistamines, and antibiotic agents if sinusitis is present.^{2,9} The mechanism by which the cough reflex becomes sensitized in these patients is uncertain. The sensitization may result from occult postnasal drip, or the airway cough nerves may be sensitized by a reflex mechanism. Irritation of the nose causes bronchoconstriction in patients with asthma, and it also induces laryngeal constriction and secretions in the nose and lower respiratory tract in human subjects.⁴²

GER

GER has been found to be a common cause of chronic dry cough in published case series. Routine investigations for chronic cough are incomplete without a search for GER when other causes have been excluded.⁸ Until recently, it was uncertain whether the association of cough with GER is coincidental or pathologically related. Although cough resulting from GER may present with typical symptoms of dyspepsia, it is occult in the majority of patients.⁴³ Although some patients may have reflux up to the pharynx and may even aspirate, those events are not a prerequisite for cough; reflux into the distal esophagus is sufficient to sensitize the cough reflex.

In a series of investigations, Ing et al.⁴⁴ confirmed the pathogenetic nature of GER with a chronic dry cough. This work was possible because the esophagus is relatively easily accessible to study. They identified patients with a chronic dry cough in whom the only abnormality was GER discovered with 24-hour ambulatory esophageal

pH monitoring. Patients with GER had a significant amount of cough compared with age-matched control subjects without GER or cough. Instillation of 0.1 N hydrochloric acid and physiologic saline during a Bernstein test produced significant cough in the patients compared with the control subjects; this effect was blocked with lignocaine infusion and, of note, with inhalation of ipratropium bromide and not with intraesophageal perfusion of ipratropium bromide. The investigators argue that sensitization of the cough reflex may occur by a local esophageal-tracheobronchial reflex. In this study the sensitivity of the cough reflex was not measured, and the control group did not include patients with GER without cough. It may be argued that chronic cough may aggravate or produce GER, but the cough occurred within 1 minute after a reflux episode in 71% of the GER incidents. These findings need to be confirmed in studies that include appropriate control groups, and further investigations into local reflex pathways are necessary.

Most patients respond satisfactorily to medical treatment and simple antireflux measures. Prolonged treatment may be necessary.¹

Idiopathic cough

Although some reports suggest that the cause of chronic cough can be determined with successful treatment in >90% of patients,¹ there is no doubt that there is a subgroup of patients in whom a specific cause cannot be identified, in whom there is no response to empirical therapy, and who have a sensitized cough reflex.^{4, 7, 10} Ambulatory cough recording in our patients with idiopathic cough confirmed the severity of coughing.⁷ Endobronchial biopsy specimens obtained from patients with idiopathic cough showed an increase in airway calcitonin gene-related peptide and vasoactive intestinal peptide-immunoreactive nerves.⁴⁵ It is unclear whether these features represent the effects of airway inflammation or whether they represent the sequelae of chronic trauma to the airway wall after intractable coughing.

CONCLUSIONS

Chronic dry cough is an important clinical problem. Sensitization of the cough reflex is a common feature in these patients irrespective of the underlying cause. The pathogenetic mechanism of sensitization is unclear. A better understanding of the cough reflex is necessary to help answer this question and to devise appropriate antitussive agents. The synthesis of neuropeptide antagonists that can

be used safely in human beings may open new research opportunities in the investigation of the pathophysiologic basis of cough.

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DISCUSSION

P. König. The difference between cough-variant asthma and full-blown asthma may perhaps be not so much a difference in mechanism as a quantitative difference, the cough-variant form being at the mildest part of the spectrum. There is some evidence for that idea from Corrao WM et al. (*N Engl J Med* 1979;300:633-7), who showed that bronchial hyperreactivity in cough-variant asthma is significantly lower than in full asthma. Clinically, at least in children, most of my patients with cough-variant asthma respond to bronchodilators alone, and relatively few need either cromolyn sodium or inhaled steroids, so it could just be a quantitative difference. The patients you described in whom the asthma was amenable to treatment, but who still continued coughing, may have what used to be called habit cough, when the cough itself causes a mechanical irritation of the cough receptors of the epithelium and a hyperresponsive reflex is perpetuated. This "habit cough" responds well to suggestion, that is, when patients are told simply to stop coughing for longer and longer periods of time.

U. Lalloo. In some patients, cough-variant asthma does represent a very early form of asthma—what we might even call "preclinical asthma." The important point is that cough is a very prominent symptom in these patients, whereas it is less so in a whole population of patients with asthma. It may represent a distinct type of inflammation in asthma in these patients, but I agree that because of their response to corticosteroids it represents early inflammation in asthma. With respect to habit cough, we have a few such

patients in our clinic, some of whom have responded very well to psychotherapy. I think the entity of an idiopathic, chronic dry cough does exist if patients have consistently demonstrated hyperresponsiveness to various tussive stimuli in the laboratory and the 24-hour ambulatory recorder has confirmed the coughing.

C. E. Mapp. At least in adults with occupational asthma, dry cough may be the only presenting symptom, but this does not mean that these people have mild asthma. It may be very hyperreactive, and the prognosis may be poor.

J. G. Widdicombe. In the case of postnasal drip, in experimental animals it is, I think, impossible to produce cough from areas supplied by the glossopharyngeal trigeminal nerve, that is, the pharynx and areas above it. Is it not most likely that inflammation is spreading down to the larynx?

U. Laloo. That is correct, and in fact Irwin RS et al. (*Am Rev Respir Dis* 1990;141:640-7) have shown that there is reversible upper-airway obstruction and probably inflammatory edema of the vocal cords, although in some patients the postnasal drip or the clinical appearance of typical inflammatory changes in the pharynx cannot be identified, but treatment aimed at these changes does produce a response.

J. M. FitzGerald. We have been systematically monitoring pH in patients, particularly with asthma, and we are about to embark on a randomized controlled trial because one of the problems with reflux in asthma is that it has been hard to show efficacy in terms of spirometry and FEV₁. With much more aggressive therapy, as much as 60 mg of omeprazole (Losec) per day, there were effects on spirometric findings. I wonder how much pH monitoring has been done in cough-variant asthma and whether it is just a manifestation of reflux in a subpopulation of people with asthma? Have you done pH monitoring systematically in your patients with asthma to rule out this possibility?

U. Laloo. That is an important consideration. If we cannot find an obvious cause in our patients, we would

resort to pH monitoring as well, but if the histamine or methacholine PC₂₀ is abnormal most clinicians would not investigate further, so it is a possibility.

S. T. Holgate. With regard again to cough in children, it is a very major symptom in asthma. Doull has just completed a study of 4500 children in the community and found that if cough was a predominant symptom it inhibited the diagnosis of asthma, whereas if wheezing and other symptoms predominated then the general practitioners diagnosed asthma (Doull IJM, Williams AA, Freezer NS, Holgate ST. Descriptive study of cough, wheeze and school absence in childhood. *Thorax* 1991;51:630-1). It seems that cough as the predominant symptom can prevent the diagnosis of asthma and thus the appropriate treatment.

E. R. Bleeker. It appears that cough may not correlate with bronchial reactivity or airflow obstruction. This situation seems paradoxical, because cough-variant asthma is diagnosed on the basis of hyperresponsiveness and response to a drug that relieves airflow obstruction.

U. Laloo. "Cough-variant asthma" refers to a distinct group of patients who have cough with an abnormal bronchial reactivity. I agree with the paradox, which is highlighted by the response to β -agonists, which cannot be explained whatever hypothesis is proposed for the cough.

L. T. Rodwell. One test that we do in our respiratory laboratory to investigate cough that may be associated with asthma is isocapnic hyperventilation challenge. This test identifies the people who have cough that is not associated with airway hyperresponsiveness. Can you comment on the mechanism of this type of cough? Maybe tachykinins are released?

U. Laloo. No, I cannot. I think that to explain the cough as a predominant symptom, the subject of neurogenic inflammation must be invoked, and, as I said, we will probably understand it better when we look at the effect of tachykinin antagonists. Currently our understanding is too incomplete to be definite.