

## Review article

# Clinical diagnosis of wheezing in early childhood

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Wheezing is one of the most common symptoms of respiratory disease in childhood. Epidemiologic studies from various countries have shown that 10-15% of infants in the first year of life and up to 25% of children under 5 years of age present to their physician with wheezing respiratory illness (40, 67). The majority of infants and young children with recurrent wheezy, lower respiratory tract symptoms are very likely to have asthma, regardless of age of onset, evidence of atopic disease, precipitating causes, or frequency of wheezing (71). Since asthma in infancy can be confused with various other conditions which produce similar signs and symptoms, and physiologic changes, the initial evaluation of a wheezing infant should aim at the exclusion of alternative diagnoses.

## Differential diagnosis

There is a wide variety of congenital and acquired conditions which result in narrowing of the intrathoracic airway and which present with cough and wheeze (Table 1). The differential diagnoses of alternative diseases which present with wheezing can be established by clinical history, physical examination, laboratory investigations, and response to treatment (27).

### Clinical history

A different set of diagnoses should be considered when obstructive symptoms present in the neonatal

Table 1. Congenital and acquired conditions associated with wheeze cough in infants and young children

Common	Uncommon	Rare
"Asthma syndrome"	Bronchopulmonary dysplasia	Congestive heart failure
Infections Bronchitis Pertussis Tuberculosis	Foreign body in trachea, bronchus, or esophagus	Congenital vascular anomalies
Recurrent inhalation-aspiration	Cystic fibrosis	Mediastinal masses Bronchitis obliterans Immune deficiency diseases Tracheobronchial anomalies

Modified from Reisman et al. (55).

period, when underlying congenital abnormality should be strongly suspected. Prematurity, particularly if associated with the need for mechanical ventilatory support and frequent suctioning, may lead to tracheal or bronchial stenosis secondary to granulation tissue scarring or the development of bronchopulmonary dysplasia (BPD). Previous surgery for a tracheoesophageal fistula suggests tracheomalacia, gastroesophageal reflux (GER), and recurrent fistula as possible causes of wheezing. Recurrent choking or coughing associated with difficulties of sucking and swallowing should suggest pulmonary complications of inhalation. Vomiting and regurgitation may be the initial symptoms in the patient with esophageal malfunction, i.e., GER, which may also present with the sudden onset of choking/coughing characteristic of foreign-body aspiration.

The age of the patient at the onset of symptoms, i.e., less than 18–24 months, and the season of the year at presentation, i.e., winter or spring, should suggest viral bronchiolitis as the cause of the wheezing (26).

### Physical examination

The physical examination of an infant with respiratory distress should first distinguish between lower airway obstructive disease, which classically presents with wheezing and emphysema, and disorders primarily involving the upper airways, which usually present with inspiratory stridor (62). The pediatrician should next determine whether wheezes are unilateral or symmetric, monophonic or polyphonic,

whether they are associated with crackles or with brassy-sounding cough, and whether the child seems to be chronically ill (55). This will be helpful in differentiating localized from diffuse obstruction, and pneumonia from upper airway obstruction, and will also help in assessing the possibility of chronic lung diseases.

The associated symptoms and signs in the wheezy infant that are helpful in differential diagnosis are outlined in Table 2.

### Laboratory investigation

There are few laboratory investigations that are useful in the initial evaluation of the wheezy infant. Routine *serologic tests* may help to evaluate the eventual presence of an active infectious process, i.e., specific antimicrobial assays, or an immune deficiency state, i.e., serum immunoglobulin quantitation, or may be indicative of an allergic disease, i.e., serum IgE or eosinophilia. Although food allergens may occasionally be associated with wheezing, inhaled allergens appear to be unimportant precipitants of wheezing in infancy. An increased prevalence of IgE antibody to inhaled allergens is evident in wheezing patients after the age of 2 years, and a significant association between wheezing and sensitization is generally observed after the age of 4 years (18).

Pertussis may often be mistaken for asthma in this age group: a careful consideration of this possibility should include an assessment of lymphocytosis and appropriate cultures of nasopharyngeal and respiratory secretions in the early stage of the disease. Since cultures and fluorescent antibody tests are almost always negative after 4–5 weeks of symptoms, the enzyme-linked immunosorbent assay for detection of antibody to pertussis toxin or filamentous hemagglutinin should be performed for diagnosis.

Two important and sometimes overlooked diagnostic procedures in infants with recurrent chronic respiratory symptoms are the *tuberculin test* (5-TU) and the *sweat chloride test* since wheezing may be the initial presenting symptom of both pulmonary tuberculosis (4) and cystic fibrosis (30).

Methods for measuring *pulmonary function in infants* have been developed in the past decade: flow-volume curves in infants can be generated and obstruction to airflow assessed by the rapid chest compression technique (42). Forced expiration is induced at end-tidal inspiration by rapidly inflating a thoraco-abdominal jacket. Flow and volume are measured by a face mask and pneumotachometer. The flow on forced expiration at the volume of resting functional residual capacity is called  $V_{max}$  FRC. Infants without asthma have a linear or convex expiratory curve, as do normal older children. In lower airway ob-

Table 2. Clinical features in wheezing infant that are helpful in differential diagnosis

Clinical features	Diseases associated with wheezing
1) Episodic recurrent illness Environmental trigger Viral upper respiratory infection Responsive to treatment	"Asthma syndrome"
2) First episode during epidemic (November–April) Under 24 months age Low grade fever Rhinorrhea	Bronchiolitis
3) Active disease in family member or community	Pertussis Tuberculosis
4) Associated with feeding Fatigue, apnea, tachypnea Swallowing dysfunction Regurgitation, vomiting	Recurrent inhalation Gastroesophageal reflux (GER)
5) Prematurity Mechanical ventilation Prolonged oxygen therapy	Bronchopulmonary dysplasia (BPD)
6) Sudden onset of cough choking in previously healthy infant Unilateral signs	Foreign-body inhalation
7) Steatorrhea	Cystic fibrosis
8) Failure to thrive	Cystic fibrosis Bronchopulmonary dysplasia Tracheoesophageal fistula
9) Positional changes Concomitant stridor	Anomalies of great vessels: tracheomalacia
10) Heart murmurs Cardiomegaly	Cardiac disease
11) Symptoms presenting in neonatal period	Malformations
12) Cervical or other lymphadenopathy Manifestation of systemic disease	Mediastinal and pulmonary masses
13) Chronic severe symptoms after bronchiolitis	Bronchiolitis obliterans
14) Chronic infections Failure to thrive	Immunodeficiency

Characteristic features of various potential disorders may be absent and yield no clues to what is occurring in individual patient.

struction, the curves become concave and  $\dot{V}_{\max}$ , FRC decreases. Moreover, as in older children with asthma response, bronchodilator and bronchoconstrictor stimuli can be assessed (42). Besides reversible airway obstruction, other information can be obtained by the flow-volume loop. A flattened inspiratory phase suggests an airway obstruction localized above the vocal cords – laryngomalacia, for example – while flattening of the expiratory limb is characteristic of intrathoracic airway obstruction as in tracheomalacia (3).

Other ways to assess the severity of infant respiratory disease and the efficacy of bronchodilator therapy are resistance measurements and evaluation of functional residual capacity by body plethysmography or gas dilution. This last technique can be used to evaluate gas mixing, which is a sensitive indicator of obstructive lung disease in infants, children, and adults. Useful information can be obtained by monitoring the respiratory rate during quiet sleep by capnography or measuring nasal thermal changes, and by measuring chest wall motion by respiratory inductance plethysmography. The quantitation of the tidal expiratory flow pattern as the ratio of the time to peak tidal expiratory flow ( $T_{me}$ ) divided by the expiratory time ( $T_e$ ).  $T_{me}/T_e$  may show low values in obstructive lung disease and abnormally shaped tidal expiratory flow-time curves (1).

In infants with recurrent or persistent wheezing who have not had previous *radiologic investigation*, a posterior and lateral chest radiograph is strongly indicated to exclude parenchymal lung disease, as well as congenital anomalies of the lung, cardiac diseases, and foreign bodies (76). The barium swallow procedure with careful observation of swallowing is indicated if the plain chest radiograph is inconclusive and there remains a suspicion of recurrent inhalation or anatomic abnormalities. Persistent wheezing which is unresponsive or poorly responsive to appropriate treatment should be investigated by *fiber-optic or rigid bronchoscopy* (88, 89). The now standard pediatric flexible bronchoscope is 3.5 mm in diameter with a 1.2-mm internal suction channel. Although it is quite possible to perform flexible bronchoscopy with this instrument in small infants, including premature infants, the added airway resistance limits the duration of the procedure to rather short times. Very thin flexible bronchoscopes (1.8 and 2.3 mm in diameter, and 2.7 mm in diameter with distal angulation) appear to be a significant new clinical tool for observation of airway dynamics with relatively little mechanical interference also if inserted through existing endotracheal or tracheostomy tubes (88). Diagnostic flexible bronchoscopy is indicated in specific conditions such as stridor, persistent atelectasis, wheezing, recurrent pulmonary infiltrates, lung lesions of unknown cause,

chronic cough, and hemoptysis, and to assess injury from toxic or milk inhalation. The 3–5-mm-diameter instrument can be used to obtain samples or aspiration of airway secretions and mucous plugs (88). The rigid bronchoscope is more suitable for the removal of foreign bodies, excision of granulation tissue, and examination of tracheoesophageal fistulas (89).

#### *Response to treatment*

The final diagnostic criterion is a trial of appropriate asthma therapy (16). Nevertheless, there remains much controversy about the use of  $\beta_2$  adrenergic agents in wheezing infants (35, 60). However, it has been observed that the failure of some studies to demonstrate beneficial response may be due to a number of potential methodologic problems. These include the use of sedation, the study of patients in the recovery phase of the disease when bronchospasm may not be the prominent component of the bronchoconstriction, and finally the assessment of airway responsiveness with parameters unlikely to be sufficiently sensitive to detect bronchodilation (6). Recent studies of infants with acute asthma have shown that the administration of nebulized  $\beta_2$  agonists results in improved clinical score in the majority of patients studied (5, 6). Furthermore, in infants with persistent symptoms, trial of an inhaled steroid is indicated. Both budesonide (8) and beclomethasone dipropionate (22) administered by aerosol and mask resulted in significant clinical improvement, less concomitant medication use, and fewer admissions to hospital in children aged, respectively, 11–36 and 12–26 months. The combination of inhaled  $\beta_2$  agonist and inhaled steroid has been shown to be effective for acute wheezing in children up to 18 months of age (16). Data on sodium cromoglycate in this age group are limited (25).

### **Specific conditions**

#### *Bronchiolitis and other viral infections*

Viral lower respiratory tract infections are the commonest cause of wheezing in infants. The airway caliber in infants is small; therefore, mucosal edema following viral infection is relatively more constricting than in older children and more prone to cause wheezing. Improved viral isolation techniques from aspiration of nasal secretion and the application of immunofluorescence or polymerase chain reaction technology have suggested an age-dependent relationship between wheezing and viral infections: respiratory syncytial virus (RSV) and coronavirus are isolated more frequently in association with wheezing in younger children, influenza A and adenovirus in older children, and rhinovirus in children of all ages. Bronchiolitis is a primary clinical disorder,

being the first episode of acute wheezing in a child less than 2 years of age. Hyperinflation, bronchial wall thickening, and areas of collapse-consolidation are the most frequently observed radiographic abnormalities (50). In the very rare patients who do not improve and who have persistent radiographic abnormalities, obliterative bronchiolitis should be suspected and confirmed by bronchography, ventilation-perfusion scans, high-resolution computed tomography (7), and, occasionally, lung biopsy (50).

It has been suggested that viral infections may promote or increase the chance of atopic sensitization (10). Welliver et al. showed that 70–80% of patients responded to RSV with IgE bound to exfoliated nasopharyngeal epithelial cells in the first 2 days after infection, but only those with persistent IgE developed clinical bronchiolitis (78). They found higher levels of anti-RSV IgE in the nasal secretions of patients with wheezing illness compared with illness without wheezing during both acute and convalescent stages of viral infection (80). Recurrent episodes of wheezing were observed almost exclusively in infants with the highest nasal IgE response (79). However, it is premature to conclude that virus-specific IgE is causal in this process. It is also possible that an immunologic deficiency, such as low levels of IgG1 and IgG2, predisposes some infants to the development of a more severe infection of RSV and to full clinical expression of bronchiolitis (12). This has also been shown to be strongly associated with passive smoking: hospital admission for infants with bronchiolitis is more frequent if the mother smokes (56).

There is also very little epidemiologic support for the suggestion that viruses can potentiate sensitization to other allergens (23). In a prospective study on the development of allergic diseases in children born with at least one atopic parent, respiratory tract infections were less common in the first year of life of those children who developed atopic symptoms (14). A lower prevalence of asthma and atopy was observed in children living in the former East Germany, where they were exposed early to day-care settings and consequently to viral infections compared with children living in the former West Germany (74). In this country, an inverse relationship between sibship size and the prevalence of one or more positive skin-prick tests to common aeroallergens has been reported (75). Moreover, the prevalence of hay fever and eczema throughout childhood is greater in the firstborn child than in younger siblings: the more older siblings present in the family, the less the probability of an atopic diagnosis (68). The most logical explanation of these observations is that infections acquired by household contact in early life protect against the subsequent development of atopic symptoms (69).

Recent studies of the differentiation of the TH1 and TH2 lymphocyte populations suggest that infections appear to activate mainly the TH1 subset of T-helper cells, preventing the proliferation of TH2 cell populations which promote B-cell IgE production (54). The suggestion that severe viral infections may damage the airways, making them more likely to develop asthma (33, 38), has not been definitely shown in children not otherwise predisposed to develop the disease (32, 33).

#### *Inhalation syndromes*

Inhalation or aspiration of foreign substances, i.e., food or exogenous materials (see below), is an important and frequently unrecognized cause of recurrent wheezing in young children, and many of these patients may be considered to have difficult-to-control "asthma" (53).

Disordered sucking and swallowing, esophageal malfunction with regurgitation into the pharynx, and abnormal communication between the airways and alimentary tract are common causes of recurrent inhalation of milk, other gastric contents, and food-stuff. The presence of lower respiratory tract symptoms in patients with a predisposing condition should arouse the suspicion of inhalation-induced disease. The first diagnostic step is to observe the child during feeding for difficulty with sucking or swallowing, the appearance of fatigue or loss of interest in feeding after the first few ounces, tachypnea, or apnea (29). The classic finding of coughing with feeding may be absent owing to depression of the cough reflex from repeated stimulation of the sensitive receptors in the larynx and trachea. Furthermore, if the amount of milk or food inhaled is small, it may be difficult to associate the respiratory symptoms with feeding.

If the history and physical examination are suggestive, a chest radiograph should be performed. Findings vary from infiltrates in dependent areas such as the right upper lobe in infants who inhale in the supine position, and the lower lobes in older children who usually inhale in the upright position. Although there is often hyperinflation, the chest radiograph may be completely normal. The next diagnostic step is the barium esophagogram, which allows evaluation of the swallowing mechanism and direct visualization of any aspiration of radiocontrast medium into the trachea. However, this is an insensitive diagnostic test for GER. Continuous pH monitoring of the lower esophagus, esophagoscopy, and esophageal biopsy are the best diagnostic procedures in this case (49). Radionuclide scintigraphy (milk scan) offers a physiologic approach and allows detection of both GER and aspiration. A long recording time considerably increases the sensitivity

of the method with no further radiation exposure (41, 72). Although qualitative assessment of the presence of lipid-laden macrophages in bronchial washing may be a helpful nonspecific finding, quantitation of these cells has been claimed to be a better test for the diagnosis of recurrent aspiration of milk in children (15).

#### *Foreign-body inhalation*

A history of sudden onset of symptoms in a previously healthy child, wheezing in localized areas of the lung fields, and evidence of collapse or unilateral hyperinflation with mediastinal shift, are suggestive features (31). Usually the diagnosis is made within 1–7 days because the ingestion is often witnessed by the parents or carers in most infants (52). However, a delay in diagnosis may occur due to unobserved aspiration, or failure to appreciate the importance of symptoms by the parents or, less frequently, by the physician (83). Foreign bodies are more frequently swallowed than inhaled (52). In the esophagus, they most frequently cause dysphagia but may also cause wheezing and cough owing to tracheal compression. The radiologic investigation should include the region from the mouth to below the diaphragm. A negative radiologic investigation does not exclude a foreign body, and if the clinical features suggest this possibility, bronchoscopy should be performed.

#### *Bronchopulmonary dysplasia (BPD)*

BPD is defined as a respiratory disorder after acute neonatal injury with incomplete recovery as determined by significant clinical, radiologic, and blood gas abnormalities (arterial oxygen pressure < 60 mmHg in room air) beyond 28 days of postnatal age (48). Although the cause is not known with certainty, the condition is most commonly seen in premature infants who require assisted ventilation and oxygen therapy. Improvement of lung function usually occurs during the first year of life. However, recurrent wheezing and respiratory difficulties may persist into early childhood and may be aggravated by the bronchial hyperreactivity and GER which are commonly seen in these patients. The radiographic manifestations of the disease include patchy areas of atelectasis, hyperinflation, and fibrosis (47). The "bubbly" appearance with diffuse streaks of infiltrate and widespread cystic change in the lung may suggest Wilson-Mikity syndrome.

#### *Cystic fibrosis (CF)*

Recently, newborn-screening programs have been introduced which allow the diagnosis of CF shortly after birth before the onset of clinical symptoms. The

immunoreactive trypsin assay (IRT) is a major advance, providing a laboratory diagnostic procedure with 99% sensitivity and a false-positive rate of only 0.2–0.5% (81). If undiagnosed at birth, because of parental reluctance to participate in widespread neonatal screening programs, most children may present in the first year of life with the onset of recurrent respiratory symptoms and failure to thrive. It was found that 25% of such infants have recurrent or persistent wheezing owing to diffuse small airway disease (30). Therefore, wheezing appears to be more common among infants with CF than among the normal population. Thus, a sweat chloride test should be performed both in the newborn infant with positive IRT as a confirmatory test as well as in any infant with recurrent wheezing whether or not symptoms of malabsorption are present.

#### *Cardiovascular anomalies*

Cardiac conditions with large left to right cardiovascular shunts can result in a distended pulmonary artery and/or enlarged left atrium which may compress large airways and cause wheezing (44). Moreover, the distension of the pulmonary vascular bed as a consequence of left ventricular failure or obstructed pulmonary veins may result in bronchiolar wall edema with increased peripheral resistance and wheezing. Clinical and radiologic evidence of cardiac disease should be pursued with further investigations including electrocardiography, echocardiography, and angiography. Those responsible for such infants should have a high index of suspicion because obstructed pulmonary venous return may be present in the absence of cardiac murmurs and cardiomegaly (55).

Vascular rings are another rare cause of tracheal and/or esophageal compression in infants and children (Table 1). In most patients, this malformation appears early in life, and respiratory symptoms are more common than evidence of esophageal obstruction. Stridor is the most common symptom in these patients, but wheezing, respiratory distress, recurrent respiratory infections, or reflex apnea may also be present. In order to maintain a certain degree of tracheal patency, these infants tend to lie with their necks hyperextended. Neck flexion may reproduce symptoms and is usually resisted by the child since it aggravates the obstruction. The diagnostic approach to such infants includes chest roentgenography followed by barium swallow study, which usually provides sufficient information to predict whether left or right thoracotomy is indicated (73). Although invasive angiography may delineate vascular detail, noninvasive techniques such as Doppler and color-flow imaging (9), as well as fast computed tomography and magnetic resonance imaging (17), are

well suited to demonstrate the tracheoesophageal anatomy in addition to the presence of a vascular ring.

#### *Mediastinal masses*

Mediastinal masses such as tumors, thymic lesions, bronchogenic and enterogenic cysts, angiomatous lesions, and enlarged lymph nodes causing tracheal or bronchial compression may present with cough and persistent wheeze. The onset of symptoms may be gradual or acute, associated with manifestations of systemic disease and cervical or superclavicular lymphadenopathy. As many as one-third of all mediastinal masses are asymptomatic and are discovered incidentally (20). Although a chest radiograph will usually reveal the mass, some bronchogenic cysts often may not be visible on plain radiographs, which will usually display unilateral hyperinflation, leading to confusion with congenital lobar emphysema. In this case, the failure to make the correct diagnosis may lead to an unnecessary resection of normal lung tissue (19). The appropriate investigation in such cases is the barium swallow study, which localizes the mass according to pressure effects on esophageal contour. Computed tomography may also be helpful in distinguishing solid from cystic lesions, and magnetic resonance imaging may provide additional specific diagnostic detail in the delineation of the content of the cystic lesion and the location of the mass in relation to other anatomic structures. Ultrasound may be useful in detecting motion or pulsation of a vascular anomaly (13). Bronchoscopy may be helpful in locating the site of airway compression (76, 88). As described previously, in the assessment of mediastinal adenopathy, tuberculin skin testing is mandatory, as well as the evaluation of urinary excretion of vanillylmandelic acid (VMA) for diagnosis of neurogenic tumors.

#### *Anomalies of the tracheobronchial tree*

Anomalies of the tracheobronchial tree may cause respiratory distress, life-threatening apneic spells, recurrent pneumonia, cough, dyspnea, cyanosis, and wheezing (37). In general, symptoms are increased by activity and intercurrent infection. Inspiratory stridor is the main symptom of laryngeal obstruction, which is occasionally characterized also by inspiratory and expiratory wheezing. Harsh, brassy-sounding cough, inspiratory and expiratory wheezing, and apneic spells are most prominent in tracheal obstruction. Inspiratory and prolonged expiratory wheeze, expectoration of mucopus, and variable degrees of breathlessness associated with focal hyperinflation or collapse of the lung are typical of bronchial problems. Tracheal and bronchial anomalies

include agenesis, atresia, webs, intrinsic stenosis, or external compression by mediastinal masses, anomalous vessels, or tracheoesophageal fistulas (37). The tracheobronchial tree may be abnormally compliant due to a deficiency of the cartilage support of the trachea (tracheomalacia) or bronchi (bronchomalacia, congenital lobar emphysema). This condition may be localized in one segment or generalized, primary or secondary to compression or infection (11, 82).

Any abnormal primary disease of the tracheobronchial tree, with abnormal compliance, should be considered in the differential diagnosis only after external compression and localized causes of airway obstruction have been excluded. These diagnoses may be difficult on plain chest film since some degree of dynamic collapse of the trachea occurs normally during crying episodes and normal expiration (46). The barium swallow study may be the next step, but, usually, laryngobronchoscopy is necessary for proper diagnosis. Again, the tracheal collapse may be missed if rigid ventilating bronchoscopy examination is performed while the patient is under general anesthesia and no spontaneous inspirations can be visualized. Performance of flexible fiber-optic bronchoscopy in infants who are spontaneously breathing and sedated can be more informative in this situation. The trachea and the bronchi may be seen to collapse during expiration, or a pulsatile compressing vessel can be identified. In addition, intraluminal anomalies will be identified with this procedure. Bronchoscopy, however, may be hazardous in infants with congenital lobar emphysema because anesthesia may cause further air trapping in the affected lobe with consequent impairment of the already limited respiratory function. However, the typical radiologic finding and the exclusion of bronchogenic cyst will allow precise diagnosis.

#### **And when it is asthma, can we still use the label "asthma"? What is going to change in the next few years?**

In infants and toddlers, asthma is likely to be a heterogeneous group of conditions which share the clinical findings of wheezing and respiratory distress and some common risk factors such as exposure to passive smoking, difficult living conditions, and increased risk for boys (43).

In the past, terms such as "wheezy bronchitis", "asthmatoïd bronchitis", and "spastic bronchitis" have been used to describe wheezing in the very young. The term "asthma" was avoided because episodic wheeze triggered by a viral infection in early childhood had a more benign prognosis than the disease in older children precipitated by a number of other factors in addition to viral infection (24, 59).

The label "asthma" was used mainly in older children when aeroallergen responsiveness had begun. This distinction was later found to be associated with both underdiagnosis of asthma and its inappropriate treatment with antibiotics (2, 34, 63). Consequently, pediatric pulmonologists suggested that all wheezing in infancy and early childhood should be labeled asthma (71). This resulted in more appropriate treatment with bronchodilators and anti-inflammatory agents and in reduced morbidity, but also, as stated by Wilson, in "a loss of pathophysiological precision which may have implications that are not purely academic" (84).

Although wheezing lower respiratory tract illness in early childhood and asthma share some common risk factors, sufficient data exist to show that their relative importance differs between each condition (61, 64, 85). Several indices of neonatal lung function are reduced in infants who subsequently develop episodes of wheezing associated with viral infection (39, 70). Evidence does not link wheezing in the first 2 years of life with atopy (28). In contrast, most schoolchildren with asthma are atopic, and the severity of the disease in this age group is clearly related to the degree of atopic sensitization (90). Wheezy infants have been shown to have a level of airway responsiveness which is the same in young infants (66) or decreased in 3-year-olds (86) compared with controls. Instead, atopy and increased bronchial hyperresponsiveness are two markers often found to be associated with asthma at school age and beyond (57, 58). Furthermore, the pattern of wheeze is episodic with prolonged symptom-free periods in early life and both episodic and intercurrent symptoms in atopic schoolchild asthma (61, 85). Moreover, the medium-term prognosis of the episodic viral wheeze of the first 2 years of life is excellent in the vast majority of subjects since very few of them develop childhood asthma (21, 51, 65). As Silverman reported, "the differences between viral induced wheezing of early childhood and atopic schoolchild asthma are so striking that one can only conclude that the two disorders are totally independent" (61). Thus, the disorder of many recurrently wheezing infants and toddlers could be labeled "wheezy bronchitis" rather than "asthma" (36, 61, 64, 84, 85). However, "wheezy bronchitis" is more a description of symptoms than a diagnosis, and probably we should use the term "asthma syndrome" until the pathophysiology of the disorder has been fully clarified in all the pediatric ages. Because asthma is an underdiagnosed problem, it could be dangerous to avoid the term "asthma" and the word "syndrome" can be used to describe the set of symptoms and signs which occur together in wheezing children.

The acquisition of more precise information will

be made possible in the near future by the development of new techniques in the evaluation of pulmonary function, not only in infants but also in children of preschool age. The full potential of this investigational tool is still unrealized because of the lack of standardized methods and reference values obtained from sufficient numbers of subjects. A number of problems must be resolved in the coming years before measurements of pulmonary function in infants can be recommended for wide clinical use in healthy and sick infants. The potential sources of variation in the measurements need to be characterized and limited in order to obtain reproducible results, which, we must remember, are difficult to interpret and can be obtained with a certain degree of reliability only after substantial training with the different techniques. For this reason, we must develop training programs in infant lung function testing, at least for simple noninvasive methods which could be used as an objective epidemiologic tool.

The advances occurring in cellular and molecular biology, together with the development of skills in "spelunking in the pediatric airways" (87), by means of the flexible fiber-optic bronchoscope, will allow detailed evaluation of the anatomy and physiology of the airways with relatively little mechanical interference.

## Conclusion

Asthma has recently been defined as "a chronic inflammatory disorder of the airways in which many cells play a role, in particular mast cells and eosinophils. In susceptible individuals, this inflammation causes symptoms which are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment, and causes an associated increase in airway responsiveness to a variety of stimuli" (45). Because of the scanty information concerning the pathology of asthma in pediatric patients, the concept of eosinophil-mediated airway inflammation was not incorporated in the definition of asthma recently elaborated by an international committee of pediatric pulmonologists (77). Therefore, pediatricians are still using a vague definition of the disorder (76). Now we are again in the middle of a debate between two distinct schools of thought: whether wheezing in infancy and wheezing in later childhood are distinct clinical entities of distinct etiology, or whether they are caused by a common underlying defect. Although recent studies (61, 64, 84, 85) support the first thesis, information concerning the pathophysiologic characteristics of the two conditions is limited. This is true not only of wheezing in infants but also in school-age asthmatic children. The distinction between the episodic viral wheeze (wheezy bronchitis)

and the atopic wheeze (asthma) will allow a better definition of the anatomy and the physiology of the airways in the two conditions but will carry the risk of undertreatment, as previously observed (2, 63). Until more information is generated, the term "asthma syndrome" could be used to label both viral- and allergen-induced asthma in children. However, a wide range of congenital and acquired disorders associated with wheezing (Table 1) should be excluded by clinical history, physical examination, and laboratory tests. The erroneous inclusion of all wheezing within the "asthma syndrome" will be a dramatic backward step for both the generation of scientific knowledge and the application of appropriate treatment.

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