Chapter 2
Asthma: Pathophysiology and Diagnosis

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Introduction

Although asthma is a common disorder affecting approximately 7.8% of the United States population (Schiller et al. 2006) or 23 million Americans, the pathogenesis of this disease remains to be fully elucidated. Extensive research over the last few decades has yielded a better understanding of asthma. We know that the basic features of asthma include episodic airways inflammation, airways hyperresponsiveness, and mucous hypersecretion. Although we understand the basic clinical features of asthma, the links between symptoms, physical signs, and underlying pathophysiological mechanisms are still being delineated. Asthma is a heterogeneous disease process with varying phenotypes and presentations. In this chapter, we will briefly explore some major theories of asthma pathogenesis, both new and old. We will also explore how understanding the pathophysiology of asthma can help us to understand the symptoms and presentation of asthma, as well as the best strategies for diagnosing this disease.

Pathology and Histology

What Do the Lungs Look Like in Asthma?

The autopsies of patients who have died of asthma gave researchers the first clues as to the possible etiology of this disease. Although there have been many advances in the treatment of asthma, death from this airways disease is still an unfortunate outcome in a minority of patients. Before describing the abnormal features of the asthmatic airway, we must first briefly describe the basic features of the normal airway.

Asthma is thought to be a disease of the small airways. If one thinks of the lungs as a series of tubes that continues to divide, the tubes get smaller and smaller until they end in small air sacks (called alveoli), where the exchange of gas occurs. The characteristics of the larger tubes as compared to the smaller tubes are very different. In the lung, the larger tubes such as the trachea and main bronchus are supported by both cartilaginous rings and smooth muscle. However, as the tubes get smaller, these cartilaginous rings disappear and only a layer of smooth muscle remains (Fig. 2.1). These smaller tubes are called bronchi and bronchioles. Without the support of cartilage, when smooth muscle contracts, the airways become increasingly narrow. Smooth muscle surrounds other tubular structures in the human body, such as arteries, where smooth muscle contraction dictates the flow of blood to vital organs. Similarly, in the lungs, contraction of smooth muscle in the bronchioles determines the air flow. The cross-sectional area of all the bronchioles is much larger than the cross-sectional area of the biggest airway. Therefore, contraction of smooth muscle can greatly increase airway resistance and diminish the flow of air into the lungs by decreasing size of the small airways.

The cells that line the respiratory tract are known as *the respiratory epithelium*. These cells vary in appearance and function. Some cells have hair-like structures (cilia), while other cells produce mucous. Beneath these cells lie connective tissue and more glands that secrete mucous. In the trachea, cartilage, and smooth

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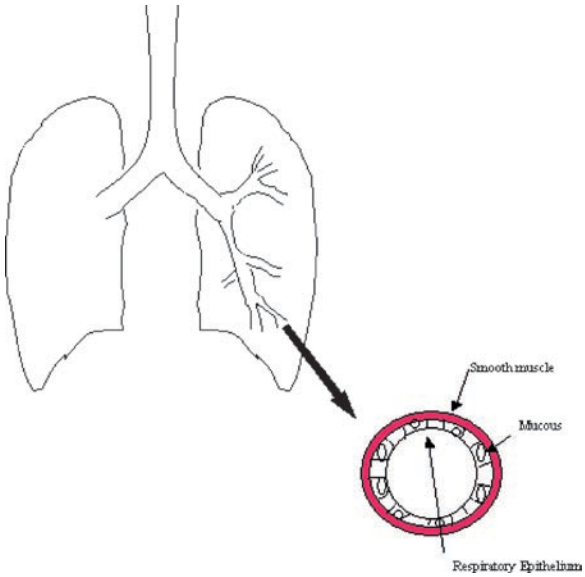

Fig. 2.1 The basic structure of the respiratory bronchiole. The bronchiole differs from the larger airways in that it is surrounded only by smooth muscle without cartilage support. Also note the cells lining the airways consist of mucous secreting cells

muscle is present beneath these glands. As the airways become increasingly smaller, the amount of cartilage starts to decrease and smooth muscle becomes more prominent. In the smallest airways, such as the bronchioles, there is no longer any cartilage. The connective tissue and glands decrease and smooth muscle lies beneath the respiratory epithelium. There are also many small blood vessels that lie beneath the airway supplying nutrients to both the respiratory epithelium and smooth muscle cells. In asthma, these blood vessels can become leaky, allowing the infiltration of inflammatory cells and fluid, which can cause edema.

Asthma, at its core, is an inflammatory disease. In response to a variety of stimuli, some in the environment such as allergens, and some reflecting changes within the body as occurs with exercise, a cascade of reactions that we characterize as inflammation is triggered. Autopsies of patients with fatal asthma have shown many derangements consistent with inflammation in the structure of the airways. In addition, mucous plugs fill the airways. The cells that produce mucus appear larger and are more numerous than in patients without asthma. The bronchioles also appear edematous with an increased number of inflammatory cells (such as eosinophils, neutrophils, and mast cells) that infiltrate the airways. The connective tissue is thickened and the respiratory epithelium is denuded. In addition, the amount of smooth muscle that surrounds the airways is increased (Fig. 2.2); whether this is due to muscle contraction and hypertrophy or is another process secondary to inflammation is still up for debate. It was thought that these dramatic changes were specific to patients with fatal asthma; bronchoscopic biopsies of patients with mild asthma, however, have demonstrated some of the same features. Although these findings can be patchy, biopsies of patients with mild to moderate asthma have shown a significant amount of inflammation as demonstrated by denuded epithelium, thickened basement membrane, and infiltration of inflammatory cells including mast cells, lymphocytes, and eosinophils (Busse and Lemanske 2001).

Another hallmark of asthma is that it represents a potentially reversible disease process. Between asthma attacks or during mild attacks, the airways can appear normal (Barrios et al. 2006). If asthma continues to progress, however, these changes become more permanent. This process is termed *airway remodeling*, and is

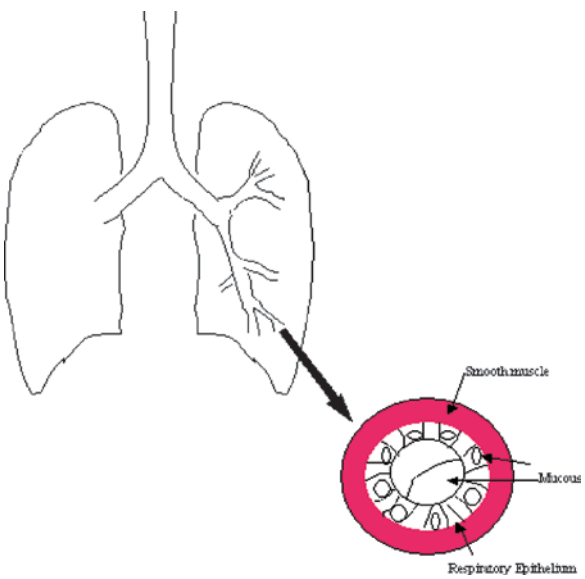

Fig. 2.2 Schematic of the respiratory bronchiole during an asthma attack. The airway is lined by the respiratory epithelium which is made of ciliated and mucous producing cells. These mucous producing cells increase mucous production. Mucous then plugs up the airway, making it harder for the asthmatic to breathe. Underneath the respiratory epithelium lies a layer of smooth muscle. When the smooth muscle contracts, the airway becomes smaller, decreasing airflow

thought to be due to persistent airway inflammation (Holgate et al. 1999). Patients with airway remodeling have thickened airway walls, with an increase in the amount of tissue directly under the respiratory epithelium, and larger smooth muscle mass (Busse and Lemanske 2001). Once remodeling has occurred, the medications used to reverse obstruction of the airways become less effective and symptoms may be more chronic.

Pathogenesis

Introduction

As mentioned earlier, the three basic features of asthma are airways inflammation, airways hyperresponsiveness, and mucous hypersecretion. These three features lead to bronchoconstriction and airflow obstruction, which manifest as wheezing and dyspnea in the patient with asthma. The challenge for most researchers has been to uncover triggers of airways inflammation in the patient with asthma. Several theories have emerged such as the TH2 hypothesis, the Hygiene hypothesis, the infectious causes hypothesis, and the Dutch hypothesis. What these theories have in common is that in the susceptible individual, there is an exuberant immune response after exposure to a substance whether it be an allergen, a virus, or something else. This increased immune response leads to airways inflammation and bronchoconstriction. Why this occurs is still debatable.

Allergy and the Immune System

Many researchers have tried to identify the main causes of airways inflammation. Abnormalities of the immune system, which protects our bodies from infection, have been thought to be major contributors to the development of asthma. More specifically, allergic responses have been considered to be the main determinants of the asthma phenotype. Extensive research over the years, however, has shown that there are different phenotypes of asthma and not all are mediated by allergies. Even so, we will first explore the allergy-driven *TH2 hypothesis* before describing some of the other theories of asthma pathogenesis.

The immune system is an intricate and complicated structure, the details of which are too complex to explore here. However, to understand asthma, one must have some understanding of how the immune system works. In order to fight infection, the human body has developed a complex system to identify foreign intruders and to "remember" them in case of further invasions. This is called the *adaptive immune response*. That way, the body can be ready immediately for the next attack. Yet to exist in this world, the immune system cannot recognize everything foreign as being dangerous or else we would not be able to smell flowers or eat food without coughing, sneezing, or developing fevers. Life would be unbearable. The immune system, therefore, has developed a way to distinguish between benign and malignant foreign particles or *antigens*. There are times, however, for unclear reasons, when the immune system recognizes benign antigens such as dust, animal dander, or food as being "dangerous." When this occurs, we say that the person has an "allergy." When the human body develops allergies, the bronchospasm, cough, and wheeze that develop is an exaggerated response to a benign particle.

What are the steps involved from being exposed to a piece of dust to developing wheezing? It is clear that this process does not happen to everyone and that only susceptible individuals have this problem. Over the last several decades there have been several basic immune mechanisms described including antibody-mediated and cell-mediated immunity, that are thought to be responsible for airways inflammation and obstruction in response to an allergic stimulus.

Antibody-Mediated Immunity

One of the most important immune cells is called the *lymphocyte*. These cells are the building blocks of the immune system. There are two types of lymphocytes, the *B-cell* and the *T-cell*. When activated, some B-cells differentiate into *plasma cells* which then produce antibodies that are released in the blood. When an antibody recognizes a foreign pathogen or *antigen*, the antibody attaches to the antigen and neutralizes it. In allergic diseases, a benign particle, or *allergen*, acts as an antigen. Another immune cell called the *macrophage*, then recognizes the antibody–antigen or

antibody–allergen complex, absorbs the complex and destroys it. The human body makes several different types of antibodies that have slightly different functions. They are subdivided in to five classes of isotypes called IgA, IgM, IgG, IgD, and IgE. The antibody most important to asthma is the IgE isotype. IgE differs from the other isotypes in that instead of circulating freely in the blood and extracellular fluid, IgE is bound to *mast cells*. Mast cells reside in the airways and are loaded with enzymes that are released once the mast cell is stimulated by the IgE–allergen complex. In developing countries, the IgE-mediated immune response is important in fighting and killing parasites. However, in developed countries, IgE-mediated immune responses are most responsible for allergic reactions.

The *immediate hypersensitivity response* is IgE-mediated and is one of the most important causes of asthma. When IgE recognizes an antigen (or in this case *allergen*), a cascade of events occur that cause the degranulation and release of toxic inflammatory molecules from these mast cells (including proteolytic enzymes and histamine), which were meant to destroy foreign intruders (Wills-Karp 1999). Even when no such intruders are present, these toxic molecules cause the airways to become inflamed. The toxic molecules attract more immune cells to the area, thereby worsening the inflammation. Blood vessels become engorged and leaky, thereby allowing cells to migrate out of the blood stream and into the tissues. In asthma, the mast cells attract white blood cells called *eosinophils* to the area. They also initiate the production of inflammatory chemicals, *leukotrienes*, that are important in asthma. Leukotrienes have been implicated in inducing airway hyperresponsiveness, eosinophilia, and mucous hypersecretion (Bochner and Busse 2005).

Asthmatics typically have two phases during an asthma attack, the early and late response. It is thought that when the allergen activates IgE and mast cells, the histamine, leukotrienes, and cytokines released cause immediate constriction of smooth muscles that can resolve in approximately 1 h. However, 4–6 h later, another bout of airways obstruction can occur. This late reaction is thought to be due to different cytokines that are being released by the mast cells, eosinophils, macrophages, and lymphocytes (Busse and Lemanske 2001). The late response is responsible for prolonged asthma attacks.

Cell-Mediated Immunity

The T-cell differs from B-cells in the kind of antigen to which they respond. B-cell antibodies identify whole molecules. T-cells, on the other hand, do not rely on antibodies but rather develop receptors that recognize small pieces of a molecule. This makes it easier to recognize and destroy very small particles such as viruses. T-cells also differ from B-cells in their diversity. There are several different types of T-cells called cytotoxic T-cells, type 1 helper T-cell (TH1 cells) and the type 2 helper T-cell (TH2 cells). The roles of all these different T-cell types are too involved to explain here. In general the TH1 and TH2 cells differ in the types of immune reactions that they promote. In asthma, the TH2 cells often recognize the same allergens as B-cell antibodies do and help to activate the B-cell. The cytokines that the TH2 cell secretes to "help" the B-cell often contribute to the development of airways inflammation in the patient with asthma.

The TH2 cell does not rely on IgE antibodies but instead recognizes the allergen directly through its own receptor. The TH2 cell then activates and releases the cytokines to attract and activate more immune cells. This process was discovered when it was recognized that antibody-deficient mice (who do not make IgE molecules) were able to develop asthma (Corry et al. 1998). In this scenario, when TH2 cells are activated, the release of cytokines act directly on airway smooth muscle to induce airway bronchospasm (Corry et al. 1998; Wills-Karp et al. 1998). These cytokines also increase mucous secretions, airway inflammation and eosinophilia in the same way that leukotrienes do, but through a different mechanism.

To further complicate matters, the cytokines (such as IL-4) released by the TH2 cells also contribute indirectly to the immediate hypersensitivity response. IL4 is a key player in mast cell maturation (Madden et al. 1991), IgE secretion (Finkelman et al. 1988) and eosinophil recruitment to the lung (Corry et al. 1998). These immune responses, therefore, potentiate each other, showing how asthma can be the result of several different simultaneous processes.

TH2 Hypothesis

The observation that TH1 and TH2 cells promote different types of immunity generated the idea that

perhaps one type of immunity is dominant in a particular individual. Specifically, that in one person, the TH1 cell-mediated immunity could be more active than the TH2 cell-mediated immunity. Because TH2 cell-mediated immunity has been associated with allergen-induced inflammation, it was thought that individuals who had predominantly TH2 cell-mediated immunity would be more prone to asthma and allergy. This is the basis for the TH2 hypothesis.

Further research has suggested that TH1 and TH2 cells regulate each other. For example if the TH2 cell is more active, it will release chemicals to suppress the TH1 cell and vice versa. When tested in the lab, chemicals from TH1 cells were found to decrease production of TH2 cells (Scott 1991). The question then becomes, what determines which TH cell mediated immunity dominates in an individual?

Hygiene Hypothesis

As the TH2 hypothesis gained popularity, the idea that the environment may determine which TH response dominates in a particular individual began to emerge. Exposures to certain pathogens or allergens at a young age (or even during the neonatal period) could determine if a person would have a TH1 or a TH2-mediated immunity (Table 2.1). Furthermore, if a person had a predominantly TH2-mediated immunity, then that person would be more susceptible to allergic diseases and/or asthma. This hypothesis has been dubbed the "hygiene hypothesis." However, the idea that immunity is either TH1 or TH2 mediated is too simplistic as evidence has shown there is a complicated interaction between these two that is still being explored. That being said, we will explore briefly the hygiene hypothesis and the rationale behind this intriguing idea.

Table 2.1 Factors promoting TH1 and TH2 phenotype

Factors promoting TH1 phenotype	Factors promoting TH2 phenotype
Endotoxin exposure	Use of antibiotics
Rural or farm setting	Western lifestyle
Older siblings	Urban setting
Daycare	
Infections (Hepatitis A, HSV 1, tuberculosis, toxoplasma)	

Asthma is more common in Western countries (The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee 1998), suggesting there may be an environmental reason for the increased prevalence of the disease in these areas. The term "hygiene hypothesis" alludes to the idea that perhaps it is the decreased exposure to infections and allergens in the Western world that promotes TH2-mediated immunity. Furthermore, use of antibiotics has been associated with increased risk of asthma perhaps by decreasing exposure to infections that would promote the TH1 mediated immunity (Cohet et al. 2004; Droste et al. 2000). Interestingly, asthma is more prevalent in urban settings when compared to rural or farm settings (von Mutius 2000). Intense epidemiological research has looked at why this may be true. Several studies have looked at how exposure to *endotoxin* early in life could affect development of wheezing and asthma. Endotoxin, a component of (gram-negative) bacterial cell walls, can induce inflammation and cause bronchoconstriction when inhaled by asthmatics (Michel et al. 1989). Interestingly, endotoxin promotes TH1-mediated response and has been found to increase production of TH1-related cytokines (D'Andrea et al. 1992; Gereda et al. 2000; Lapa e Silva et al. 2000; Le et al. 1986). It appears that endotoxin is more abundant in farm settings, likely due to increased exposure to livestock, than in nonfarm settings (von Mutius et al. 2000). Although in decreased quantities, endotoxin can also be found in common household dust. Researchers have asked whether it is the exposure to endotoxin that predicts the development of asthma thereby explaining the differences in asthma prevalence between urban and rural/farm settings.

Litonjua et al. (2002) studied children from Boston, MA who were less than 5 years old. The results of this study, which was conducted over 4 years, showed that children who were exposed to higher endotoxin levels initially had increased wheezing during the first year of life. However, as the children became older, they had a progressive decline in wheezing. By age 5–9 years, children who had higher endotoxin exposure had less wheezing when compared to children who had lower endotoxin exposure. This paradoxical relationship whereby increased endotoxin exposure increases risk of wheezing early in life, but decreases risk of wheezing later in life, suggests that exposure to endotoxin may have "protective" effects. By enhancing TH1-mediated immunity, endotoxin exposure may

decrease the development of asthma and/or allergy in susceptible individuals.

When studying other exposures that may enhance the TH1-mediated response it has been shown that previous exposure to *Mycobacterium tuberculosis*, hepatitis A, *Toxoplasma gondii*, Herpes Simplex 1 and the common cold have been associated with decreased risk of allergy or asthma. Viruses and bacteria activate cell-mediated immunity (TH1 response). The German Multicenter Allergy Study studied children from birth to 7 years of age and found that children who had more colds with a runny nose had less wheezing (Illi et al. 2001). Similarly, the Tucson Children's Respiratory Study, which followed children from birth, found that children who had more siblings or attended daycare from an early age were more likely to have wheezing at age 2 but increasingly less likely to have asthma as they became older (at age 6, 8, 11, and 13) (Ball et al. 2000).

The hygiene hypothesis, however, has remained very controversial. As stated earlier, the simple TH1 versus TH2 model does not hold true in many instances. For example, in rural Africa where parasitic diseases are common, infection with certain parasites (*Shistosoma* species) (van den Biggelaar et al. 2000) and Ascaris hook-worm (Scrivener et al. 2001) was associated with decreased prevalence of asthma and allergy. Parasitic diseases activate the TH2 response and require IgE to fight off these infections. Therefore, one might think that factors favoring the TH2 phenotype would increase the incidence of asthma and allergy. However, on closer inspection, it is thought that another factor may be "bypassing" the TH2 response in parasitic diseases. Another group of T-cells called *regulatory T-cells* that produce a cytokine called Interleukin-10 (IL-10), may be increasingly active during parasitic infections. It is thought that these regulatory T-cells can override the TH2 response. In a mouse experiment, injection with IL-10 producing T-cells decreased the allergic response in these animals (Cottrez et al. 2000). In other experiments, IL-10 in combination with IL-4 caused B lymphocytes to produce IgG instead of IgE (Jeannin et al. 1998). This line of research is promising in further clarifying the immune responses that are contributing to the asthma and allergy phenotype.

Lastly, the hygiene hypothesis does not explain the cause-effect relationships that occur later in life. In other words, once an individual has established an allergic response, repeated exposures do not decrease this response. In the endotoxin example, individuals with established asthma have increased airways inflammation, bronchoconstriction, and susceptibility to viral illnesses when exposed to endotoxin (Reed and Milton 2001). Endotoxin exposure is a common cause of asthma in the workplace and repeated exposures in asthmatic individuals leads to chronic bronchitis and emphysema (Reed and Milton 2001). Instead of mitigating the allergic reaction, repeated exposures to endotoxin in the person who already has asthma causes worsening disease. This example suggests that the hygiene hypothesis may only be relevant early in life and cannot be extrapolated to the adult setting.

Viral/Bacterial Infections

Since the 1970s there has been a well-established relationship between asthma and respiratory tract infections (Blasi et al. 2001). Many patients with asthma have worsening of their symptoms in the setting of a respiratory infection. In children, studies have shown up to 45% of asthma exacerbations are related to respiratory infections (Mertsola et al. 1991). Likewise, in adults, up to 37% of asthma exacerbations were associated with respiratory infections (Teichtahl et al. 1997). However, whether these infections are involved in the etiology of asthma or the progression of disease has remained unclear. There is also interest in whether respiratory infections play a significant role in the TH1/TH2 or hygiene hypotheses as well. Although more commonly associated with viruses, several specific bacteria such as *Chlamydia pneumoniae* and *Mycoplasma pneumoniae* have been increasingly associated with asthma.

C. pneumoniae and *M. pneumoniae* are two common bacterial respiratory infections and are typically associated with pneumonia. *C. pneumoniae* is different from most other bacteria in that it must invade cells, such as respiratory epithelial cells and macrophages, in order to replicate. However, because *C. pneumoniae* does not have to destroy the cell that it invades; it can persist as a latent infection by allowing infected cells to proliferate. Latent infections can be quiescent without causing symptoms. If triggered, however, they can erupt into an acute infection. Cold sores, for example, are due to latent infection with Herpes

Simplex virus that develops into an acute infection from time to time. *C. pneumoniae* has been implicated in acute exacerbations of asthma (Allegra et al. 1994) and chronic asthma (Black et al. 2000).

C. pneumoniae has been associated with asthma since the 1970s. Since then, efforts to quantify this association have been attempted. Several studies have measured antibodies against *C. pneumoniae* in the blood of asthma patients and found an increase in certain types of antibodies (IgA) to *C. pneumoniae* when compared to controls (Berkovich et al. 1970; Gencay et al. 2001; Huhti et al. 1974). Antibody studies, however, are difficult to interpret since the presence of antibodies does not confirm whether an infection is past, latent, or acute. It has been suggested that chronic infection with *C. pneumoniae* is more prevalent in asthmatics (Biscione et al. 2004; Gencay et al. 2001). When using methods to directly test for presence of the bacteria in nasal aspirates of asthmatics and their non-asthmatic spouses over a 2 month period, it was found that 22% of the asthmatics and 9% of the spouses had presence of the organism at least once during the study period (Biscione et al. 2004). However, it was still unclear as to whether the increase in positive tests for *C. pneumoniae* in asthmatics truly represents active infection or colonization.

It is logical to ask that if *C. pneumoniae* infection is associated with asthma, then does treatment with antibiotics improve symptoms and outcome? Unfortunately the results have been mixed. Several studies have shown that treatment of asthmatics with antibiotics for 6–8 weeks have shown decreases in eosinophil counts (Amayasu et al. 2000) and improvements in peak expiratory flows (PEF) (Black et al. 2001) but that the effect on pulmonary function tests were modest at best. Most recently, a double-blinded, randomized, placebo-controlled trial attempted to more accurately assess the effect of antibiotics (against *C. pneumoniae* and *M. pneumoniae*) in the setting of an acute asthma exacerbation (Johnston et al. 2006). Patients with an acute asthma exacerbation were randomized to take placebo or an antibiotic for 10 days in addition to regular asthma treatment. Although asthma symptoms improved in the antibiotic group, there was no difference in PEF. Interestingly, 61% of the subjects studied had evidence of infection from either *C. pneumoniae* or *M. pneumoniae* or both but unfortunately there was no correlation between antibiotic response and history of infection in this study.

Results have been similar with *M. pneumoniae*, a common bacteria responsible for "atypical" or "walking" pneumonia. Like *C. pneumoniae*, it has been implicated in the etiology, progression, and clinical course of asthma, but treatment with antibiotics has not yielded significant improvements. It is the smallest free-living organism and is different from other bacteria in that it does not have a cell wall. It infects the respiratory epithelium and disables the ciliated cells responsible for clearing mucus and foreign particles from the airways. Like *C. pneumoniae*, *M pneumoniae* can persist as a chronic infection. Although it does not enter cells like *C. pneumoniae*, it can burrow between cells, evading host defenses and establishing residence in the airways.

Despite unclear results in small clinical trials assessing the effectiveness of treatment with antibiotics in asthmatics, there is still much interest in what role these bacterial infections play in the development of asthma. As discussed earlier, the hygiene hypothesis suggests that exposures to certain infections early in life may induce a TH1-mediated immunity resulting in a decreased propensity for asthma. However, once the allergic phenotype is established, recurrent exposures to a pathogen or allergen exacerbates the disease. Researchers looked at this phenomenon in an allergic-asthma mouse model. Chu and colleagues exposed mice to *M. pneumoniae* at different times and observed the response (Chu et al. 2003). When they infected the mice before exposure to an allergen, the mice had significantly less bronchial hyperresponsiveness, and lung inflammation and had increased production of cytokines associated with the TH1 response. Conversely, when they infected the mice after exposure to an allergen, they developed increased bronchial hyperresponsiveness, and lung inflammation, and produced cytokines associated with the TH2 response (IL-4). This line of research is very interesting and suggests that both *C. pneumoniae* and *M. pneumoniae* may have varying importance in the development and progression of asthma based on when the infection occurs.

Although we have been discussing the role of bacterial infections in asthma pathogenesis, viral infections have been implicated in the etiology of asthma as well. Viral infections during infancy have been associated with the development of asthma. This has been most convincing in studies of *Respiratory Syncytial Virus* (RSV). Most children are infected with RSV by 2 years of age (Simoes 1999) and many are hospitalized.

RSV can cause respiratory distress, wheezing, and fever. It can cause a "bronchiolitis," inflammation of the respiratory bronchioles described earlier. Many have observed that children who suffered from RSV bronchiolitis as an infant had a higher propensity to wheeze for years after the infection (Stein et al. 1999). Sigurs and colleagues (2005) studied a group of children who were hospitalized with RSV bronchiolitis as infants (<1 year old). They compared this group, which was followed until age 13, to a group of children who had never been hospitalized with RSV bronchiolitis. These researchers found that children in the RSV group had increased wheezing and airways obstruction. What was also interesting was that these children had increased allergies to common inhaled allergens. This research suggests there may be a relationship between early RSV infection and the development of asthma and allergies later on in life. However, other studies have shown that infants infected with RSV "outgrew" their wheezing and did not go on to develop asthma in adolescence (Taussig et al. 2003). Whether RSV is merely a risk factor for asthma or is a causative agent in asthma pathogenesis remains unclear.

In addition to being implicated in asthma pathogenesis, viral infections are commonly associated with asthma exacerbations (Venarske et al. 2006). Often, when a person develops an asthma attack, there is usually an inciting factor or "trigger" associated with the attack. For many asthmatics, the common cold can precipitate an attack. In fact, viruses have been associated with up to 85% of asthma exacerbations in children (Johnston et al. 1995) and 60% of exacerbations in adults (Nicholson et al. 1993). It has been shown that during times when viral syndromes are "going around" there are increased admissions to area hospitals with asthma exacerbations (Johnston et al. 1996).

The reason why upper respiratory viruses have been associated with asthma exacerbations, however, has remained unclear. *Rhinovirus*, one of the viruses responsible for the common cold, has been most frequently associated with asthma exacerbations. One study found that infection with rhinovirus was associated with an increase in asthma-related hospitalizations (Venarske et al. 2006). Some have suggested that viruses may potentiate the inflammatory response to allergens causing bronchospasm and airways obstruction in asthma patients (Busse and Lemanske 2001; Calhoun et al. 1991). Others have proposed that asthma may cause abnormalities in the immune system that makes it harder to fight viral infections in the airway (Papi and Johnston 1999). The role of rhinovirus and other viral illnesses (such as *influenza, parainfluenza, and coronavirus*) in causing or contributing to asthma exacerbations needs to be further clarified.

Dutch Hypothesis

Before delving into what the Dutch Hypothesis is, we must first briefly explain the differences between asthma and chronic obstructive pulmonary disease (COPD). As we have been discussing, asthma is characterized by reversible airflow obstruction, airways hyperresponsiveness, and increased mucous secretion. Typically, asthma does not cause progressive loss of lung function and the lung parenchyma itself remains intact. Usually, asthma presents in childhood or young adulthood. On the other hand, COPD, a term used to describe chronic bronchitis, emphysema, and a variety of less common conditions such as bronchiectasis, is commonly associated with smoking and presents in older adulthood. Even though COPD is also characterized by airflow obstruction, it is usually irreversible or only partially reversible. There is also progressive loss of lung function. Asthma and COPD are commonly thought of as distinctly different diseases. Asthma has been described as an inflammatory airway disease mediated by a dysregulated immune response (as described by the TH2 hypothesis). COPD, on the other hand, is thought to occur when destructive enzymes damage the lung in response to some inflammatory stimulus (i.e., cigarette smoke).

The Dutch Hypothesis was first proposed in the 1960s and is one of the older but still relevant theories on asthma/COPD pathogenesis. During that time, tuberculosis was the most common respiratory illness but as effective treatment for tuberculosis became available, Drs. Orie and Sluiter began to notice that obstructive lung diseases were very common with similar characteristics in both younger and older patients (Postma and Boezen 2004). They proposed, in the first Bronchitis Symposium held in Groningen, Netherlands, that obstructive airways diseases such as asthma, chronic bronchitis, and emphysema should be considered not as different diseases but as different manifestations of one disease entity, which they called *chronic nonspecific lung disease* (CNSLD) (Postma and Boezen 2004).

They hypothesized that both genetic and environmental factors contribute to the pathogenesis of CNSLD and that it is the interaction between these two that determines what phenotype a person will develop. One example of an interaction between a person and his/her environment is smoking. Tobacco smoke has been highly associated with COPD. However, only 10% of smokers get COPD suggesting that there is a genetic propensity for a person to develop COPD in response to cigarette smoke. There has also been an association between passive smoke exposure and the development of asthma in children. According to the Dutch hypothesis, the time of tobacco smoke exposure, whether in childhood or adulthood, and the type of exposure, passive or active, determines if a person with genetic susceptibility develops the asthma or COPD phenotype.

The Dutch hypothesis, as it is now known as, has been controversial. Efforts to try and test this hypothesis have been flawed as study designs do not lend to testing a process that spans a lifetime. Also, current studies of asthma and COPD have had strict inclusion criteria that try to eliminate subjects who have aspects of both, which limits our ability to determine if the pathogenesis of the two is similar. Over the years, however, there has been some evidence to support the Dutch hypothesis. Clinically, there are populations of asthma patients who have loss of lung function similar to COPD (Jeffery 2000; Ulrik et al. 1995). Similarly, there are patients with COPD who have reversible airflow obstruction (Bousquet et al. 1996). These observations suggest that there is considerable overlap between asthma and COPD.

Other observations have contributed to the blurring between asthma and COPD. There is evidence to suggest that both conditions are secondary to lung inflammation. In the past, different types of inflammation were described in patients with asthma and COPD. In asthma, it was thought that the inflammatory process was confined to the airway and that in COPD, the inflammatory process was confined to the lung parenchyma. However, there have been some studies that have shown that there are inflammatory cells, such as eosinophils and neutrophils, within the lung tissue in some subjects with asthma (Kraft et al. 1996; Wenzel et al. 1999). Additionally, biopsies of COPD subjects have shown high numbers of eosinophils in the airways especially during acute exacerbations (Saetta et al. 1994). Asthma and COPD share histologic features suggesting that there is substantial overlap between these two disease processes.

There have been several other features of both diseases that suggest a common pathogenesis. For example, the airways of asthma and COPD patients are similar. Both have an increase in mucous secreting cells lining the airways. Increases in smooth muscle surround the airways, however, was thought to be unique to asthma. Recent studies have shown that there is also an increase in smooth muscle among COPD patients as well (Jeffery 2000). Finally, changes in the lung parenchyma itself have shown some similarity among asthma and COPD subjects. Typically, as already mentioned, asthma is thought to be strictly an airways disease that does not affect the lung parenchyma or alveoli. However, the destructive enzymes found in COPD lungs have also been found in biopsies of asthma lungs as well (Atkinson and Senior 2003; Bousquet et al. 1996).

Studies are ongoing to further assess whether asthma and COPD are two distinct diseases or different presentations of the same disease. Over the years, the popularity of the Dutch Hypothesis has waxed and waned. However, there has been growing scientific evidence to support this hypothesis, which highlights that asthma is indeed a complex and heterogeneous disease process.

Asthma Subtypes

Although the majority of asthma is initially triggered by allergies, there are several different phenotypes of asthma that have different characteristics from the common allergy-induced asthma. "Intrinsic asthma," aspirin-induced asthma (AIA), and exercise-induced asthma (EIA) are a few asthma subtypes that have unique characteristics not readily associated with allergens. There are, however, several other subtypes of asthma, such as gastroesophageal reflux associated asthma, obesity-related asthma, menstrual cycle-related asthma, and nocturnal asthma that are also included in the asthma syndromes, but will not be discussed here.

Intrinsic Asthma

The term "intrinsic asthma" has been used to describe patients who suffer from asthma but do not have

typical features of atopy or allergies. This is in contrast to the allergy-induced ("extrinsic") asthma we have been discussing. Patients with "intrinsic" asthma do not have allergies, family histories of atopy, abnormal serum IgE levels, or hypersensitivity reactions to skin prick-tests. The clinical course of patients with intrinsic asthma differs as well. Usually, patients with intrinsic asthma tend to be older, have later onset of asthma, and more severe disease (Ulrik et al. 1995). For many years, it was believed that "intrinsic" asthma represented a different pathological process leading to asthma and that the distinction between "intrinsic" and "extrinsic" (allergy-induced) asthma was very apparent. More recently, however, the differences between "intrinsic" and "extrinsic" asthma have become less clear. In one study, lung biopsies of patients with extrinsic asthma were compared to patients with intrinsic asthma (Humbert et al. 1996). Both had similar inflammatory cells and cytokines present, suggesting that a similar process was occurring in both forms of asthma regardless of whether the patient had allergies or not. These findings have prompted researchers to view "intrinsic" asthma differently. Instead of thinking of "intrinsic" asthma as being different from "extrinsic" asthma, there may only be differences in the triggers leading to the same causative pathways for asthma (Humbert et al. 1999). For example, some have suggested that intrinsic asthma may be a form of autoimmunity, triggered by a respiratory viral illness. In other words, antibodies made to the initial viral illness may now be initiating a cascade of inflammation leading to asthma (Humbert et al. 1999). Others believe that patients with "intrinsic" asthma are actually allergic to something that researchers have not yet been able to identify (Humbert et al. 1999). The pathogenesis of "intrinsic" asthma has not been elucidated and may reflect a heterogeneous process rather than a single disease entity. Although similarities between "intrinsic" and "extrinsic" asthma exist, the concept that asthma does not necessarily represent a solely allergy-related disease is important and speaks to the complexity of asthma.

Aspirin-Induced Asthma

One could consider AIA a kind of "intrinsic" asthma for which we know the trigger. Aspirin is one of the most widely taken medications in the world. In the United States alone, over 80 billion tablets per year are consumed. As such, the recognition of AIA is important as AIA may represent 10–20% of the asthma population (Sturtevant 1999). The AIA syndrome usually includes a triad of symptoms: nasal polyps and nasal congestion, sinusitis, and asthma with chronic symptoms. Patients with AIA often have chronic severe asthma with acute symptoms triggered after ingestion of aspirin or a similar drug (such as ibuprofen). Many times, symptoms can begin within 3 h after ingestion of aspirin with a profuse runny nose, swollen eyes, and flushing of the face in addition to wheezing. Breathing can become severely impaired, requiring hospitalization, and can progress to respiratory failure.

Although symptoms begin shortly after exposure to aspirin, AIA is not an allergic reaction per se. Skin prick tests with aspirin are usually negative, indicating that an antibody to aspirin does not exist in patients with AIA (Babu and Salvi 2000). Instead, aspirin blocks enzymes and, by doing so, causes increased production of cytokines called leukotrienes. These leukotrienes, in turn, promote inflammation and asthma in the susceptible individual. AIA is an example of how different mechanisms can lead to asthma.

Exercise-Induced Asthma

Like AIA, EIA is also not allergen mediated. It is very common with reports of 40–90% of asthmatics affected (Bundgaard 1981; Tan and Spector 2002). Many asthmatics experience increased airways resistance during exercise. Because of the dyspnea experienced during exercise, many patients with asthma often do not pursue aerobic activities as much as their non-asthmatic counterparts and are less fit as a result (Garfinkel et al. 1992). EIA, therefore, is important to recognize and treat so that patients with asthma can become more involved in exercise. Patients with asthma often feel better when they are physically fit (Ram et al. 2005). It is also thought that EIA may be triggered by moving large amounts of air in and out of the lungs. If asthmatics are more fit, they may breathe less heavily with mild to moderate exercise thereby decreasing the triggers for EIA (Ram et al. 2005).

The mechanism for EIA is debated. Two of the most common theories are the *osmotic hypothesis* and the

thermal hypothesis. The thermal hypothesis suggests that bronchoconstriction during exercise is due to changes in temperature and water content of the airways (McFadden and Gilbert 1994). As large volumes of air move in and out of the lungs, the airways warm and humidify that air (also known as conditioning). Although the airways warm and heat air continuously (regardless of whether we are exercising or not) when we are quietly breathing with low tidal volumes, only a portion of the airways heat and humidify the air. During exercise, however, ventilation can increase by a factor of 20. As ventilation increases, the conditioning of air moves from the upper airways to the lower airways where more movement of heat and water from the airway cells is required to heat and humidify the air (McFadden and Gilbert 1994). When exercise stops and ventilation decreases, the airways rewarm quickly as they are no longer losing heat and water to the air. This cycle of cooling and rewarming is associated with airway narrowing and bronchoconstriction. Breathing warm humidified air ameliorates exercise-induced bronchoconstriction and breathing cold dry air worsens it (Bundgaard et al. 1982). It is not entirely clear why the airways narrow in response to rapid cooling and rewarming although increased blood flow and subsequent airway edema is thought to play a role (McFadden and Gilbert 1994; McFadden et al. 1986).

The osmotic hypothesis, on the other hand, suggests that airway dehydration during exercise causes a series of events leading to airway smooth muscle contraction and increased airways resistance (Anderson 1984). Proponents of the osmotic hypothesis argue that it is water loss, not changes in temperature that lead to bronchoconstriction. During exercise, large volumes of air move in and out of the lungs as respiratory rate and tidal volume increase. This movement of air is thought to cause evaporation of water in the airways. It is thought that the water loss causes an increase in osmolarity, which then triggers cells to release inflammatory chemicals, which in turn act on smooth muscle to contract. The loss of water in the lungs is also thought to cause an increase in blood flow to the lungs that can cause edema of the airways and even worsening airway constriction (Anderson and Daviskas 2000). Observations that EIA occurs when subjects breath gases of varying temperature but similar water content supports the osmotic hypothesis (Ingenito et al. 1988). Treatment of EIA usually consists of using a bronchodilator before exercise

Physiology

Until now, we have discussed the pathogenesis of asthma and possible mechanisms for increased airways inflammation. This inflammation in turn leads to air flow obstruction and airway hyperresponsiveness. But what does this mean in terms of how asthma manifests clinically? How does this lead to symptoms of shortness of breath? What happens to respiratory physiology when asthma occurs?

The hallmark of asthma is reversible airways obstruction. As the airways become narrowed during an asthma attack, resistance of the airways increases and airflow into the lungs is diminished at the same level of respiratory effort. One could imagine this by comparing the difference between blowing into a large straw versus a small straw. If one blows the same volume of air through the large and small straw, it will take a significantly longer time to blow out all the air through the small straw because flow is greatly diminished. The lungs are more complex than the one straw system, however, as smaller and smaller branching airways have differing lengths, compliances, and different types of air flow (laminar and turbulent). Because of this, there comes a point when no matter how hard one blows, flow will not increase. This is called airflow limitation.

One of the most common complaints in patients with asthma is that they have difficulty breathing in. There are several reasons for this. With increased bronchoconstriction there is diminished air flow and increased airways resistance. In order to compensate for the increase in airways resistance, the inspiratory muscles must generate greater tension. Imagine that instead of blowing through the small straw, that one tries to breathe in through the small straw. The amount of effort required to take in a breath will increase. However, it turns out that the increased work of breathing associated with inhalation is complicated by a second factor, hyperinflation of the lungs and chest wall. Furthermore, inhalation is an active process; muscle activity is required. Exhalation, on the other hand, is typically passive during quiet breathing. The normal elastic properties of the lungs and chest wall push air out of the lungs during exhalation.

Now imagine trying to blow out through the small straw and then continue to breathe in and out through this small straw. Although one may not be aware of it, as one continues to breathe in and out through that small straw, a process called “dynamic hyperinflation”

is occurring. In other words, because it takes longer to exhale out all the air when air flow is decreased, one may initiate the next breath before all the air is exhaled from the last breath. The volume of the lung and chest wall then increases. The next breath is even harder to take in because at higher lung volumes, the inspiratory muscles operate at a shorter length and are less able to generate tension. In addition, the compliance of the lungs and chest wall is reduced at higher lung volumes. This means that the respiratory system is stiffer and more work is required to take in a breath. You can try to experience this by taking a breath in before you have fully exhaled the last breath. When a group of patients with mild asthma were given medication to induce bronchoconstriction, hyperinflation was the greatest indicator of how short of breath they felt (Lougheed et al. 1993). Surprisingly, an increase in airways resistance did not correlate with how dyspneic the subjects felt. This points to the importance of hyperinflation as a cause of dyspnea in the asthmatic patient.

Hyperinflation can also induce "length-tension inappropriateness" another mechanism that may contribute to dyspnea in asthma. If tension is generated in the muscle but it does not shorten appropriately because of the mechanical load on the system (similar to when trying to lift a weight that is too heavy), there is a discrepancy between the tension generated in the muscle and the degree to which it shortens (Campbell and Howell 1963). This concept has been broadened to include discrepancies between the neurological output to the muscles and the mechanical response of the respiratory system (neuromechanical dissociation). If the inspiratory muscle force generated does not match the expected change in lung volume, feelings of breathlessness may occur (Campbell and Howell 1963). Hyperinflation contributes to neuromechanical dissociation in several ways. The hyperinflated lung places the respiratory muscles at a mechanical disadvantage making these muscles less effective in creating tension. Therefore, even though the brain is sending out a message to the respiratory muscles to contract, the force generated and the change in lung volume may not match what the brain expects, causing neuromechanical dissociation. Hyperinflation also creates an inspiratory load that the respiratory muscles have to overcome before flow into the lungs can occur. This phenomenon is called "auto PEEP" or positive end expiratory pressure. What this means is that if the lungs have residual air in them because one could not fully exhale, there is still positive pressure in the lungs at the end of the breath. Normally, exhalation is a passive process akin to letting air out of a balloon. When we exhale, the pressure in our lungs equilibrates to atmospheric pressure. If one does not fully exhale, however, there may be a few centimeters of H_2O pressure left in the lungs before inhalation begins. The flow of air travels from areas of low pressure to high pressure. In auto PEEP, the inspiratory respiratory muscles must first overcome this pressure gradient to equilibrate to atmospheric pressure, and only after that can negative pressure be generated so that air can flow into the lungs. Thus, there is a period of time when the respiratory muscles are firing but no air is flowing into the lungs and, therefore, there is no change in lung volume. Imagine walking about while breathing through a mouthpiece that is connected to a valve that does not open until you generate a negative pressure of 5 or 7 cm H_2O with your inspiratory muscles. It is not surprising that individuals with auto-PEEP complain of shortness of breath.

However, there are many patients with mild asthma who complain of chest tightness or difficulty breathing with only mild bronchoconstriction, levels of airways obstruction not associated with hyperinflation. These symptoms cannot be readily explained by increased work of breathing alone. Several studies have elucidated what may be occurring in this groups of patients. Taguchi et al. (1991) tested subjects by having them inhale a medication that causes bronchoconstriction and compared the respiratory sensation associated with an asthma-type reaction in the lungs to what the subjects felt when breathing through a high resistance (like our straw example). Although the degree of hyperinflation was the same in both conditions, subjects felt more short of breath when they were given a medication that caused bronchoconstriction. This sensation of shortness of breath was relieved when the subjects breathed in lidocaine (a topical anesthetic). This study suggests that there are nerve receptors in the lungs that contribute to the sensation of breathlessness during bronchoconstriction. Binks et al. (2002) tried to clarify further the mechanism behind the chest "tightness" often described by asthmatics during an attack. They gave patients inhaled medication to provoke bronchoconstriction. They then placed these patients on a mechanical ventilator thereby eliminating the effort required by the patient to inhale by having a

machine breathe for them. Even though the patients felt like it required less effort to breathe on the ventilator, they still experienced the sensation of chest tightness. They then put subjects without bronchoconstriction on a mechanical ventilator and increased the end expiratory volume to mimic hyperinflation. Even though their lungs were hyperinflated, the subjects did not experience chest tightness. This experiment suggests that the feeling of chest tightness is separate from the effort of breathing during an asthma attack. Although the effort to breathe is related to bronchoconstriction and the resultant increased work of breathing, tightness may be caused by changes within the airway itself that lead to stimulation of pulmonary receptors, which may send messages to the brain creating the sensation of tightness.

Bronchoconstriction may also affect the delivery of oxygen into the lungs. If airflow to the lungs is diminished, it is hard to get air in and out and, therefore, the movement of oxygen into the lungs and carbon dioxide out of the lungs is impaired. The human body, however, has developed an interesting system to deal with changes in airflow and oxygen delivery to the lungs. The body has a tremendous ability to constrict blood flow to areas of the lung that have low oxygen levels. This phenomenon is called hypoxic vasoconstriction. In response to low oxygen levels in the lungs, the body will decrease flow of blood to these areas and divert blood to areas of the lung with normal oxygen levels. Because asthma is a heterogeneous disease process, some areas of the lung will experience inflammation and bronchoconstriction while other areas of the lung will be relatively normal. Therefore, the body usually can maintain adequate oxygen levels even in the face of mild to moderate asthma attacks.

Another mechanism that contributes to near normal oxygen levels during an asthma attack is hyperventilation. During a mild or moderate asthma attack, the patient will typically hyperventilate. Possible reasons for hyperventilation include stimulation of pulmonary receptors as well as behavioral factors (shortness of breath and anxiety can lead to hyperventilation). The rapid replacement of oxygen in the alveoli during hyperventilation helps to maintain normal oxygen levels in the blood.

In patients with fatal or near-fatal asthma, however, hypoxemia may blunt the sensation of dyspnea or uncomfortable breathing, making it more difficult for individuals to recognize the severity of their problem, thereby leading to a delay in seeking medical treatment. Although hypoxemia is not a common feature of asthma, the body's attempts to divert blood to normal lung is insufficient when bronchoconstriction becomes severe. If there is little normal lung to which to divert blood, oxygen levels will start to decrease. In people without asthma (Chronos et al. 1988), or with other lung diseases such as COPD (Lane et al. 1987), hypoxemia itself can provoke shortness of breath. Unfortunately, when patients with asthma become hypoxemic, the ability to feel short of breath or chest tightness may diminish (Eckert et al. 2004).

Diagnosis

Symptoms

Just as the pathogenesis of asthma is relatively complex, the signs and symptoms of asthma can be confusing as well. Asthma can present with a paucity or overabundance of symptoms, and can coexist with other illnesses. There are also many disease processes that can mimic asthma, thereby confusing health care providers. Finally, because asthma is an episodic disease, patients can have normal exams and pulmonary function tests between "attacks," which makes diagnostic studies insensitive to the presence of asthma. According to the National Heart Lung and Blood Institute, the diagnosis of asthma should be considered in anyone who has episodic airways obstruction, reversible (or at least partially reversible) airways obstruction, and in whom other diagnoses have been excluded (Teichtahl et al. 1997). We will review the presenting symptoms of asthma, the role of diagnostic studies (such as pulmonary function tests, peak flow, and methacholine challenge tests (MCT)) and the conditions that may mimic asthma and which should be considered in difficult cases.

Many patients with asthma will initially present with wheezing, a high pitched sound usually heard during exhalation. As the airways narrow and airways resistance increases, there is more turbulent flow causing vibrations that we hear as a "wheeze." Some have argued that the opening and closing of airways also contributes to this vibration. However, a lack of wheezing does not exclude the diagnosis of asthma.

First, because asthma is an episodic disease, wheezing is not always present; patients who present to their health care provider during an asymptomatic period can have a completely normal exam. Second, the sound of wheezing actually decreases if airways resistance becomes severe. If airways resistance becomes so high that air flow is severely reduced, as in cases of extreme bronchoconstriction, turbulent flow can no longer be heard. Therefore, a patient who presents with a severe asthma attack can initially have wheezing that subsequently quiets down or stops. Instead of interpreting the lack of wheezing as an improvement in asthma, one must be vigilant that this does not signify a worsening of airways obstruction. Similarly, complete absence in breath sounds, or a "quiet chest" can also signify worsening airways obstruction and impending respiratory failure.

Some patients never develop wheezing as a symptom of asthma. There are many patients whose initial symptom is cough. This phenomenon has been termed "cough-variant" asthma. Gastroesophageal reflux disease (GERD), postnasal drip, and asthma are the three most common causes of chronic cough (Irwin et al. 1990). Because asthma is so common in the diagnosis of chronic cough, empiric treatment with bronchodilators (beta-agonists, which cause smooth muscle relaxation) is a common diagnostic test to evaluate if asthma is the cause of chronic cough. However, there is complex relationship between GERD and asthma. Acid reflux can cause bronchoconstriction through a neural reflex that leads to increased airways resistance. Postnasal drip also has many associations with asthma as both can be presentations of the allergic phenotype. Therefore, GERD, postnasal drip, and asthma often coexist and treatment of all three conditions may be needed to resolve chronic cough. Asthma, however, can present as cough alone and should be considered as a diagnosis in those individuals who present with chronic cough.

Dyspnea and shortness of breath are common symptoms of asthma (Table 2.2). Many respiratory diseases, however, present with feelings of dyspnea; distinguishing asthma from other diseases, such as COPD, can be difficult when based on symptoms of dyspnea alone. To complicate matters, the perception of dyspnea in patients with asthma is variable and does not necessarily correlate with objective measurements of lung function. Most concerning are those patients whose perception of dyspnea is "blunted" despite having severe airways obstruction as measured by the forced expiratory volume in 1 s (FEV1). Briefly, the FEV1 is the volume of air exhaled in the 1st second of a forced expiration after a maximal inhalation. In other words, it is the amount of air exhaled after the patient is asked to take a deep breath in and blow out as hard as she can. The FEV1 is reported as a percent predicted, when compared to patients of the same height, age, sex, and race. A reduction in FEV1 is associated with increased airways resistance in patients with asthma. Several studies have shown that patients with substantial airways resistance have minimal symptoms. Furthermore, symptoms in general do not correlate with objective measures of lung function (Foo and Sly 1991; Hewson et al. 1996; Molema et al. 1989; Teeter and Bleecker 1998). Asking whether dyspnea is present or absent or even asking about the intensity of dyspnea may not be specific enough to assess the presence or severity of asthma. What may be more useful is understanding the language of dyspnea. Different respiratory diseases have distinct characteristics to their shortness of breath. This is not unlike cardiovascular disease and chest pain. Over the years, we have come to recognize different representations of ischemic chest pain and that not all patients present with the typical left-sided chest pain. We have now come to recognize jaw pain, arm numbness, indigestion, belching, and chest pressure as anginal equivalents. Similarly, dyspnea has many diverse characteristics and varying presentations.

Table 2.2 Common symptoms of asthma

Common symptoms of asthma
Wheezing
Cough
Shortness of breath
Dyspnea
Chest tightness
Mucous production

Researchers have compiled a group of phrases used to describe shortness of breath by patients with different lung and heart diseases that are listed in Table 2.3 (Simon et al. 1990). They found that patients experiencing an asthma attack chose phrases describing increased "work/effort" and "tightness" when asked to describe their dyspnea (Mahler et al. 1996). Further research has tried to assess the use of specific descriptors of dyspnea in assessing severity of an asthma attack. Moy et al. (1998) asked patients, in the midst of

an asthma attack, to describe their feelings of shortness of breath (using Table 2.3) when they first presented to an emergency room and after treatment with bronchodilators. These patients were also asked to rate the severity of their dyspnea and were given breathing tests to objectively assess lung function. What was interesting was that these patients reported improvement in their feelings of shortness of breath after treatment with bronchodilators even if they had no improvement in their FEV1, an objective measure. Importantly, some aspects of their breathing discomfort improved more than others. For example, patients reported persistent feelings of increased "work" or "effort" of breathing, which better correlated with the severity of their diseases. In contrast, the sense of chest tightness improved after administration of bronchodilators. Moy et al. (1998) hypothesized that chest "tightness" may reflect bronchoconstriction, whereas "work" or "effort" may reflect ongoing inflammation and airways obstruction present during the later stages of an asthma attack. Therefore, medications that immediately dilate the airways by relaxing smooth muscles (such as bronchodilators) would provide relief from chest "tightness." However, the "work" of breathing would persist because of obstruction due to ongoing airways inflammation. Unaware of these relationships between dyspnea and asthma, doctors may discharge patients from the emergency room or hospital before their lung function has improved (Salmeron et al. 2001). In a study of asthma management in French emergency rooms, 24% of patients with severe asthma were discharged 2 h after presentation when lung function was still poor (Salmeron et al. 2001). This may be because patients reported improvements in symptoms despite persistent airway resistance. Practitioners, therefore, should be cautious when interpreting the patient's perception of dyspnea, and should attempt to distinguish between changes in chest tightness and the work or effort of breathing. Objective measures of lung function should be used routinely to manage patients in the midst of an acute exacerbation.

Finally, the patterns of symptoms may help to diagnose asthma. For example, many asthmatics may have worse symptoms during certain seasons when allergies are increasingly prevalent. Others may have increased difficulty breathing at night or upon awakening in the early morning and may have improvements of their symptoms during the day. It is important to try and establish whether symptoms are persistent or episodic and whether certain triggers can be identified.

Table 2.3 Descriptors of dyspnea

Descriptors of dyspnea
I feel that my breathing is rapid
My breath does not go out all the way
My breath does not go in all the way
My breathing is shallow
My breathing requires effort
My breathing requires more work
I feel that I am smothering
I feel that I am suffocating
I feel a hunger for more air
I feel out of breath
I cannot get enough air
My chest feels tight
My chest is constricted
My breathing is heavy
I feel that I am breathing more

From Moy et al. (1998)

Diagnostic Tools

Medical History

The medical history is one of the most important tools in diagnosing asthma. As mentioned earlier, common symptoms of asthma include episodic wheezing, cough, shortness of breath, chest tightness, increased work or effort of breathing, and difficulty inhaling. These symptoms, however, can occur with other respiratory illnesses, and taking a detailed history may help to support or refute the diagnosis of asthma. Going back to previous discussions on asthma pathogenesis, we outlined several hypotheses including the TH2 hypothesis, the hygiene hypothesis, the role of viral and bacterial illnesses, and the Dutch hypothesis. Understanding these hypotheses helps the clinician recognize factors that support the likelihood of asthma in an individual (Table 2.4). For example childhood onset of wheezing in association with other allergic symptoms would suggest TH2-mediated immune dysregulation and asthma. A family history of asthma and/or COPD could suggest a genetic propensity to develop respiratory disease in response to a particular insult as suggested by the Dutch hypothesis. Alternatively, a childhood history of RSV disease

Table 2.4 Asthma pathogenesis hypotheses and possible corresponding medical histories

Possible mechanisms for asthma pathogenesis	Possible associated medical history
TH2 hypothesis	• Childhood onset • History of allergies, sinusitis, rhinitis, or nasal polyps • Association with allergy seasons, mold exposure, animal fur/dander
Hygiene hypothesis	• Childhood onset • History of allergies, sinusitis, rhinitis, or nasal polyps • Home environment (dust exposure) • Childhood environment (urban vs. farm, presence or absence of siblings, etc)
Viral/bacterial infections	• History of severe respiratory illness as a child (possibly RSV) • Frequent common colds
Dutch hypothesis	• Family history of respiratory diseases • Exposure to passive/active smoke • Disease progression
Other associations	• GERD • Exposures to exhaust, perfumes, strong smells • Strong emotions • Exercise-induced • Cold air exposure • Aspirin-induced

requiring hospitalization could suggest asthma as the etiology of his/her symptoms.

Physical Exam

Often times the physical exam can be normal, especially if the patient is not having any symptoms of asthma. In those cases, one must rely on the medical history to help establish the diagnosis. If, however, a patient is experiencing symptoms at the time of the physical exam, there are some findings that increase the likelihood of asthma. For example, if airways obstruction is so significant that the patient cannot exhale all the air out before taking another breath, the lungs can become "hyperexpanded." When hyperexpansion occurs, it is more difficult to breathe because the chest wall is at a mechanical disadvantage. Patients will begin to use "accessory muscles" to breathe. These muscles are not commonly utilized in quiet breathing, but if breathing becomes more labored they are recruited to assist in the movement of the chest wall. These accessory muscles include the neck muscles and abdominal muscles. Also, the activity of the intercostals muscles between the ribs can become more apparent during labored breathing. If breathing becomes more difficult, some patients will hunch over or assume the "tripod" position with their hands on their knees, leaning forward while sitting; this position transforms the pectoralis muscles, normally used to move the arms, into breathing muscles that elevate the chest wall.

After observing how the patient is breathing, auscultation of the chest can be informative as well. As discussed earlier, wheezing is a common sound of early airways obstruction. Usually a wheeze is heard on exhalation. With increasing airways resistance, however, inspiratory wheezes can be heard as well. The inspiratory to expiratory, or "I:E," ratio is also reduced, meaning the expiratory phase is prolonged during airways obstruction. Usually, when listening to a patient's chest, the clinician instructs the patient to breathe deeply, which results in an I:E ratio of 1:1. If airways obstruction is present, however, the I:E ratio can decrease to 1:2 because the lungs take longer to empty.

In cases of severe asthma attacks, a phenomenon called "pulsus paradoxus" can occur. The term "pulsus paradoxus" describes what happens to the pulse or systolic blood pressure during inspiration. Normally there is a slight weakening of the pulse during inhalation and a slight strengthening of the pulse during exhalation. This happens because of the small pressure swings in the chest that occur when we inhale and exhale and the effect that these slight changes of pressure have on the heart's ability to pump blood. During a severe asthma attack, the work of breathing increases tremendously and the pressure swings in the chest become more pronounced. A person can generate −70 to −100 cm of H_2O pressure (normal is between −2 and −5 cm of H_2O pressure) which causes a severe strain on the heart's ability to pump effectively. The pulse then becomes very weak during inspiration and returns during exhalation. This physical finding is called "pulsus paradoxus" and is a sign of severe airways obstruction and possible impending respiratory failure.

The rest of the physical exam can help to identify if the patient is prone to allergies. For example, examination of the nose may reveal mucosal swelling or nasal polyps to suggest allergic rhinitis. Similarly the eyes may be itchy, red, and teary. Skin exam may

review rashes, such as hives or eczema, indicative of an allergic skin disorder. Taken together, if the physical exam is consistent with allergies in the context of shortness of breath and wheezing, the likelihood of asthma is increased.

Imaging

Most imaging will be normal in patients with asthma. In some cases, one might see evidence of hyperinflation on a chest X-ray (CXR) with flattening of the diaphragm. The main purpose of imaging, however, is to assess the patient for other conditions that may mimic asthma such as chronic eosinophilic pneumonia, bronchiectasis, cryptogenic organizing pneumonia, and emphysema among other diseases. Additionally, a chest CT may be useful if the CXR is unrevealing but the suspicion of asthma is still suspect. Chest CT's can more accurately show abnormalities of the airways, such as foreign bodies or tracheomalacia, which may be the cause of wheezing. It can also better image chronic bronchitis or bronchiectasis that may not be readily evident on a CXR. We recommend starting with a CXR in a patient newly diagnosed with asthma to exclude other possible causes of his/her symptoms.

Pulmonary Function Tests

Pulmonary function tests can be very helpful in diagnosing asthma. As mentioned earlier, measurement of FEV1 is important in diagnosing airflow obstruction. FEV1 is the amount of air exhaled during the 1st second of a forced exhalation after maximal inhalation. The forced vital capacity (FVC) is the amount of air exhaled in total after the patient blows out for as long as possible (at least 6 s); the air remaining in the lungs after such a maneuver is the residual volume (RV). If the FEV1/FVC ratio is less than what would be predicted for that person, then airflow obstruction is present. However, diseases such as chronic bronchitis, emphysema, or cystic fibrosis, all present with airflow obstruction. What increases the likelihood of asthma is the reversibility of the airflow obstruction. Often times in the lab, when we suspect that a person has asthma, we will assess the FEV1 and FVC before and after a bronchodilator. If the FEV1 increases by as least 12% and 200 cc, the patient has a significant response to bronchodilators suggestive of asthma. Wide variations in FEV1 over time with repeated pulmonary function testing are also suggestive of asthma. However, because these tests are very effort dependent, fluctuations in FEV1 can be due to patient effort rather than true reversible airways disease. In moderate to severe asthma, the patient may not be able to exhale fully during the vital capacity maneuver. The result is a diminished FVC and an elevated RV.

There are many instances when patients will not be experiencing airflow obstruction during pulmonary function testing, making it harder to diagnose asthma. Another strategy is to ask the patient to measure his PEF at home at various times during the day. This can be accomplished by asking the patient to use an inexpensive peak flow meter. Similar to the FEV1 measurement, the PEF assesses the rate at which air exits the lung during a forced expiration after maximal inspiration. In asthma, PEF is usually lowest in the morning and highest between noon and 2 p.m. (Quackenboss et al. 1991). The patient makes PEF measurements several times a day and a 20% difference in values between the highest and lowest flow measurements is suggestive of asthma.

If, after obtaining the history, physical exam, CXR, and pulmonary function tests, the diagnosis of asthma is still in doubt, a bronchoprovocation test to induce airways obstruction may help to establish or exclude the diagnosis. Commonly, a bronchoprovocation test is useful when conventional therapies for asthma do not resolve the patient's symptoms. The physician must decide whether to intensify the medical regimen or question the diagnosis of asthma. A MCT can help confirm or exclude a diagnosis of asthma and guide further therapy (Fig. 2.3).

The hallmark of asthma is bronchial hyperresponsiveness, meaning that the airways constrict robustly in response to an irritant or other stimulus. Methacholine is a medication that causes constriction of the smooth muscles around the airways. When given in high enough doses, a person with normal airways can have bronchoconstriction with methacholine. In asthmatics, however, the airways will constrict with very small doses that usually do not affect the normal airway. The MCT is administered in a monitored setting. The subject inhales a solution of methacholine in increasing doses. After each inhalation, FEV1 and FVC are measured. If there is a decrease of 20% in the FEV1 after an inhalation of a certain dose of methacholine, the test is stopped. This is called the PC20, the provocation

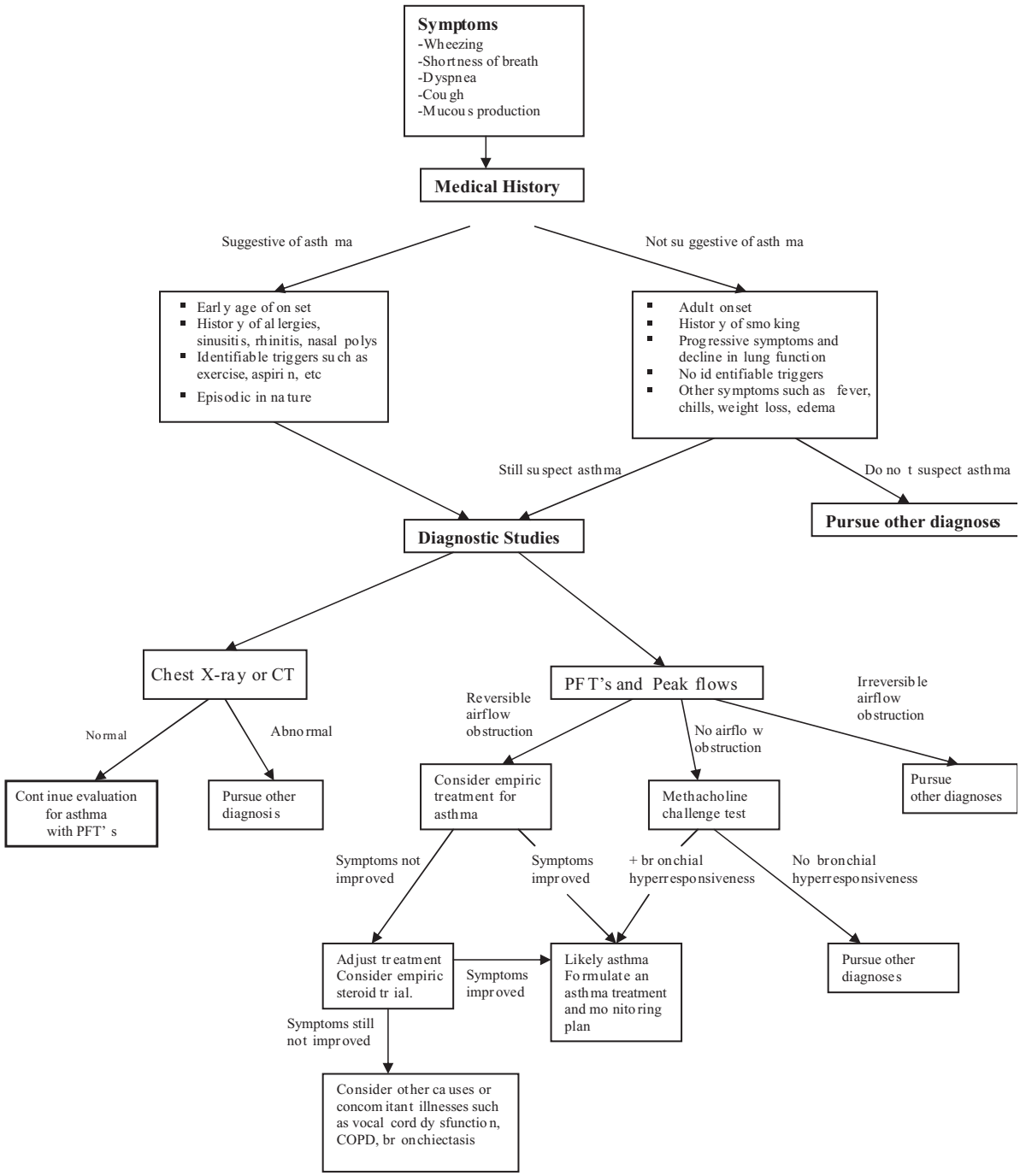

Fig. 2.3 Algorithm for asthma diagnosis

concentration that is required to decrease the FEV1 by 20%. As outlined in the Table 2.5, the degree of bronchial hyperresponsiveness depends on how much methacholine is required to cause significant bronchoconstriction. The MCT is a useful test for diagnosing asthma but the results must be interpreted in the context of all the information known about the patient. It is not 100% diagnostic.

Table 2.5 Degree of bronchial hyperreponsiveness after administration of methacholine

Methacholine challenge test	
PC20 (mg/ml)	Bronchial hyperresponsiveness
>16	Normal
4.0–16	Borderline
1.0–4.0	Mild
<1.0	Moderate to severe

From ATS AJRCCM 2000 (Crapo et al. 2000)

Although the MCT is not a foolproof test, it is helpful in trying to obtain the correct diagnosis in a patient with asthma-like symptoms. In a study of patients evaluated for dyspnea and cough who did not improve with asthma treatment, 82.5% had negative MCT (Chevalier and Schwartzstein 2001). As a result of these negative tests, bronchodilators were discontinued and other causes for dyspnea and cough were pursued and then treated. Other studies have shown that even a previous history of asthma did not reliably predict a positive MCT (Pratter et al. 1989). The MCT, therefore, is a powerful tool to help establish the diagnosis of asthma in some cases and exclude it in others, thereby allowing the patient to receive the treatment she needs.

Mimickers of Asthma

All that wheezes is not always asthma. Often times, in difficult cases, other diagnoses should be explored if the diagnosis of asthma is in question. These are usually cases in which the patient does not respond to treatment or has a physical exam or history that seems inconsistent with asthma. The mimickers of asthma can be categorized into diseases affecting the large airways, small airways, and lung parenchyma. Non-pulmonary causes should also be considered.

One of the most difficult diagnoses to make is vocal cord dysfunction (VCD). VCD can present like asthma and patients usually have a history of asthma that has not been responsive to steroids or bronchodilators. Because they continue to wheeze despite therapy, these patients can be exposed to large doses of steroids and bronchodilators putting them at risk for complications of these medications. Although the etiology of VCD is not fully elucidated, it is more common in young adults with psychiatric disorders. It occurs when the vocal cords adduct (come together in the midline) during inhalation and exhalation creating airflow limitation at the level of the vocal cords. The lungs and airways themselves, however, are normal. The patient adducts the vocal cords subconsciously and can often appear to be in respiratory distress. VCD presents with similar symptoms and signs as asthma, such as shortness of breath and wheezing. In extreme cases, however, patients with VCD can hypoventilate and be intubated for respiratory failure. Unlike asthma, however, wheezes cease after intubation because the endotracheal tube bypasses the vocal cords, the site of obstruction. After intubation, the patient with VCD is easily ventilated and can be removed from mechanical support within 24 h.

Definitive diagnosis of this disorder can be difficult and usually requires direct visualization of the vocal cords during symptomatic episodes. Physical exam during an episode usually reveals a monophonic wheeze heard loudest over the throat. Patients may have trouble vocalizing while wheezing and symptoms can come on suddenly without warning. Treatment requires intense speech therapy during which these patients learn techniques for relaxed throat breathing. With treatment, patients with VCD can come off steroids and bronchodilator therapy and live a better quality of life. In extreme cases, a tracheostomy is performed to bypass the site of recurrent obstruction.

Other problems of the large airways that can cause wheezing included foreign bodies in the large airways. Aspiration of nuts or other food products can cause foreign bodies to get trapped in a large airway. In severe cases, these foreign bodies can act as a ball-valve causing hyperinflation and eventual respiratory distress. Immediate removal of the foreign body by a trained bronchoscopist is required. Besides aspirated objects, congenital abnormalities, such as vascular rings or laryngeal webs, can cause obstruction of the trachea and lead to wheezing and shortness of breath. Other masses, such as tumors, can cause obstruction of the airways as well and with similar presenting symptoms. Lung cancer and carcinoid tumors may cause focal airway obstruction. In patients who have had prior intubations, tracheal stenosis as a late complication of endotracheal intubation can also present like asthma. A bronchoscopy to inspect the airway is usually required to make this diagnosis. Even if the airway is normal, structures outside of the airway can be abnormal and can cause compression resulting in obstruction. Lymph nodes, vascular structures, or tumor can impinge upon the large airways in this manner. Often times, a chest CT is helpful in making this diagnosis.

Sometimes the airways can be affected by other disease processes such as bronchiectasis. Bronchiectasis is a common disorder that can present with signs and symptoms similar to asthma. Patients with bronchiectasis have distorted and abnormal airways usually due to an infectious process. People can develop bronchiectasis as a sequelae of a severe necrotizing lung infection or toxic gas exposure. In necrotizing pneumonia, the abnormal airways usually are confined to the region of the lung where the original infection took place, whereas toxic gas exposure can cause more diffuse bronchiectasis. Because the airways are abnormal, it becomes more difficult to clear infections from bronchiectatic lung and recurrent infections occur. Some patients develop bronchiectasis after aspirating a foreign object that gets lodged in the airway. The object makes it difficult to clear pus, creating recurrent persistent infections and progressive damage to the airway. Other patients may develop bronchiectasis as a result of an underlying condition that makes the patient prone to lung infections and impairs the ability of the body to clear infections despite appropriate antibiotics. Such conditions include cystic fibrosis (a genetic disorder causing thick mucous plugs that are difficult clear) and immunodeficiency states. Regardless of the underlying cause for bronchiectasis, the presentation is similar with daily cough productive of purulent sputum, recurrent pulmonary infections, shortness of breath, and wheezing. The wheezing associated with bronchiectasis may be due to airflow obstruction associated with mucous plugging or distorted airways. Unlike asthma, the airflow obstruction is not completely reversible. Asthma, however, can also exist concomitantly with bronchiectasis. If a patient with wheezing has recurrent pulmonary infections or daily cough productive of purulent sputum, the diagnosis of bronchiectasis should be considered. Chest imaging can determine if the airways are distorted or abnormal to confirm the diagnosis of bronchiectasis.

Other airway diseases can also mimic asthma. In children, congenital abnormalities such bronchopulmonary dysplasia should be considered. In adults, diseases such as sarcoidosis can cause wheezing, cough, and dyspnea as well. Sarcoidosis is a disease of unclear etiology in which non-caseating granulomas affect the lymph nodes and airways. Airway or lymph node biopsy is often required to make the diagnosis. Diseases such as COPD are also common in adults and can mimic asthma as well. Occasionally, asthma and COPD can coexist.

Diseases that affect the lung parenchyma can cause wheezing, cough, and shortness of breath. Chronic eosinophilic pneumonia, in which eosinophils infiltrate the peripheral lung parenchyma, can present with wheezing and usually requires high doses of steroids to treat. Hypersensitivity pneumonitis is also a disease of the lung parenchyma, usually affecting the upper lobes and precipitated by exposure to some inhaled substance such as mold, flour, bird allergens, etc. Hypersensitivity pneumonitis can present acutely with fevers, cough, and dyspnea or less acutely with cough, wheezing, and shortness of breath. Other diseases that affect the lungs, such as pulmonary emboli or pneumonia, can also mimic asthma. Imaging, careful history, and physical exam may help to distinguish these conditions from asthma.

Processes that affect the pulmonary vasculature can also present as asthma does. As noted above pulmonary embolism can present with shortness of breath and wheezing. Although wheezing is not a common symptom of pulmonary embolism, it has been reported in the medical literature (Calvo-Romero et al. 2003). Although the etiology of wheezing in pulmonary embolism is not clear, possible mechanisms include an inflammatory reaction resulting from the embolism or the release of chemicals such as bradykinin that may lead to bronchoconstriction and wheezing. Congestive heart failure can also cause dyspnea, cough, and wheezing (often termed cardiac asthma) due to pulmonary edema. When the heart fails to pump adequately, fluid builds up in the pulmonary lymphatics and pulmonary venous capillaries, which then causes edema of the lungs and can promote wheezing.

Other conditions that may mimic asthma include reactions to medications such as angiotensin converting enzyme I inhibitors (ACE-I), which can cause chronic cough. GERD can also cause both cough and bronchoconstriction as mentioned earlier. Aspiration can cause wheezing and cough due to inflammation of the airways. In cases of GERD, the patient may be unaware of these episodes. In severe cases, if routine treatment of GERD (including proton pump inhibitors and behavioral modification) does not alleviate the problem, procedures to tighten the lower esophageal sphincter are needed to prevent reflux.

A careful history, physical exam, and clinical acumen are required to identify when a diagnosis of asthma

just doesn't seem right. Clues, such as poor response to asthma therapy, persistent instead of episodic symptoms, or constitutional symptoms (weight loss, fever, nausea/vomiting), can be useful in stimulating a search for non-asthma diagnoses. Chest imaging can be helpful in excluding diseases of the lung parenchymal, and bronchoscopic imaging may further help diagnose large airways obstruction.

Summary

We have briefly reviewed general theories of asthma pathogenesis including the TH2 hypothesis, the hygiene hypothesis, the Dutch hypothesis, and the role of infectious diseases in asthma. These theories demonstrate that asthma is a heterogeneous disease with multiple causative mechanisms in susceptible individuals. We reviewed the physiology of asthma and its relationship to symptoms such as dyspnea. We outlined a diagnostic approach to asthma based on symptoms, history and physical exam. In cases in which the asthma diagnosis is still in question, a MCT may help to support or exclude the diagnosis. Finally, an awareness of conditions that mimic asthma is important when confronted with a patient who may have atypical features or who fails to respond to therapy.

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