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Special Features of Asthma in Children*

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The prevalence of asthma and chronic bronchitis in children younger than 17 years averages approximately 9 percent in the United States, Australia, and Great Britain. Several surveys suggest that the prevalence of these disorders is higher in children less than 12 years of age than in older teenagers, and that boys are more often affected than girls[1-6] (Table 1). The differences in reported prevalence are due to variations in the definition of these common diseases and the methods used to collect the information (questionnaires, interviews, diagnosis confirmed by physicians, retrospective vs prospective studies, census tract surveys, or private practice data).

Despite considerable advances in our understanding of the pathophysiology and treatment of reactive airway diseases (asthma, bronchiolitis, acute and chronic bronchitis), they continue to cause considerable morbidity. According to the most recent information for the United States, reactive airway diseases caused 388,000 hospitalizations in children under 15 years of age in 1982, with an average length of stay of 3.9 days.[6] If we assume a *per diem* cost of hospitalization of $350, this amounts to an annual expenditure of approximately $530,000,000 for hospitalizations alone. In addition, there were 10,677,000 physician office visits for reactive airway disease in children less than 15 years old; at a charge of $20 per visit, this would add another $200,000,000 in costs for outpatient care, so that the total treatment expenditures amounted to approximately $750,000,000 for 1982. Asthma accounted for about half of the hospital admissions and 40 percent of office visits. In our Children's Hospital, asthma was responsible for 2 percent of all and 17 percent of respiratory disease-related admissions during the period of 1980 to 1983. These statistics indicate that reactive airway diseases remain a major and costly health care problem in the pediatric age group. It is hoped that the application of enlightened and anticipatory care, health education, and appropriate self-management practices will reduce hospitalizations and office visits, lessen the cost of comprehensive care, and improve the lives of these children.

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Natural History of Childhood Asthma

Several longitudinal studies of the natural history of asthma in childhood have shown that the disease starts during the first year of life in at least 30 percent of pediatric patients, in over 50 percent before 2 years of age, and in about 80 percent by the time they reach school age.[9] There is no evidence that early onset of the disease is associated with an unfavorable prognosis.[9,10] The general severity of asthma plays, however, an important role in the eventual outcome. When asthmatic children are followed up until young adulthood, it appears that most improve as they get older.[1,7,10,11] Patients who are mildly affected in early childhood have a better than 50 percent chance to go into long-term remission (>three years) between 14 and 21 years of age; the likelihood of getting worse is less than 5 percent. The remaining youngsters who started out with mild asthma will continue to have intermittent problems. When the disease is severe at 14, the chances of going into a long-term remission are poor (<5 percent); nevertheless, approximately half of these patients will improve as they get older, but they will remain active asthmatic patients, and a few will even get worse. In a prospective study of 331 7-year-olds with wheezing before the age of 7 years, two thirds were still symptomatic at 21.[11] Others have observed a more favorable prognosis,[12] but it is quite clear that the optimistic notion that "most children outgrow their asthma" is not true. Table 2 summarizes the general trends which can be expected in childhood asthma. Carefully analyzed, prospective surveys have demonstrated that childhood asthma is associated with a high incidence of hay fever, eczema, positive skin tests, and

Table 1—*Cumulative Prevalence of Asthma and Bronchitis in Children in the United States, Australia and Great Britain (1962–81)**

Source	Year of Survey	Year of Publication	Country	Age Group, yr	Prevalence, % Boys	Girls	Av	Males:Females
Border et al[1]	1959–60	1962	USA	6–9	15.1	13.7	14.4	1.10:1.0
				10–14	14.4	9.7	12.1	1.48:1.0
				15–19	8.7	7.0	7.8	1.24:1.0
				6–19	12.7	10.1	11.4	1.26:1.0
Gibson[2]		1966	Australia	Primary school			7.9	
Williams and McNicol[3]		1969	Australia	<10			11	1.5 :1.0
NCHS[4]	1970	1973	USA	<17	8.1	5.8	7.0	1.47:1.0
Lebowitz et al[5]	1970	1975	USA	<15	13.5	15.0	13	1.07:1.0
Blair[6]	1970–73	1974	Great Britain	5–15			8	
				0–20			6	
Peat et al	1971–76	1980	Australia	13.9	11.5	6.1	9	1.9 :1.0
				17	3.7	2.2	3	1.7 :1.0
NCHS[6]	1980–81	Unpublished	USA	<17			7.0	
				<17			7.6	

*NCHS = National Center for Health Statistics.

Table 2—*General Long-term Course of Childhood Asthma*

Initial Status	Gradual Improvement	Likelihood of Intermittent Activity	Likelihood of Long-term Remission	Chance to Get Worse
Mild	yes	40%–50%	50%–60%	~5%
Severe	yes	95%	<5%	~5%

elevated IgE levels, the highest incidence occurring in the most severely affected youngsters.[6,13]

A number of factors influence the development and persistence of asthma in childhood (Table 3). We have already discussed the role of severity of childhood asthma on its persistence into adulthood (Table 1). Heredity is another important determinant of whether reactive airway disease will develop. There is a 50 percent chance of asthma in the offsprings when both parents and a 25 percent chance when only one parent has asthma. When 1 identical twin has asthma, the other does not always develop the disease; however, the incidence of asthma is 4 to 5 times greater in identical than in dizygotic twins.[12]

Several childhood illnesses predispose to the development of asthma. They include bronchopulmonary dysplasia, bronchiolitis, croup, cystic fibrosis, and possibly surgical repairs of pyloric stenosis and hernias. The incidence of reactive airway diseases, Eustachian tube dysfunction, and recurrent ear infections is high in prematurely born infants with bronchopulmonary dysplasia. In our experience, over 50 percent of these infants develop chronic reactive airway disease. Five to 50 percent of infants who have bronchiolitis during the first few months of life develop asthma;[14] the fraction approximates 40 to 50 percent in those who have indications of or a family history of atopy.[15,16] In a recently published study, 75 percent of infants with bronchiolitis developed wheezing during a 2-year follow-up, and 60 percent had hyperinflation on pulmonary function tests.[17] It has also been shown that children with recurrent croup have heightened upper and lower airway reactivity, indicating that they are at risk to develop asthma.[18]

Children with cystic fibrosis and significant pulmonary involvement frequently develop abnormal airway reactivity[19] and asthma-like signs and symptoms. As long as there is little evidence of chronic obstructive pulmonary disease (FEV_1 >80 percent of predicted values), there is no consistent increase in airway sensitivity to inhaled methacholine. When there is mild airway obstruction, approximately 40 percent of the patients demonstrate mildly increased airway responsiveness, and when the FEV_1 is less than 40 percent of predicted values, over 80 percent of patients show excessive airway sensitivity to inhaled bronchoconstrictors. It is possible that other forms of chronic airway disease and acute lung injury may also predispose children to the development of asthma.

Table 3—*Factors Influencing Development and Course of Asthma in Childhood*

- Severity of asthma (see Table 2)
- Heredity
- Other diseases
  - Bronchopulmonary dysplasia
  - Bronchiolitis
  - Croup
  - Cystic fibrosis
  - Surgical repair of pyloric stenosis or hernias during infancy (?)
- Environment
  - Antigenic exposure
  - Socioeconomic factors
  - Smoke
- Breast feeding
- Premenstrual period and pregnancy
- Medications
- Airway reactivity

There is some evidence that surgical repairs of pyloric stenosis or inguinal hernias during infancy increase the chances for the development of asthma or allergic rhinitis. Johnstone et al[20] noted that infants who underwent such surgical procedures had a 5 to 10 times greater chance of developing asthma and a 2.5 times greater chance of getting allergic rhinitis than control subjects. The incidence for either respiratory problem to develop was 36 percent following pyloric stenosis repair and 55 percent following herniorrhaphy, compared to 10.6 percent in infants who did not have either surgery. The reason for this high incidence of asthma following abdominal surgery in infancy is not clear; however, when we consider that these babies were intubated, just as those with bronchopulmonary dysplasia, I wonder whether upper airway injury secondary to intubation was the common precursor which caused the respiratory tract to become hyperreactive.

Environmental factors have an important influence on the incidence of asthma. Early, repeated and intense exposures to airborne antigens increase the risk of airway sensitization. Some allergens are more asthmagenic than others, and animal danders, molds, and house dust appear particularly likely to sensitize the airways. While food allergies can produce gastrointestinal and dermatologic problems in children, they rarely cause asthma. When food is implicated in the pathogenesis of asthma, it usually produces problems during the first year, and asthma is then often associated with eczema. Asthma is very rare in the children of primitive tribes of Western Africa.[21] It has been postulated that this is due to the endemic presence of intestinal parasitic infections causing high levels of IgE, thus preventing these people from developing IgE antibodies to airborne allergens. When they move to urban environments, and when their intestinal infestations are brought under control, the incidence of asthma becomes that of the nonindigenous population. There is no consistent evidence that socioeconomic environments influence the development of reactive airway diseases,[5] although once asthma is present, crowded living conditions favor the spread of viral respiratory tract diseases which, in turn, are major triggers of acute reversible airway obstruction. There are no indications that emotional maladjustments cause asthma, although they may act as triggers. Exposure to smoke can activate latent airway disease,[22] and there is a dose-dependent relation between parental smoking and wheezing in children.[23]

Breast feeding during the first few months of life may

lessen the risk of asthma in later life;[9,24] it must be admitted, however, that the information on this point is inconclusive at this time.[13] During the premenstrual period and pregnancy, chronic asthma may temporarily get worse in teenage girls. Occasionally, asthma may start for the first time during pregnancy, and it is often difficult to control.

There are several medications which can affect the course of asthma unfavorably. Aspirin and other nonsteroidal inflammatory agents can elicit a triad of airway obstruction, nasal polyposis, and sinusitis, which may be difficult to treat. Approximately 10 to 13 percent of children with asthma will experience a worsening of airway obstruction when they ingest aspirin.[25] Sodium salicylates do not have the same effects as acetyl salicylates. Tartrazine yellow, a widely used coloring agent, may bring on bronchospasm in some patients who also have an idiosyncrasy to aspirin. Recently, metabisulfites have been implicated in producing acute bronchospasm in sensitive individuals.[26] While this latter idiosyncrasy has not been described in children as yet, it is likely that there are some who are sensitive to this common food preservative. Parasympathomimetics and β-adrenergic blocking agents may elicit acute attacks of airway obstruction in selected patients. Since these agents are not widely used in the pediatric age group, they do not pose a major threat to children with asthma.

Abnormal, excessive airway reactivity and sensitivity to many bronchospasm-provoking stimuli are the major and basic pathophysiologic features which separate asthmatic from nonasthmatic children. Although greater than normal responses to inhaled methacholine have been reported in some normal subjects and quite a few patients with allergic rhinitis who do not have clinical asthma,[27] there is a strong negative correlation between the dose of bronchoconstrictors needed to elicit a 20 percent reduction in expiratory flow (FEV_1) and the severity of asthma, as indicated by the amount of medications needed to control symptoms of airway obstruction.[28]

There are several clinical and laboratory abnormalities which have value in predicting an unfavorable long-term course of asthma, listed in Table 4. They include a long history of persistent asthma, chest deformities, the presence of many positive skin tests, persistent wheezing in early life, moderate pulmonary function abnormalities at 14 years of age, and significant eczema before 2 years of age.

Triggers

Viral respiratory tract infections constitute the most important trigger of asthma in children. Respiratory syncytial, influenza, parainfluenza, and corona viruses are the major, but not exclusive agents responsible for the initiation of acute and sometimes sustained airway obstruction. The virally-induced attacks usually last 3 to 4 days and may precipitate status asthmaticus. Since young children have had little exposure to respiratory viruses, they may develop 6 to 12 virally-induced infections and asthma attacks per year. This high attack rate can continue until immunity to these infectious agents gradually develops. There is no evidence to suggest that bacterial respiratory tract infections will trigger acute bronchospasm or nonbronchospastic airway obstruction in children with asthma.

Hyperpnea, regardless of how initiated, will elicit asthma in susceptible subjects. The magnitude of the bronchospastic response to physical exertion is determined in large part by preexisting airway hypersensitivity and hyperreactivity, by the magnitude of exercise-induced or voluntary hyperpnea, and associated factors such as the season, recent antigenic exposures, the presence or recent history of viral infections, recent vaccinations against influenza, medications taken, air pollution, weather, and probably still other, unidentified factors.[29] Hyperpnea-induced bronchospasm is, in large part, a function of heat loss from the respiratory passages which, in turn, is related to the temperature and humidity of inhaled air.[30] Antigen- and probably hyperpnea-induced airway obstruction are mediated by chemical messengers which are produced by the mast cells surrounding and in the lumen of bronchioles and bronchi. The postexertional response is lost or lessened for 30 to 40 minutes after strenuous activity, which is probably due to temporary exhaustion of mediator stores.[29] Warm, humid air will also lessen hyperpnea-induced bronchospasm. Since children are spontaneously more active than adults, exercise-induced bronchospasm is particularly common in this age group.

Both antigenic exposures and exercise may produce immediate and late airway obstruction.[31,32] It has been postulated that late responses may be the cause of some nocturnal and early morning attacks of asthma. Immediate responses to aeroallergens can usually be blocked or lessened by inhaled or oral bronchodilators; late responses can usually be prevented by beclomethasone inhalation or oral prednisone; and both antigen and exercise-induced immediate and late responses can often be blocked by cromolyn sodium.

Besides airborne antigens, there are many other irritants in the environment which can produce bronchospasm in susceptible children. These include cigarette smoke, smoke from wood fires and stoves,[22] cooking fumes, strong perfumes, and other airborne particles. Forced expiratory maneuvers, laughing, sneezing, and coughing may also elicit bronchospasm. Most of these triggers produce airway constriction by vagally mediated reflex mechanisms (Fig 1) and can be blocked by inhaled atropine.[33,34] Emotional upsets and suggestion[35,36] can cause acute bronchospasm in asthmatic children. While these attacks are sometimes initiated by hyperventilation, other CNS mechanisms are probably also involved.

Table 4—*Factors Indicating Unfavorable Prognosis in Childhood Asthma

Predictive Factors	Patients With Moderate or Severe Asthma at 21 Yr, %
Persistent asthma at 10 yr	84
Barrel chest at 10 yr	83
Many positive skin tests at 10 yr	73
Continued wheezing between 0 and 24 mo	72
FEV_1 >2 SD below normal at 14 yr	61
Significant eczema <2 yr	58

*Data extracted from reference 10.

Presentation and Diagnosis

Most infants and young children who experience an acute exacerbation of asthma present with tachypnea, wheezing,

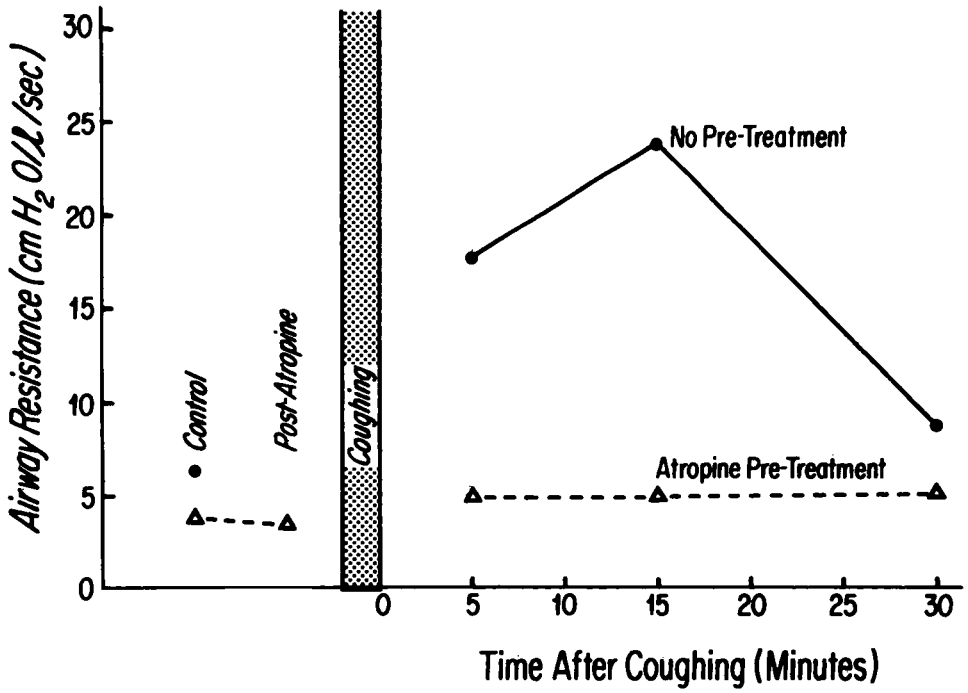

FIGURE 1. Demonstration of cough-induced bronchospasm in an asthmatic child, blocked successfully by inhaled atropine aerosol. (Reproduced with permission from reference 33.)

coughing, and often fever. There are signs and symptoms of airway congestion, coryza, pharyngeal and nasal inflammation, and sometimes exudates. There may also be middle ear effusions or infections. There can be suprasternal and intercostal retractions, use of accessory respiratory muscles, and cyanosis. The reversibility of signs and symptoms, even with optimal therapy, can be slow in status asthmaticus, particularly in infants. In small children, this is primarily due to the small size of their peripheral and central airways, and the plugging which results from small amounts of secretion, edema, bronchospasm, and necrotic epithelial debris. The differential diagnosis in the young child between bronchiolitis and asthma is difficult, if not impossible, even when a respiratory syncytial virus infection has been documented. Whenever clinical bronchiolitis recurs, it is likely that the infant has asthma. I do not like to commit myself to the diagnosis of asthma during the first attack of wheezing; however, when an infant or young child wheezes and coughs with most viral respiratory tract infections, the diagnosis is probably asthma. The major and frequently associated signs and symptoms of childhood asthma are listed in Table 5.

Table 5—*Signs and Symptoms of Childhood Asthma*

Major Features	Associated Features
Tachypnea	Rhinitis
Wheezing	Croup
Cough	Eczema
Intercostal and suprasternal retractions	Increased AP diameter
	Harrison sulcus
Excessive use of accessory muscles	Pectus carinatum
	Elevated shoulders
Postexertional dyspnea	Eustachian tube dysfunction
	Cyanosis
	On chest x-ray film
	Recurrent atelectasis
	Peribronchial thickening
	Hyperinflation

It should be remembered that not all asthmatic children wheeze and that wheezing does not always indicate the presence of this common disease. While wheezing is the most common sign of reactive airway diseases, some patients wheeze but do not have asthma. In these youngsters, causes such as recurrent aspiration, gastroesophageal reflux, pulmonary edema, foreign bodies, bronchial adenomas, upper or central airway obstruction by anatomic lesions such as hemangiomas, extraairway vascular channels, lymph nodes, or cysts, and even intraairway malignancies, may have to be ruled out. Hypersensitivity pneumonitis and periarteritis are rare in children but can cause wheezing. Cystic fibrosis is an important cause of wheezing and must be ruled out by an appropriately performed sweat test. The reversibility of airway obstruction following the administration of an effective bronchodilator is a good diagnostic aid and should be used whenever the diagnosis of asthma is considered and the child is old enough to perform pulmonary function tests.

Chronic cough is a common variant of reactive airway disease. Many of these patients never wheeze and have normal pulmonary function tests, but have evidence of hypersensitive airways, as indicated by positive exercise provocation tests[37] or abnormal responses to inhaled methacholine or histamine.[28,38] The majority of these patients respond favorably to conventional asthma management. We should be reluctant to accept the diagnosis of chronic bronchitis in children, since most cases of chronic cough turn out to have reactive airway disease or, sometimes, cystic fibrosis.

When asthma becomes chronic, chest deformities may develop, particularly when the disease is severe. Chest deformities include pectus carinatum, a Harrison sulcus, an increase in the AP diameter of the thorax, or abnormally

elevated shoulders. All of these abnormalities suggest chronic hyperinflation and poorly controlled small airway obstruction. The presence of a barrel chest at 10 or 14 years of age has been shown to be associated with a poor prognosis.[39]

The diagnosis of asthma can be aided and should be confirmed by pulmonary function tests.[40] These tests include spirometric assessments of forced expiratory air flow, flow-volume loops, and measurements of lung volumes, airway resistance, and conductance. When there is doubt about the existence of reactive airway disease, bronchial challenge tests may also be indicated. For the older child (>6 to 7 years), the tests are basically the same as those performed in adults. For the preschool child, modifications of standard tests have been developed. They include partial flow-volume curves, body plethysmographic evaluations of the functional residual capacity and airway resistance, and measurements of respiratory system resistance by forced oscillation. In the office and the clinic, peak flow meters are very useful, and good results can often be obtained in 4- and 5-year-olds. Performing the pulmonary function tests in the young child require some cooperation; therefore, training is recommended, and experienced, friendly, motivated technologists are needed to obtain optimal results. We should also remember that arterial blood gas measurements are important measures of ventilation/perfusion relationships and thus of lung function. Assessments of lung functions before and after bronchodilator administration are extremely valuable for initial and follow-up evaluations, since they are the best means of assessing objectively and in quantitative terms the severity, reversibility, and progression of airway obstruction. The aim of therapy in children with asthma is to normalize lung function as much as possible without causing undesirable side effects from drug therapy.

Complications

Childhood asthma can give rise to a number of complications which are rarely seen in adults. They include the development of pneumothorax, pneumomediastinum, and subcutaneous emphysema. Atelectasis is very frequent in preschool children, is usually subsegmental, but may involve a whole lobe, especially the right middle lobe. Atelectasis is so frequent because the young child's airways are small and easily plugged by secretion and epithelial debris, and collateral ventilation is poorly developed. Atelectasis is often mistaken for pneumonia on the chest x-ray film. Chest deformities indicate the presence of long-standing, poorly controlled small airway obstruction and hyperinflation. When the chronic airway obstruction is reversed, it usually takes several months or even years before chest deformities are corrected. Growth delays are common in children with severe and often steroid-dependent asthma. While the growth velocity may be delayed, the vast majority of asthmatic children eventually reach normal height and weight. Only when large doses of steroids are used for extended periods of time (>5 mg/m²/day) will growth be permanently altered.[39] Long-term use of steroids poses a risk of posterior capsular cataracts, especially in children who show retardation of bone age.[41] Behavioral and school problems develop occasionally in children with severe asthma.[42] Frequent hospitalizations, school absenteeism, interruptions of normal childhood activities, and interference with normal relationships among peers are the probable causes of these maladjustments. A few patients with severe asthma develop allergic bronchopulmonary aspergillosis. This diagnosis should be considered in any child who has severe asthma, recurrent pulmonary infiltrates, marked skin test positivity to *Aspergillus fumigatus* antigen, elevated IgE (>1,000 units/L), eosinophilia, sputum containing brown or pinkish plugs, and sputum from which *A fumigatus* has been cultured.

Treatment

Our therapeutic goal is to normalize and maintain normal lung function, thus optimizing childhood activities and lessening recurrences of exacerbations of asthma. Treatment includes bronchodilators, corticosteroids, parasympatholytics, cromolyn sodium, and, rarely, special adjuncts such as troleandomycin or erythromycin in the problem case. In addition to pharmacologic therapy, patient and family education is important,[43,44] and very occasionally psychotherapy may be needed.[42] Both parents and sometimes siblings, babysitters, and close relatives benefit from participating in asthma education programs. All persons involved in the care of children with asthma need to learn about the chronic nature of this illness. Their cooperation is mandatory if a successful outcome is to be achieved. We also invite teachers, coaches, interested friends, and parents of preschool children with asthma to our Family Asthma Programs.[43] Parents, as well as the pediatric patient should be taught, in age-appropriate terms, the pathophysiologic mechanisms which are responsible for airway obstruction, and the reasons why certain drugs have to be taken. They have to learn the names and side effects of the medications, the warning signs and triggers of asthma, and the role that the patient, his family, friends, and other caretakers play in self-management. Lifestyle changes, such as cessation of smoking by parents or siblings, discontinuation of the use of wood-burning stoves,[22] getting rid of household pets, and adjustments in participation in household chores and selected recreational activities, such as horseback riding, may be required. It is to be hoped that the needed changes can be made without causing resentment. Our Family Asthma Program has been effective in increasing participation of the children in various activities, lessening school absenteeism, reducing emergency room and physician office visits, and improving coping with the disease.[44] We also believe that a Family Asthma Program will increase compliance with prescribed treatment programs, and it usually enables parents and children to develop healthier and more realistic attitudes toward this chronic disease.

In the drug therapy of asthma, we rely primarily on the supervised and frequently reviewed use of theophylline, β_2-adrenergic agonists (especially by the inhaled route), and cromolyn sodium. Treatment should achieve normalization of lung function without causing undesirable side effects. Whether this goal has been reached and is sustained is best evaluated by periodic reviews of the health status, pulmonary function tests, and measurements of theophylline blood levels when indicated. Theophylline blood levels should be assessed whenever there are signs of toxicity or failure of a good response at reasonable doses. For the management of acute bronchospasm, we use repeated inhalations of

β_2-adrenergic agonists or injected terbutaline. Both forms of therapy can be given at home by appropriately trained caretakers. I favor injected terbutaline over epinephrine because of less tachycardia, pallor, and excitement and more prolonged bronchodilation following terbutaline injections. When there are frequent recurrences of bronchospastic attacks, when a chronic cough is believed to be due to reactive airway disease, or when a child's small airway obstruction does not resolve, long-term therapy with inhaled and oral bronchodilators or cromolyn should be considered. The availability of aqueous cromolyn and bronchodilators and moderately priced compressor-activated nebulizers has made the administration of these drugs possible in very young children. Inhalation chambers and spacers have also helped with the administration of metered-dose aerosols in school-aged children and teenagers who find it difficult to coordinate inhalation and activation of the metered-dose cartridges. Parents must be advised that long-term treatment may be required for years. We should replace episodic with anticipatory care, and acknowledge that asthma is a chronic disease which requires a comprehensive and often long-term therapeutic approach.

The use of inhaled and oral steroids is occasionally needed to bring severe asthma under control. While we must retain a healthy respect for corticosteroids, we should not commit an asthmatic child to invalidism just because we do not want to use oral prednisone or inhaled beclomethasone or triamcinolone. The skilled and cautious use of these agents will often result in complete normalization of lung function and a return to normal life. Inhaled steroids should be used whenever possible to minimize systemic side effects. We hope that aqueous forms of topical steroids will be available soon, so that we may administer them by compressor-operated nebulizers to infants and small children. There is no evidence at this time that effective, long-term control of asthma will influence the natural history of its outcome;[10] however, anticipatory care can improve the quality of life for these patients significantly.

Since exercise is an important trigger of asthma in childhood, many young patients can be helped by the inhalation of bronchodilators or cromolyn before planned physical activities. This usually allows participation in competitive and recreational sports. Coaches and physical education teachers must permit the use of preexertional medications and should be instructed in how to deal with asthma attacks when they occur. While it is occasionally necessary to excuse a child from participation in athletic activities, this should be avoided whenever possible. It is important that parents, coaches, and children select the athletic activity which is best tolerated. Indoor swimming in not too heavily chlorinated pools is a favorite sport for many asthmatic children, but most sports can be engaged in with a proper and selective treatment program.[39]

Some children with asthma develop bronchospasm after forced expiratory maneuvers, laughing, sneezing, coughing, or exposures to irritating fumes or smoke. These patients may be helped by inhaled atropine sulfate or one of its analogs[33,34] (Fig 1). Additional aspects of specific drug therapy and self-management in asthma have been reviewed in other articles in this issue.

Behavior modification and other psychotherapeutic measures may be helpful in reversing emotionally induced attacks of bronchospasm and emotional maladjustments which develop occasionally in severely affected children.[42]

Drug Toxicity

Drug toxicity and interactions differ in children and adults. Theophylline doses have to be adjusted to age. Infants require lower doses than the 1- to 12-year-old child. After 12 to 14 years of age, doses usually have to be reduced also. Tremors, hyperactivity, headaches, nausea, vomiting, and even seizures and hematemesis are encountered in children, but seizures are a relatively late and rare complication. Children may start bedwetting when starting theophylline therapy, and behavioral changes and school problems are not infrequent. Poor attention spans, restlessness, and poor writing skills are occasionally noted by parents and teachers. The complications of theophylline toxicity can be very serious. Whenever there are concerns about theophylline toxicity, blood levels must be obtained. Even when blood levels are within the therapeutic range, drug doses must be reduced whenever undesirable side effects have developed. With the availability of long-acting, slow-release preparations, suicides have been attempted, especially by teenaged girls. Overdoses and toxicity must be treated aggressively, including gastric lavage, gastric administration of charcoal, and charcoal hemoperfusion. Mild theophylline toxicity can be precipitated without a change in theophylline dosing by the simultaneous use of cimetidine, erythromycin, and other antibiotics in the macrolide group. Changes in diet during acute and viral infections may alter the rate at which theophylline is broken down, and alterations in airway reactivity have been observed following influenza vaccination.[45,46] The combination of oral β_2-adrenergic agents and theophylline may potentiate toxicity from either drug. For this reason, inhalation therapy with β_2 bronchodilators is favored, since inhaled bronchodilators elicit fewer systemic side effects than orally administered agents. It is possible that some of the remaining mortality in asthmatic children is due to drug toxicity rather than respiratory failure and its associated complications.

Steroid toxicity does not develop rapidly. Five-day courses of therapy (as long as they are not repeated too frequently) are generally safe and can be stopped without tapering. Long-term use, however, is potentially dangerous and we must look out for undesirable side effects such as cataracts,[41] hypertension, growth disturbances, or unacceptable weight gains. When children who take or have taken prednisone within 3 months require surgery or have a serious accident or injury, they should be given a stress dose of steroids (75 mg/m^2 of cortisone acetate intramuscularly, or the same dose of hydrocortisone intravenously).

The desire of teenagers, especially girls, to be no different from their peers often leads to a phase when they deny the existence of their illness and stop taking all medications. With good anticipatory counseling, this can usually be avoided. However, when good control of asthma is suddenly lost, the rebellious nature of teenagers should be kept in mind as a causal factor in their unexpected deterioration. Theophylline blood levels can be a useful guide in determin-

ing whether these patients take their medications.

Summary

Asthma in children has many special features which deserve consideration. This disease is probably underdiagnosed and is often undertreated. Vague, persistent respiratory symptoms, especially chronic cough, may often be due to asthma. Chronic bronchitis is extremely rare in the pediatric patient and is a manifestation of reactive airway disease or cystic fibrosis. The absolute severity, the extent of the disease, responses to treatment, and long-term course should be evaluated by repeated pulmonary function tests. Fortunately, asthma responds well to pharmacologic and supportive therapy, and it is important to approach its management as that of a chronic rather than episodic illness. Therapy should include comprehensive, closely supervised drug therapy, health education, and a program of self-management. Asthma usually starts before youngsters enter school, and the majority get better as they get older. Nevertheless, many children with moderate or severe asthma will continue to be troubled by intermittent or chronic airway obstruction into adulthood, and they require long-term, anticipatory treatment programs. Comprehensive care will optimize the quality of life for the affected children and their families, and it will minimize the discomfort and restrictions to which some of them have been subjected unnecessarily. Asthma in childhood, especially when not well controlled, may constitute a risk factor for the development of chronic obstructive pulmonary disease in adulthood; however, this is as yet only suspected and not proved.[47]

References

1 Border I, Barlow PP, Horton RJM. The epidemiology of asthma and hay fever in a total community, Tecumseh, Michigan. J Allergy 1962; 33:513-23
2 Gibson H. Report on asthma survey in Tasmania school children. National Asthma Foundation of Tasmania, 1966
3 Williams H, McNicol KN. Prevalence, natural history and relationship of wheezy bronchitis and asthma in children. An epidemiological study. Br Med J 1969; 4:321-5
4 National Center for Health Statistics (Division of Health Interview Statistics). Prevalence of selected chronic respiratory conditions, United States—1970. DHEW publication no. (HRA)74-1511 (Vital and health statistics 1973; series 10, no. 84)
5 Lebowitz MD, Knudson RJ, Burrows B. Tucson epidemiologic study of obstructive lung diseases. I. Methodology and prevalence of disease. Am J Epidemiol 1975; 102:137-52
6 Blair H. The incidence of asthma, hay fever and infantile eczema in an East London group practice of 9145 patients. Clin Allergy 1974; 4:389-99
7 Peat JK, Woolcock AJ, Leeder SR, Blackburn CRB. Asthma and bronchitis in Sydney school children. I. Prevalence during a six-year study. Am J Epidemiol 1980; 111:721-7
8 National Center for Health Statistics (Division of Health Interview Statistics). Vital and health statistics; 1980 and 1981 surveys. Unpublished data
9 Blair H. Natural history of childhood asthma. Arch Dis Child 1977; 52:613-19
10 Martin AJ, Landau LI, Phelan PD. Predicting the course of asthma. Aust Paediatr J 1982; 18:84-87
11 Martin AJ, McLennan LA, Landau LI, Phelan PD. The natural history of childhood asthma to adult life. Br Med J 1980; 280:1397-1400
12 Kuzemko JA. Natural history of childhood asthma. J Pediatr 1980; 97:886-92
13 Martin AJ, Landau LI, Phelan PD. Natural history of allergy in asthmatic children followed to adult life. Med J Aust 1981; 2:470-4
14 Wohl MEB, Chernick V. Bronchiolitis. Am Rev Respir Dis 1978; 118:759-81
15 Zweiman B, Schoenwetter WF, Hildreth EA. The relationship between bronchiolitis and allergic asthma. A prospective study with allergy evaluation. J Allergy 1966; 37:48-53
16 Rooney JC, Williams HE. The relationship between proved viral bronchiolitis and subsequent wheezing. J Pediatr 1971; 79:744-7
17 Henry RL, Hodges IGC, Milner AD, Stokes GM. Respiratory problems 2 years after acute bronchiolitis in infancy. Arch Dis Child 1983; 58:713-16
18 Zach MS, Schnall RP, Landau LI. Upper and lower airway hyperreactivity in recurrent croup. Am Rev Respir Dis 1980; 121:979-83
19 Mellis CM, Levison H. Bronchial reactivity in cystic fibrosis. Pediatrics 1978; 61:446-50
20 Johnstone DE, Roghmann KJ, Pless IB. Factors associated with the development of asthma and hay fever in children: the possible risks of hospitalization, surgery and anesthesia. Pediatrics 1975; 56:398-403
21 Godfrey RC. Asthma and IgE levels in rural and urban communities of The Gambia. Clin Allergy 1975; 5:201-7
22 Honicky RE, Apkom CA, Osborne JS. Infant respiratory illness and indoor air pollution from a woodburning stove. Pediatrics 1983; 71:126-8
23 Weiss ST, Tager IB, Speizer FE, Rosner B. Persistent wheezing. Its relation to respiratory illness, cigarette smoking, and level of pulmonary function in a population sample of children. Am Rev Respir Dis 1980; 122:697-707
24 Kaufman HS, Frick OL. Prevention of asthma. Clin Allergy 1981; 11:549-53
25 Vedanthan PK, Menon MM, Bell TD, Bergin D. Aspirin and tartrazine oral challenge: Incidence of adverse response in chronic childhood asthma. J Allergy Clin Immunol 1977; 60:8-13
26 Stevenson DD, Simon RA. Sensitivity to ingested metabisulfites in asthmatic subjects. J Allergy Clin Immunol 1981; 68:26-32
27 Townley RG, Bewtra AK, Nair NM, Brodkey FD, Watt GD, Burke KM. Methacholine inhalation challenge studies. J Allergy Clin Immunol 1979; 64:569-74
28 Neijens HJ, Duiverman EJ, Kerrebijn KF. Bronchial responsiveness in children. Pediatr Clin North Am 1983; 829-46
29 Cropp GJA. Exercise-induced asthma. In: Middleton E Jr, Reed CE, Ellis EF, eds. Allergy, principles and practice, 2nd ed. St Louis: CV Mosby, 1983; 1003-14
30 Haynes RL, Ingram RH, McFadden ER. An assessment of the pulmonary response to exercise in asthma and an analysis of the factors influencing it. Am Rev Respir Dis 1976; 114:739-52
31 Pepys J, Hutchcroft BJ. Bronchial provocation tests in etiologic diagnosis and analysis of asthma. Am Rev Respir Dis 1975; 112:829-59
32 Lee TH, Nagakura T, Papageorgiou N, Iikura Y, Kay AB. Exercise-induced late asthmatic reactions with neutrophil chemotactic activity. N Engl J Med 1983; 308:1502-5
33 Cropp GJA. Bronchial asthma in children. Schweiz Med Wochenschr 1979; 109:253-64
34 Cropp GJA. Role of the parasympathetic nervous system in the maintenance of chronic airway obstruction in asthmatic children. Am Rev Respir Dis 1975; 112:599-605
35 McFadden ER Jr, Luparello T, Lyons HA, Bleecker E. The mechanism of action of suggestion in the induction of acute asthma attacks. Psychosom Med 1969; 31:134-43
36 Spector S, Luparello TJ, Kopetsky MT, Souhrada J, Kinsman RA. Response of asthmatics to methacholine and suggestion. Am Rev

Respir Dis 1976; 113:43-50
37 Cloutier MM, Loughlin GM. Chronic cough in children: a manifestation of airway hyperreactivity. Pediatrics 1981; 67:6-12
38 Cropp GJA, Bernstein IL, Boushey HA Jr, Hyde RW, Rosenthal RR, Spector SL, et al. Guidelines for bronchial inhalation challenges with pharmacologic and antigenic agents. ATS News 1980; 6:11-19
39 Martin AJ, Landau LI, Phelan PD. The effect on growth of childhood asthma. Acta Paediatr Scand 1981; 70:683-8
40 Cropp GJA. Pulmonary function and bronchial challenge testing in office and hospital practice. Ann Allergy 1983; 51:13-20
41 Bhagat RG, Chai H. Development of posterior subcapsular cataracts in asthmatic children. Pediatrics 1984; 73:626-30
42 Creer TL, Kotses H. Asthma: Psychological aspects and management. In: Middleton E Jr, Reed CE, Ellis EF, eds. Allergy, principles and practice. 2nd ed. St Louis: CV Mosby, 1983; 1015-36
43 Hindi-Alexander M, Cropp GJA. Community and family programs for children with asthma. Ann Allergy 1981; 46:143-8
44 Hindi-Alexander M, Cropp GJA. Evaluation of a family asthma program. J Allergy Clin Immunol (in press)
45 Ouellette JJ, Reed CE. Increased response of asthmatic subjects after influenza vaccine. J Allergy 1965; 36:558-63
46 Empey DW, Laitinen LA, Jacobs L, Gold WM, Nadel JA. Mechanisms of bronchial hyperreactivity in normal subjects after upper respiratory tract infection. Am Rev Respir Dis 1976; 113:131-9
47 Burrows B, Taussig LM. "As the twig is bent, the tree inclines" (perhaps). Am Rev Respir Dis 1980; 122:813-16

Role of Immunotherapy in Asthma*

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Immunotherapy has long been employed in an attempt to block the allergic response of man to inhaled allergens. Although demonstrably successful in some specific clinical situations, its place in the overall management of asthma is to some extent controversial, and proper use depends on a detailed knowledge of indications, techniques of administration, and potential untoward effects. Formerly called "desensitization" or "hyposensitization," immunotherapy attempts to alter the balance of immunologic reactions to ordinarily harmless atmospheric "allergens" in a fashion that will minimize the response of the allergic person's airways upon reexposure to the allergen.[1] As immunologic reactions are highly specific, use of the method presupposes that accurate diagnosis of the offending allergens has been arrived at and that materials (extracts) containing the essential allergens are available for immunization. Successful immunization may also improve the nonspecific bronchial hyperreactivity which characterizes asthma.

Allergic reactions of the type which cause asthma are in man probably exclusively mediated by antibodies of the IgE class. Diagnosis depends on correlation of a history of symptoms associated with specific exposures and confirmation of IgE-mediated reactivity to suspected allergens by skin testing or serologic identification of specific IgE antibodies. There is no rationale for institution of immunotherapy in the absence of a demonstration of a sensitivity caused by IgE antibodies.

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Technique

The usual procedure is to prepare one or more mixes of allergens specific for the patient and set out to immunize by a series of injections, once or twice a week, of gradually increasing doses, starting so low as to obviate any risk of untoward allergic reaction. Doses initially may double each time, but the rate of increase commonly slows as the dose nears the expected maximum. The increase may have to be slowed further if allergic symptoms develop after injections. The allergic reactions can be itchy red swellings at the site of injection or systemic symptoms of generalized itching, hives, angioedema, hay fever or asthmatic symptoms, and in the worst, but fortunately uncommon cases, frank anaphylaxis and even death.[2] Continuation of injections at a slower rate of increase in those who exhibit an adverse reaction usually results in an alteration of reactivity to the point where the projected final dose can be reached with no more than minor symptoms. A few persons have persistent and repeated allergic reactions, and abandonment of treatment or acceptance of a dose considered less than optimal may be necessary.

After a maintenance dose is reached and achieved, the interval between boosters may vary from 2 to 6 weeks, depending on dose and apparent response. Benefit is usually obvious during the first six months to 1 year and is usually maximal by 3 years of continued therapy. No guidelines define how long therapy should continue. A few studies suggest that after discontinuation of boosters benefit has faded by 6 months.[3] Many physicians attempt to stop injections after 4 years of a successful treatment program.

Controlled clinical studies of immunotherapy in model conditions such as ragweed hay fever demonstrate that: (1) clinical results depend on adequate dose, with small doses having a poor rate of success or being totally ineffective; (2) relapse may occur once booster injections are discontinued; and (3) results are specific being effective only for the allergen(s) being administered and ineffective for excluded allergens.[4,5]

Immunologic Changes

Immunologically, a variety of changes have been demonstrated that may in part be responsible for the relief of allergic symptoms. Among these changes are: (1) a rise in serum IgG "blocking" antibodies; (2) a suppression in the usual seasonal rise in IgE antibodies which follows environmental exposure and a slow decline during several years in the level of specific IgE antibodies (although complete disappearance is rare); (3) increase in blocking IgA and IgG antibodies in secretions; (4) reduced basophil reactivity and sensitivity to allergens (as determined by *in vitro* leukocyte histamine release studies); and (5) reduced *in vitro* lymphocyte responsiveness to allergens.[6-8]

Each of these changes may not be seen in every patient, and those that are important in ameliorating symptoms are not well defined. One change, however, that has some correlation with clinical results has been the titer of serum "blocking" antibodies.[9] Measurement of these serum IgG antibodies shows that once an adequate dose is reached,