CHRONIC COUGH

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PREFACE

The diagnosis and treatment of chronic cough is a moving target but one, thankfully, that is moving in the right direction. Empiric treatments are giving way to objective testing. Research drives new therapeutics and testing modalities. Patients are more frequently being treated successfully after decades of coughing through diagnostic advances and multidisciplinary collaboration. Chronic cough is being recognized more as a symptom of an underlying issue rather than as a primary diagnosis with an unclear etiology.

This book was proposed and is now realized as a clinical resource for practitioners who see and treat patients with chronic cough. It is intended as a reference for any clinician in practice or training who wants to feel more confident in their understanding, workup, and treatment of this symptom. It will especially appeal to those residents, advanced practice providers, and physicians in the fields of family practice, internal medicine, otolaryngology, pulmonology, gastroenterology, and speech-language pathology. Multiple experts from backgrounds in otolaryngology, including laryngology and rhinology, pulmonology, molecular and cellular pathology, and speech-language pathology contributed to this book.

This book's 10 chapters are designed to cover the basics of what we know, what we don't know, and what we are discovering about chronic cough. In addition, the chapters offer a platform for each chapter's authors to "think outside the box" and speak directly to the reader on their given subject matter and cover controversial or less-conventional ideas surrounding chronic cough. The book begins with an overview of chronic cough that sets the stage for the remaining chapters. After covering the highest-yield topics on the subject, the penultimate chapter puts together the previous topics as a treatment paradigm that intends to help approach a patient with refractory chronic cough in a quaternary referral setting and make headway to symptom relief.

There is no one algorithm to treating chronic cough, but there are ways to organize one's approach and this should be the goal. The final chapter of this book is an expanded version of "thinking outside of the box." It will introduce the reader to causes of chronic cough that are not commonly considered by clinicians outside of laryngology and speech-language pathology but are emerging as real possibilities for therapy.

The pendulum is swinging away from 30 years of empiric acid suppression medical therapy to more objective reflux and motility testing for pepsin-mediated laryngopharyngeal reflux disease. Considerations of novel therapeutics and diagnostic modalities for asthma are evolving and prompting consideration of other pulmonary diagnoses for chronic cough patients. Revelations in the etiology and effects of sinonasal disease and

allergy as a contributor to chronic cough are continuing to impress upon us a need for more information. The role of speech-language pathologists in the behavioral management of chronic cough is growing and proving critical. Dysphagia and dysmotility are often underappreciated causes of chronic cough and are more recently being brought into focus. Primary vocal fold pathologies and neurolaryngeal disorders are waiting to be understood in more complexity to help chronic cough patients that have an indeterminate etiology for their cough.

—Thomas L. Carroll, MD

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OVERVIEW OF CHRONIC COUGH AND ITS IMPACT ON HEALTH CARE

Seth H. Dailey and Johnny P. Mai

INTRODUCTION TO CHRONIC COUGH

Coughing is the act of rapidly expelling air from the lungs accompanied by a sharp audible sound.[1] Cough is an essential protective function, serving to clear the airway of debris and allowing for continued gas exchange in the lungs. In this protective role, cough prevents life-threatening complications. In an extreme example, pneumonia is known to be the leading cause of mortality in patients with spinal cord injuries where motor nerve paralysis leads to absent cough.[2] Cough can be a volitional action, but more often is an involuntary response to a chemical or environmental stimulus. Despite cough's critical role in airway clearance, persistent cough in the absence of an appropriate stimulus can become pathologic.

Cough is classified as acute, subacute, and chronic based on the duration of cough. An acute cough is one lasting less than 4 weeks and is often secondary to a viral etiology. A cough persisting for 8 weeks or more is defined as chronic, with the interval in between deemed subacute. Albeit arbitrary, this duration is agreed upon by both American and European task forces.[3,4]

The goal of this chapter is to introduce the reader to common causes of chronic cough. Treatment of chronic cough will be discussed only as

it pertains to diagnosis. In-depth discussion on treatment of cough is discussed in chapters to follow.

In addition to framing the discussion for subsequent chapters on the various causes and diagnosis of cough, this chapter presents the economic impact of chronic cough. Above all else, this chapter intends to relate this organic pathology back to the patients treated for the condition. By emphasizing the human toll of chronic cough, the purpose of this text is to educate the wide array of practitioners who treat chronic cough for the benefit of their patients.

PHYSIOLOGY OF COUGH

Pathophysiology of Cough

A reflex is defined as an involuntary or nearly instantaneous movement in response to a stimulus.[5] As defined, cough is indeed a reflex serving to clear the tracheal bronchial tree for gas exchange. Cough, unlike other human reflexes such as pupillary light or palmar grasp reflex, is critical for the preservation of life.

The physiologic basis of cough is broken into four distinct phases defined by distinct actions within the phase. Inspiration to fill the lungs is the first action of cough. In the second phase, subglottic pressure increases as there is compression of air against a closed glottis. The third action is marked by the explosive opening of the glottis, leading to rapid increase in airflow. During this phase, the rapid airflow moving through the airway causes a distinctive acoustic emission, which is the hallmark "cough." The sound of a cough is universally recognized and is used to differentiate between other similar expiratory respiratory efforts such as sneezing and throat clearing.[6] The final phase is the restorative phase, in which a final resting breath is taken. The act of coughing is an extraordinary physiologic event capable of producing intrathoracic pressured measured up to 300 mm Hg and airspeed up to 500 miles per hour.[7,8] This particularly violent response can result in urinary and fecal incontinence, pneumothorax, syncope, and even broken ribs.

Neurophysiology of Cough

To understand how cough becomes pathologic, it is useful to understand the neurophysiology of cough in its normative state.

In its essence, cough can be broken down into three constituents: input, processing, and output. The cough reflex involves stimulation of the afferent limb of the cough reflex, then transmission of the stimulation

to the cortical cough center and, finally, the efferent pathway, which causes the muscles of expiration to contract, producing cough.

As a caveat, much of what is known about the neuropathophysiology of cough has been inferred through studying animal models, primarily the guinea pig, rather than in vivo human studies. Therefore, despite extensive studies, there is still considerable debate concerning the exact neural sensory mechanism of cough.

Airway sensory nerves originate within either the nodose or jugular vagal ganglia,[9,10] as evident by the fact that a vagotomy or local anesthesia applied to the vagus nerve will abolish the cough reflex.[11,12] The nerve terminals can have endings either in the pulmonary airway and parenchyma or in the extrapulmonary airway, including the carina, trachea, and large bronchi. There is currently no classification schema that neatly characterizes airway afferent nerves given the degree of heterogeneity within the group. This being said, there is consensus that within primary afferent cough fibers, there are nociceptors stimulated by chemical irritants and others stimulated through mechanical means, forming a division where afferents are divided by their physiologic responsiveness to stimuli.

Stretch receptors are well-described intrapulmonary afferents stimulated by mechanical means. When activated by changes in lung volume, airway edema, or smooth muscle constriction, stretch receptor afferents within the lower tracheobronchial tree and parenchyma conduct action potentials at 10 to 20 m/s to cell bodies located in the inferior nodose ganglion. Stretch receptors are further divided into rapid adapting receptors and slowly adapting receptors. The former are more active in the dynamic phase of the respiratory cycle and the latter are more active throughout the respiratory cycle. Stretch receptors help regulate the respiratory cycle, but their role in cough remains uncertain.[13]

A third type of receptor sensitive to mechanical stimulation was first described by Widdicombe in 1954.[14] Unlike stretch receptors, these fibers are found exclusively in the extrapulmonary airway and adapt to punctate mechanical stimuli rather than stretch stimuli. These receptors precipitate an action potential in myelinated vagal afferents at a much slower velocity of 5 m/s, arguing to the uniqueness of these receptors from stretch receptors. Since the first description, the receptors have been eponymously referred to as Widdicombe receptors, then irritant receptors, but are now commonly referred to simply as cough receptors.

Chemical receptors, as the name would suggest, are relatively nonresponsive to mechanical stimulation, requiring 100 times the threshold required for mechanoreceptors. Instead, chemical receptors are sensitive to mediators found during inflammation, irritation, and changes in pH. Customarily, chemical nociceptors are defined by the presence of the ion channel transient receptor potential vanilloid 1 (TRPV1). The TRPV1 receptor binds capsaicin, the active component in chili pepper extracts and a known potent tussigenic agent. The binding affinity of TRPV1 is increased

with mediators found during inflammation including bradykinins, prostaglandins, adenosine, and serotonin, as well irritants including nicotine and ozone. An overexpression of TRPV1 can be seen in chronic cough patients.[15]

Chemoreceptors are stereotypically associated with C-fiber afferents, which are classified by their action potential conduction velocity, ranging from 1 to 2 m/ sec.[16] Though C-fibers are most common type of afferent associated with chemoreceptors, afferents with a conduction velocity of 6 m/s, known as alpha-delta afferents, have been shown to conduct action potentials from chemoreceptors.[9]

Table 1–1 provides a summary of the thoracic and extrathoracic afferents that have been associated with cough.

From one's personal experience with volitional cough and conscious cough suppression, it should be clear there is a layer of cortical control in the physiology of cough. Located in the caudal brainstem, the central cough generator receives the vagal afferents via the nucleus tractus solitarius. The ability of cough to undergo central processing is also demonstrated in the efficacy of placebo therapy, which often decreases cough.

COMMON CAUSES OF CHRONIC COUGH

The following discussion serves as a precursory introduction to familiarize the reader to common causes of chronic cough. In-depth appraisal of each etiology is included in subsequent chapters. Furthermore, although the following descriptions discuss common etiologies of chronic cough as

Table 1–1. Vagal Afferents of the Thoracic and Extrathoracic Airway

Stretch Receptors	Cough (Widdicombe) Receptors	Chemoreceptors
Location Intrapulmonary	**Location** Extrapulmonary	**Location** Extrapulmonary & Intrapulmonary
Conduction Speed 10–20 m/s	**Conduction Speed** 5 m/s	**Conduction Speed** C-fibers 1–2 m/s Aδ fibers 6 m/s
Stimulus Rapid Adapting Dynamic Respiration Slow Adapting Static Respiration	**Stimulus** Punctate Mechanical	**Stimulus** Bradykinins, prostaglandins, adenosine, serotonin, pH, capsaicin

singular entities, it is paramount for the reader to appreciate the multifactorial nature of chronic cough. As up to 93% of troublesome coughs are multifactorial, recognition of this salient concept mitigates delay in diagnosis as well as both clinician and patient frustration.[17]

Asthma

Asthma as a source of chronic cough should always be in the differential. Asthmatic patients classically present with wheezing, dyspnea, and cough of an intermittent reversible nature. These symptoms, though, are not unique to asthmatics, and are found in many other respiratory diseases. Some readers are familiar with the term Reactive Airway Disease, an imprecise term used to describe transient symptoms of cough and wheeze when confirmation of a diagnosis of asthma is lacking. The majority of adult patients will already have a diagnosis of asthma since 75% of patients are diagnosed before the age of 7, though asthma can be diagnosed at any age.[18] Therefore, it is not the definition of asthma or necessarily the diagnosis that is important as much as the recognition of the relationship between cough and asthma.

Chronic cough may be the only manifestation of asthma in a condition called cough-variant asthma. Irwin and partners found that, in their prospective study of 102 patients with chronic cough, 28% of asthmatics had only cough as a symptom.[17]

Eosinophilic asthma, distinguished by a high level of eosinophils in the serum, sputum, and tissue, is a particularly severe form of asthma.[19] Though it accounts for only 5% of asthma cases, it is the most common cause of a severe asthma and is most commonly diagnosed in adults between the ages of 35 and 50. Eosinophilic bronchitis is a condition similarly presenting with elevated eosinophils, yet differs in the fact that patients do not exhibit typical variable airway restriction and responsiveness to bronchodilators, which is the defining hallmark of asthma.[20,21] As eosinophilic bronchitis does not respond to bronchoprovocation testing, diagnosis is based on responsiveness to empiric inhaled corticosteroids. It is unclear whether eosinophilic bronchitis is separate from asthma or represents a condition along the spectrum of asthma.[22] Regardless, eosinophilic bronchitis patients invariably present with cough, triggered by inhaled allergens.

Gastroesophageal Reflux and Laryngopharyngeal Reflux

Gastroesophageal reflux disease (GERD) describes the condition where long-term flow of gastric contents flows retrograde from the stomach into the esophagus. Up to 50 episodes of reflux is considered physiologic and, therefore, in order to be classified as GERD, reflux must also cause