American Thoracic Society

Proceedings of the ATS Workshop on Refractory Asthma

Current Understanding, Recommendations, and Unanswered Questions

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Although severe, refractory asthma is an uncommon disease (likely < 5% of total asthma), it is poorly understood and, therefore, often frustrating to treat. What follows is the proceedings of an American Thoracic Society (ATS)-sponsored workshop. The participants hope it will serve as an aid to begin to define, understand, and manage these refractory patients. Perhaps more importantly, it is also hoped that these proceedings will highlight the many questions that remain, and eventually lead to improved outcomes.

REFRACTORY ASTHMA: DEFINITION AND DIAGNOSIS

John Fahy, M.D.

Asthma affects 5–7% of the population of North America and Europe, and the prevalence is increasing (1, 2). Most asthma is mild or moderate (3) and can be well controlled with β-agonists with or without usual or low doses of antiinflammatory agents. A subgroup of patients with asthma (likely < 5%) have more troublesome disease reflected by (*1*) high medication requirements to maintain good disease control or (*2*) persistent symptoms, asthma exacerbations, or airflow obstruction despite high medication use. In considering a term to describe this subgroup of asthmatic patients with troublesome disease, the workshop participants agreed on the term "refractory asthma." "Refractory asthma" is not meant to describe only patients with "fatal" or "near fatal" asthma, but it is meant to encompass the asthma subgroups previously described as "severe asthma," "steroid-dependent and/or resistant asthma," "difficult to control asthma," "poorly controlled asthma," "brittle asthma," or "irreversible asthma." Clinically, patients with refractory asthma may present with a variety of separate and/or overlapping conditions. These may include (*1*) widely varying peak flows ("brittle asthma"), (*2*) severe, but chronic airflow limitation, (*3*) rapidly progressive loss of lung function, (*4*) mucus production ranging from absent to copious, and (*5*) varying responses to corticosteroids (CS). Whether these groups form distinct clinical, physiologic, and pathologic groups is unclear.

Because severe/refractory asthma has not been consistently defined, and is relatively difficult to measure, the true size of the subgroup of patients with refractory asthma is unknown. In young male Israeli military recruits, Auerbach and coworkers (3) found the point prevalence of asthma to be 6.4%. Less than 1% of these patients had severe asthma, but severe asthma was defined narrowly as steroid dependence and an FEV_1 of less than 50% predicted. Woolcock (4) defined severe asthma as severe hyperreactivity to histamine (PC_{20} histamine [provocative concentration of histamine causing a 20% fall in FEV_1] < 0.1 mg/ml). Using this definition, Woolcock found that approximately 12% of Australian children or adults with asthma had severe asthma. It is unclear whether these studies over- or underestimate the prevalence of refractory asthma as defined in Table 1. Although the precise size of the subgroup with refractory asthma is uncertain, the economic impact of the group is not. The total cost of illness related to asthma likely ranges between 6 and 10 billion U.S. dollars (5, 6). More than 40% of its economic impact is believed to be associated with emergency room use, hospitalization, and death. A more recent study from Europe estimated that the average cost per patient with severe asthma, as defined by the International Consensus Report, is nearly six times the cost of care for a patient with mild asthma (7). It is likely that the treatment of refractory asthma described in this report utilizes even more health care dollars per patient.

Clinical Features/Natural History of Refractory Asthma

(*See* Table 1.) Refractory asthma encompasses wide ranges in both clinical symptoms and in natural history. Patients may appear to have highly labile disease, with wide swings in peak flows, while others are more chronically and severely obstructed (8, 9). Other patients produce copious amounts of phlegm, some have associated sinus disease and gastroesophageal reflux, while others do not. Despite these differences in presentation, the workshop participants considered it important to develop a "working" definition of refractory asthma. For this purpose the participants agreed that refractory asthma should be defined on the basis of medication requirements, asthma symptoms, frequency of asthma exacerbations, and degree of airflow limitation. Specifically, the group agreed on two major and seven minor criteria (Table 1), with refractory asthma being defined as one or both major criteria and at least two minor criteria. This definition is applicable only to patients in whom (*1*) other conditions have been excluded, (*2*) exacerbating factors have been optimally treated, and (*3*) poor adherence does not appear to be a confounding issue.

In considering the features that define refractory asthma, Cockcroft and Swystun argue (10) that "well controlled

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asthma" does not exclude refractory asthma. This is likely true if good asthma control and improved airway function (to the level of a mild–moderate persistent patient) can be achieved only with high doses of inhaled or oral CS with the associated concerns for long term systemic toxicity. These patients are captured in the recommended diagnostic criteria. In contrast, some patients with refractory asthma continue to have persistent symptoms or reduction in airway caliber despite high doses of inhaled or oral CS. Incompletely reversible airway narrowing in these patents may reflect airway remodeling consequent on long-standing severe airway inflammation, or, alternatively, an inability of currently available medications to reverse "potentially reversible" obstruction (*see* PATHOLOGY OF REFRACTORY ASTHMA) (11).

Whether there is a particular "natural history" that leads to the development of refractory asthma is unclear. Although mean figures suggest that pulmonary function declines more rapidly over time in patients with asthma, the perception remains that "most" of these individuals do not progress to more severe disease (12). This is especially true among children with asthma, of whom many will "outgrow" their disease (13, 14). Intriguingly, longitudinal studies suggest that the more severe the obstruction on initial presentation, the more likely the asthma is to progress or remain severe (15). In addition, two longitudinal studies now suggest that asthma presenting in adulthood is likely to have a more precipitous decline in lung function (and by inference, development of severity) than asthma that presents in childhood (16, 17). However, the factors that determine this "predisposition to severity" are not known.

Clinical Evaluation

In making the diagnosis of refractory asthma, it is important to consider and exclude other diseases in the differential diagnosis of wheeze, dyspnea, cough, and eosinophilia (18). Specifically, patients should be evaluated for other diseases, such as chronic obstructive pulmonary disease, bronchiectasis (including allergic bronchopulmonary aspergillosis and cystic fibrosis), and vocal cord dysfunction (Table 2). The diagnostic work-up of patients suspected of having chronic refractory asthma should consist of full pulmonary function tests including spirometry with a flow–volume curve, total lung capacity, residual volume, and diffusion capacity, as well as daily peak flow monitoring. Additional suggested clinical tests include serum IgE and eosinophil levels (Table 2) (18, 19). Only after diagnosing and/or treating other disorders without clinical improvement should patients be classified as having "asthma." Finally, in any person with "refractory asthma," a thorough evaluation for factors that could contribute to the severity of the disease, such as sinus disease, gastroesophageal reflux, and compliance/adherence issues (including random morning serum cortisol checks) should be performed. Patients should be thoroughly evaluated for their understanding of asthma and their ability to use a metered dose inhaler. Addressing these issues may improve asthma outcomes in a poorly defined percentage of patients with severe, but not truly "refractory," asthma. However, a proportion of these patients will remain uncontrolled, even with the best approach to diagnosis and management, and hence, qualify as having refractory asthma.

PHYSIOLOGY OF REFRACTORY ASTHMA

Charles Irvin, Ph.D.

Whether the abnormalities of pulmonary physiology in patients with severe refractory asthma are intrinsically different from those seen in milder forms of disease is poorly understood. However, there is general agreement that residual airflow limitation (a persistently low FEV_1) after optimization of a patient's asthma therapy represents an undesirable situation that warrants further therapeutic intervention.

There are three principal physiologic features of "asthma": (*1*) reversible airflow limitation with a significant ($>$ 12% change in FEV_1 or FVC) response to acute, inhaled bronchodilator treatment, (*2*) airway hyperresponsiveness, either to naturally encountered stimuli, for example, exercise, or to chemical stimuli in a laboratory setting, for example, methacholine, and (*3*) episodic airflow limitation in response to various triggers such as antigen or chronic, periodic changes such as nocturnal worsenings. Patients with mild or moderate disease may not exhibit all three of these features and can move

TABLE 1

REFRACTORY ASTHMA: WORKSHOP CONSENSUS FOR TYPICAL CLINICAL FEATURES*,†

Major Characteristics

In order to achieve control to a level of mild–moderate persistent asthma:

1. Treatment with continuous or near continuous ($\geq$ 50% of year) oral corticosteroids
2. Requirement for treatment with high-dose inhaled corticosteroids:

Drug	Dose ($\mu g/d$)	Dose (*puffs/d*)
a. Beclomethasone dipropionate	$>$ 1,260	$>$ 40 puffs (42 μg/inhalation $>$ 20 puffs (84 μg/inhalation
b. Budesonide	$>$ 1,200	$>$ 6 puffs
c. Flunisolide	$>$ 2,000	$>$ 8 puffs
d. Fluticasone propionate	$>$ 880	$>$ 8 puffs (110 μg), $>$ 4 puffs (220 μg)
e. Triamcinolone acetonide	$>$ 2,000	$>$ 20 puffs

Minor Characteristics

1. Requirement for daily treatment with a controller medication in addition to inhaled corticosteroids, e.g., long-acting β-agonist, theophylline, or leukotriene antagonist
2. Asthma symptoms requiring short-acting β-agonist use on a daily or near daily basis
3. Persistent airway obstruction ($FEV_1 < 80\%$ predicted; diurnal PEF variability $> 20\%$)
4. One or more urgent care visits for asthma per year
5. Three or more oral steroid "bursts" per year
6. Prompt deterioration with $\leq$ 25% reduction in oral or inhaled corticosteroid dose
7. Near fatal asthma event in the past

* Requires that other conditions have been excluded, exacerbating factors treated, and patient felt to be generally adherent.

† Definition of refractory asthma requires one or both major criteria and two minor criteria.

in and out of the normal range, sometimes rapidly. It is generally believed that patients with refractory asthma exhibit all three of these physiologic features, but to a more marked degree than patients with milder asthma (20). That is, airflow limitation can be demonstrated at all times, especially off medications, and is often markedly reduced (< 70% predicted); definite hyperresponsiveness is present (e.g., < 1 mg/ml for methacholine PC_{20}); and/or wide swings in lung function occur (e.g., > 20% peak expiratory flow [PEF] diurnal variability). However, most studies and treatment guidelines have used lung function (specifically FEV_1) to stage asthma disease severity. The relationship among these three variables in response to treatment remains less clear.

Patients with refractory disease often fail to respond or normalize lung function in response to β-agonist or CS treatment; that is, their lung function is residually low (9). There is likely another category of patients with severe or refractory asthma, who have relatively normal FEV_1 at baseline, and who then can rapidly decompensate to known or unknown stimuli (i.e., "brittle asthmatics") (8). Whether there are in these patients with asthma specific differences that lead to the rapid decompensation is not clear (21).

Airflow Limitation

The fixed airflow limitation of most patients with refractory asthma can be defined as a postbronchodilator FEV_1 of < 80%pred (in the presence of a reduced FEV_1/FVC) after a 7- to 14-d course of oral CS (40 mg/d for adults and 2 mg/kg per day in children). The mechanisms behind the inability to totally reverse airflow obstruction in response to CS in refractory asthma are unclear. Although some studies have suggested that patients with more severe asthma have more pronounced subepithelial collagen deposition, a study of oral CS-dependent asthma patients failed to confirm this association (*see* PATHOLOGY OF REFRACTORY ASTHMA) (22–24). Additional explanations for residual airflow limitation could include mucous plugging, smooth muscle hypertrophy and/or hyperplasia, and edema formation. Unfortunately, there is a paucity of structure–function studies in this patient population.

It is also common for some patients with "refractory asthma" to demonstrate a poor acute bronchodilator response to β-agonists, either before or after a course of high-dose CS (9). This "irreversibility" is often attributed to long-standing, uncontrolled inflammation that then eventually leads to increasingly fibrotic airways, although there are no studies that have adequately addressed this issue (25–28), This "failure to respond" could be due to a variety of factors, including (*1*) a downregulation of β receptors, (*2*) fibrosis or other structural alterations that limit dynamic responses, (*3*) unknown elements of the obstructive process that do not improve with bronchodilators or CS (but which could improve with "other therapies"), or (*4*) a different disease process altogether. Distinguishing among these possibilities represents a fruitful area of research.

Progressive loss of lung function is not seen in all individuals with asthma (14, 29). In contrast, asthmatic children with low lung function at early timepoints are predisposed to further problems in adulthood (30–32). Studies also suggest that the average rate of decline in lung function may differ between asthma that begins in childhood (usually associated with atopy) versus asthma that begins in adulthood (often "nonatopic"), with adult onset asthma having a more rapid decline in FEV_1 (16, 17). The mechanisms by which some individuals more rapidly lose lung function are not clear, but a longitudinal study of patients with asthma (including smoking patients with asthma) suggested that increased sputum production was at least one factor associated with a more rapid decline in lung function (12).

Airway Hyperresponsiveness

Airway hyperresponsiveness is a physiologic feature characteristic of asthma (20, 33–35). However, studies of more homogeneous patient populations suggest that bronchial challenge testing has a high degree of sensitivity but a lower specificity. Other airway diseases also demonstrate airway hyperresponsiveness (36), but not to the degree observed in patients with moderate to severe asthma.

It is known that airway responsiveness varies in a temporal fashion, and this is generally thought to reflect changes in disease activity and severity (36). However, this is often of little more than statistical value, as there is considerable overlap

TABLE 2

EVALUATION OF PATIENTS WITH REFRACTORY ASTHMA

1. Confirm reversible airflow limitation and quantify severity:
   a. FEV_1, peak flow, and flow–volume loop before and after bronchodilator treatment*
   b. Total lung capacity and residual volume†
   c. Diffusion capacity (in adults—usually not indicated in children)‡
2. Consider other diagnoses in differential diagnosis of cough, dyspnea, and wheeze:
   a. Chronic obstructive pulmonary disease
   b. Cystic fibrosis
   c. Vocal cord dysfunction, or other mechanical upper airway obstruction
   d. Obstructive sleep apnea
   e. Churg–Strauss syndrome
   f. Cardiac dysfunction
   g. Allergic bronchopulmonary aspergillosis (ABPA)
3. Investigate for the presence or absence of concomitant disorders that can exacerbate asthma:
   a. Allergen skin tests (atopy and allergic rhinitis)
   b. CT scan of the sinuses (sinus disease)
   c. Twenty-four-hour esophageal pH monitoring (gastroesophageal reflux disease)
   d. Chest radiograph (pulmonary infiltrates, interstitial lung disease, bullous lung disease)
   e. Blood for eosinophil count, immediate hypersensitivity skin testing to aspergillus, IgE level (Churg–Strauss or allergic bronchopulmonary aspergillosis)

* Lung function assessment is often limited to the measurement of peak flow and a single value of FEV_1. Obtaining flow–volume characteristics often reveals other causes of airflow limitation or wheezing such as fixed obstruction or vocal cord dysfunction.

† Indicated in this group of patients to confirm obstructive disease and rule out restrictive disease.

‡ Asthma is characterized by a high D_LCO value or a value in the high normal range. A low diffusing capacity suggests emphysema, pulmonary vascular disease, or interstitial lung disease.

among disease groups of varying severity (37). Airway hyperresponsiveness can also be thought of as a situation in which the airways narrow too easily or too much in response to any given dose of a provocative agent or stimulus. Therefore, some authors distinguish a separate phenotype for patients with more severe disease, in whom a larger than normal response (35) or a failure to attain a plateau in the dose–response curve occurs (38). However, the relevance (or even the occurrence) of these physiologic changes (or their response to treatment) in patients with more severe disease is not known. For example, after intensive courses of antiinflammatory medications (i.e., inhaled and oral CS), patients with refractory disease will continue to exhibit marked airway hyperresponsiveness (39). Why this occurs is unknown, but it is possible that the airway alterations responsible for hyperresponsiveness are not the same as those responsible for airflow limitation.

Variable Airflow Limitation

Asthma is also distinguished by periodic and/or reversible changes in airflow, such as measured by the variability of PEF. Unlike single measures of airflow, sequential measures of PEF variability correlate with increased airway responsiveness (40). Some, but not all, patients with refractory disease will have lower values of peak flow, show less response to therapy, and have wide diurnal swings in peak flow (9, 39, 41, 42).

Unstable variability might represent either ongoing inflammatory and/or neurogenic events, increased airway responsiveness, or temporal progression of the disease. Distinguishing among these possibilities in this group might have implications both for mechanisms and for treatment. In addition, patients with refractory asthma often demonstrate a reduced perception of airflow limitation (when measured by inspiratory load testing/Borg scales for dyspnea), and so measurement of lung function at home can help detect and then guide changes in treatment (43). Aggressive home monitoring is indicated for the patient with refractory asthma, as these patients often demonstrate low perception of their functional status. The availability of relatively inexpensive devices to measure FEV_1 and FVC, in addition to PEF, in an ambulatory setting should improve on the known problems with the measurement of PEF alone (44), but further documentation is needed.

Other Physiological Issues

Lung volume is believed to be an important determinant of overall morbidity/mortality in a variety of disease processes. Lung volumes rise in airway disease, including asthma; however, even after normalization of lung function in patients with mild asthma, lung volumes may still be abnormal. Why this is so, is unclear, but may suggest that refractory asthma involves inflammatory processes at the level of the parenchyma (small airways/alveoli). Indeed, a number of studies have shown that the pressure–volume relationships are abnormal in asthma. Measurements of peripheral lung resistance reveal that even in patients with normal spirometry there is persistent dysfunction, which relates to the decrease in PC_{20} (45, 46). Studies of peripheral airway function in patients with refractory asthma have not been performed.

The therapeutic modalities (specifically systemic CS) used to treat refractory asthma may themselves affect the overall physiologic responses of the airways. For example, excessive or prolonged systemic CS administration often leads to obesity, which in turn predisposes to sleep apnea or impaired respiratory muscle function. In such a setting, the thorax is ill prepared to cope with a severe asthma attack. Importantly, however, as treatment of sleep apnea may improve asthma symptoms, most (especially symptomatic) patients with refractory asthma with significant weight gain should be evaluated for obstructive sleep apnea (47).

Low perception of the degree of lung dysfunction appears to relate to decreases in chemosensitivity to hypoxia; whereas the response to hypercapnia is usually normal (48). Patients who have had their carotid bodies removed show similar patterns of blunted responsiveness. While one theory holds that this reduced perception is genetically based, other possibilities include a change in respiratory muscle afferent nerve traffic or altered receptor output from within the lung. One study would also suggest that the persistent presence of eosinophils in sputum (despite CS) is associated with a decrease in the perception of dyspnea (49). Better understanding of this situation is important, as reduced perception has been linked to near fatal asthma episodes (48).

ENVIRONMENTAL RISK FACTORS FOR THE DEVELOPMENT OF REFRACTORY ASTHMA

Stephen P. Peters, M.D., Ph.D.

A number of different environmental factors have the potential to produce asthma, exacerbate asthma that is already present, or interact with host factors to produce an individual who may be at risk for refractory asthma (Table 3). Unfortunately, the relationship of these factors to "asthma," per se, is more clear than the relationship to "refractory asthma." This section reviews environmental factors that have been implicated in the development of asthma. The extent to which these factors are particularly important in the development of refractory asthma is not known.

Exposure to cigarette smoke, both *in utero* and passively during infancy and childhood, is felt to predispose children to asthma and/or reduced lung function (50–55). Hanrahan and coworkers (50) reported decreased expiratory flow rates and decreased maximal flow with reference to the functional residual capacity ($V_{max}FRC$) in infants whose mothers smoked during pregnancy. Martinez and colleagues (51) reported that infants who wheezed during the first 3 yr of life and had decreased $V_{max}FRC$ at 1 and 6 yr of age were more likely to have had mothers who smoked. Weiss and coworkers (52), Martinez and coworkers (53), and Lewis and coworkers (54) reported that exposure to environmental cigarette smoke increased the probability of persistent wheezing, the probability of being diagnosed with asthma, and/or decreased lung function. Both prenatal and postnatal cigarette smoke exposure predispose infants to bronchitis and other respiratory illnesses besides asthma (56, 57). While both prenatal and postnatal cigarette smoke exposure appear to be risk factors for the development of airway obstruction and asthma, prenatal exposure may be a more important risk factor (50, 54, 55). The mechanism behind the tobacco induced risk for reduced lung function and asthma is not completely understood. Although tobacco exposure increases respiratory infections, the actual

TABLE 3

ENVIRONMENTAL FACTORS THAT COULD PLAY A ROLE IN REFRACTORY ASTHMA

1. Tobacco smoke
   a. *In utero*
   b. Environmental
2. Allergen sensitization
3. Viral infections
4. Occupational agents
5. Air pollutants
6. Stress

role of infections in promoting "asthma" remains highly controversial, with some data supporting a "protective" role for certain types of infections (58). There are even fewer data to support an influence of passive cigarette smoke exposure on allergic state, or subsequent severity of asthmatic symptoms. Active cigarette smoking does appear to hasten the decline in pulmonary function (12).

Allergen sensitization and subsequent exposure, dependent on both genetic and environmental factors, are widely understood to influence the development of asthma. An association between total serum IgE level and asthma prevalence has been recognized in asthma patients of all ages (59, 60). The linkage of total IgE levels to chromosome 5q highlights the importance of genetic factors in the development of sensitization (61, 62). In addition, the level of environmental exposure to allergen is likely to be important because sensitization to different allergens in different patient populations has been associated with asthma (63, 64) and airway hyperresponsiveness (65). The most prominent of these include *Alternaria* in children living in a desert environment (63), dust mite in adolescents living in central Virginia (63), and cat allergen in older men (65). Further insights into the relative importance of genetic versus environmental factors to the development of asthma also come from monozygotic/dizygotic twin studies (66, 67). Duffy and colleagues (67) reported that in 62 monozygotic twin pairs discordant for a history of wheezing, a positive skin test to house dust extract was the most important discriminator pointing to the presence of asthma, followed by sensitization to cat and cockroach allergens. In further support, dizygotic twin pairs, in whom one wheezed and the other did not, differed in their level of sensitization to grass pollens and to fungi. On the basis of these data, both genetic and environmental factors were considered important environmental causes of asthma. In all instances, however, little is understood regarding the specifics of the genetics for severity of disease. Preliminary evidence has linked alterations in the interleukin 4 promoter and transforming growth factor β with more severe disease, but the linkages remain weak at this time (68).

As with tobacco smoke, the relationship of allergen exposure to asthma severity is less clear. Studies have linked sensitization to *Alternaria* with an increased risk for both severe asthma (69) and death (70). In addition, one study evaluated the combined risk of sensitization and exposure in a population of inner city children with asthma (71). It appeared that the children with the greatest numbers of hospitalizations were those children with the highest sensitivity and exposure to cockroaches. Interestingly, in that study, level of sensitization and exposure to house dust mite or cats were not associated with more severe disease and outcomes. Unfortunately, studies such as this can discern only an association between cockroach sensitization and exposure, with further evidence needed before "cause and effect" can be proven. It remains to be determined whether the association between cockroach exposure in sensitive individuals and more severe disease is a direct effect of some poorly understood antigenicity factors of the cockroach or other environmental or genetic elements that may associate with cockroach exposure and sensitivity.

Interventional studies performed in Europe and involving patients with severe asthma would support a role for allergen exposure in disease severity. Patients with severe asthma who are removed from their home environment and domiciled at the high-altitude (low-allergen) clinic have been reported to have improved pulmonary function, airway reactivity, symptoms, and decreased medication needs (72). Return to their home is associated with a worsening of their disease. Again, these studies are flawed by the nonspecific nature of the intervention. Although allergen immunotherapy has been used for the treatment of refractory asthma (often with some risk to the severely obstructed patient), there are few data that support an improvement in the course of the disease. Whether this is secondary to the timing of the therapy (late in the course of the disease), or the decreasing importance of allergen in refractory disease is not clear.

A third important environmental factor associated with asthma development (but not necessarily severity) is the development of respiratory infections, especially viral infections, but perhaps also mycoplasma and chlamydia. Studies using highly sensitive techniques, including the reverse transcription polymerase chain reaction (RT-PCR), have documented viral infections in approximately half of adults with an asthma exacerbation (73), and as in many as 80–85% of exacerbations in school-aged children (74). Although viral infections in infants and children, particularly with respiratory syncytial virus (RSV), parainfluenza virus, and rhinovirus, have all been associated with wheezing episodes that may be prolonged, the importance of such infections for initiating an asthmatic state or determining its severity is unclear (reviewed in References 75 and 76). Experimental models of viral infections suggest that rhinovirus can increase the level of eosinophilic inflammation and airway hyperresponsiveness in allergic, nonasthmatic, individuals (77). In addition, some respiratory viruses may be more "asthmagenic" than others (22, 75). Studies of mice suggest that the effects of RSV on airway hyperresponsiveness may require concomitant allergic processes (78, 79). As with allergens, anatomic factors (i.e., decreased lung and airway size), genetic susceptibility, and exposure to cigarette smoke may also determine the response to the virus (76).

Agents encountered in the work place are well known to produce asthma (occupational asthma) and aggravate asthma that is already present (80). Continuous exposure can lead to progressive disease, and removal from the workplace often improves the disease. However, even with occupational asthma, removal from the work place may not completely abrogate the disease.

Finally, environmental "stress," broadly defined, appears to play a role in asthma exacerbations, at least in some individuals (81, 82). The phenotype of patients at highest risk for stress-related airway dysfunction and mechanisms by which such dysfunction occurs have not been well defined. Certainly, refractory asthma, itself, can be a stress-inducing condition, making it difficult to determine "chicken and egg" relationships between stress, anxiety, and disease severity.

PATHOLOGY OF REFRACTORY ASTHMA

Sally E. Wenzel, M.D.

The pathology of asthma, and in particular refractory asthma, remains poorly described. The limited pathology data that exist in refractory asthma have been obtained primarily from autopsy specimens. Such studies are limited by the mixed composition of patients dying from asthma, of whom only a minority may be from the refractory group as defined previously. In addition, extrapolations have been made from endobronchial biopsy, bronchoalveolar lavage, and sputum analyses of patients with mild to moderate asthma. Limitations to these sources include size of tissue sample, adequate control groups, clinical data, and concentration uncertainties. Importantly, extrapolating data from patients with mild/moderate asthma assumes that the process in refractory asthma is a pathologic extension of milder disease, without much evidence to support that concept. Finally, the clinical presentation of patients with refractory asthma varies widely, with some having highly unstable symptoms and disease, while oth-

ers have more chronic, unremitting symptoms. The pathology of these different clinical types may be quite dissimilar.

Current Hypotheses Regarding the Pathology of Refractory Asthma

Refractory asthma as an extension of mild/moderate asthma, with ongoing Th2 predominant inflammation. Autopsy studies of patients dying of status asthmaticus often show an inflammatory pattern consistent with a helper T cell type 2 (Th2) paradigm, with eosinophils and lymphocytes present in large quantities. In addition, the few endobronchial biopsy and lavage studies performed on patients with "steroid-resistant asthma" also appear to show increases in eosinophils and Th2-type cytokines, such as interleukin 4 (IL-4) and IL-5 (compared with steroid-responsive patients with asthma), which do not decrease with CS therapy (83, 84). It has been suggested that the diminished efficacy of CS in this population may be due to any number of effects of persistent inflammation. These may include downregulation of the binding affinity of the glucocorticoid receptor, upregulation of the less active glucocorticoid β receptor, decreased ability of CS to interfere with nuclear transcription factor binding or failure to suppress c-Jun N-terminal phosphorylation (85–87). In certain patients, increasing the CS dose sufficiently may improve CS binding, presumably by decreasing local inflammation (88). Bronchoscopic studies of patients with refractory asthma support the concept that some, but not all, of these patients continue to exhibit persistent eosinophil/lymphocytic inflammation despite high-dose CS (89). The factors responsible for this persistent eosinophilic process are unknown.

Refractory asthma as a "different" inflammatory process from that seen in milder forms of asthma. An alternative explanation for the poor response to CS is that a different type of inflammatory process is present, which is less responsive to CS. Studies of many patients with refractory asthma suggest that a basic pathologic difference may be present in this population, as compared with patients with milder disease, namely, the presence of the neutrophil. Multiple studies of patients with mild asthma, not administered inhaled CS, have failed to demonstrate neutrophils in higher quantities than in normal control subjects. However, pathologic studies of refractory asthma now suggest that neutrophils are present in higher quantities in the airways of these patients, than in the airways of patients with mild asthma or in normal control subjects (90, 91). In addition, neutrophils have been seen in increased numbers in patients dying of status asthmaticus, demonstrating that when death occurs within several hours of the attack, the predominant inflammatory cell is the neutrophil (92). Studies of sputum samples from patients undergoing emergency room visits for status asthmaticus, as well as studies of bronchial washes from patients intubated for status asthmaticus, also support the concept that the neutrophil may be an important inflammatory cell in more severe forms of asthma (93–95). Although the activation state of these neutrophils remains to be determined, neutrophils also can produce substances, such as matrix metalloproteinases and oxygen radicals, that could profoundly alter the structure and function of the airways. Confounding these studies, however, is the observation that neutrophils are poorly responsive to steroids. In fact, steroids may prolong the survival of neutrophils by decreasing the apoptosis of these cells (96). Therefore, at the present time, the relevance of these cells to the pathophysiologic changes of severe, refractory asthma is unknown.

Refractory asthma as structurally remodeled airways leading to fixed/irreversible obstruction. One of the hallmarks of worsening asthma has been the development of irreversible or partially irreversible disease, as defined by the poor response to bronchodilators and CS. This observation has led to the conclusion that the structural elements of the airways have changed (or remodeled), to include "irreversible" changes in the amount/type of smooth muscle, the amount and distribution of fibrosis in the airways, altered glandular components and alterations in blood vessels and subsequent edema formation. While most of these elements have been described to be "abnormal" in biopsies from patients with mild asthma or in autopsy specimens from patients who have died from status asthmaticus, the relationship of any of these elements to severity of disease (as defined clinically and physiologically) remains to be elucidated (97).

Perhaps the most commonly described abnormalities have been in the type and amount of airway smooth muscle and thickening of the subbasement membrane (SBM). Pathologic studies of endobronchial biopsies of patients with asthma have demonstrated a wide variability in SBM thickness (22, 23, 98). When subjects with refractory asthma, as defined here, were evaluated as a single group, no differences in SBM thickness were seen between these individuals and those with milder asthma (24). Interestingly subjects with asthma with persistent eosinophil inflammation may demonstrate an increase in SBM thickness (89, 99). The SBM in subjects with refractory asthma without eosinophils did not differ in thickness from that of normal control subjects. In contrast, subjects with refractory asthma with eosinophils had a thickened SBM and increased numbers of submucosal cells positive for transforming growth factor β (TGF-β), a cytokine with known fibrogenic properties (89). The thickness of the SBM in subjects with refractory asthma did not, however, appear to correlate with physiologic parameters, such as FEV_1 (24, 89). IL-11, a cytokine linked to fibrosis and airway hyperresponsiveness, has also been shown to be increased in subjects with refractory asthma (100).

Smooth muscle is also likely increased in patients with asthma who die of status asthmaticus (101), but the phenotype of the smooth muscle or the controlling factors for its hypertrophy/hyperplasia are unknown. In addition, multiple remaining elements, including glandular formation, epithelial changes, blood vessel formation, and other extracellular matrix protein amounts and distribution, must be analyzed in a similar fashion to determine which of the elements of the airway are contributing to functionally important structural changes in the airways (102–104). Unfortunately, all these studies are nearly impossible to perform on standard endobronchial biopsies, emphasizing the need to develop chronic animal models of asthma, and consideration for more invasive methods to obtain tissue.

Refractory asthma on the basis of altered distribution of inflammation and/or structural abnormalities. Autopsy studies have suggested that inflammatory processes and structural changes in asthma extend to the small airways (105, 106). Transbronchial studies of distal airway changes in living patients with asthma would support the concept that inflammation extends to the distal airways and even the alveoli (90, 107). The ability of currently available inhaled medications to reach these distal airways is not clear, but certainly suspect. This inflammation could be associated with increased smooth muscle in the distal airways (101). However, a complete evaluation of abnormalities in the inflammation or structure of the distal airways in patients with severe asthma (both living and dead asthmatics), as compared with lesser severities of asthma, has not been performed.

Refractory asthma as one or more subtypes. As alluded to earlier, the clinical presentation and progression of refractory asthma varies considerably. One study supports the heterogeneity of the pathologic processes of severe asthma, as well.

When patients with severe asthma are grouped into those with and without eosinophils (by endobronchial biopsy), differences in associated clinical and physiologic patterns appear to emerge. Those patients with eosinophils demonstrate increases in lymphocytes, consistent with a Th2-type response, while the eosinophil-negative group does not. Eosinophil-positive patients had a thickened SBM and increased TGF-β-positive cells in the submucosa, while eosinophil-negative patients did not. Eosinophil-positive patients also had evidence of subtle physiologic differences (significantly decreased FVC/slow vital capacity [SVC] compared with eosinophil-negative patients with asthma) and a dramatically increased number of near fatal events. These results would seem to support the concept that at least two different subtypes of severe asthma exist, but further study is required to fully characterize these differences. If these differences are confirmed, considerable implications for therapy will arise.

It is certainly possible, and even likely, that a combination of the above hypothesized events or other pathologic elements not yet appreciated are involved in the pathogenesis of refractory asthma. Further pathologic evaluation is warranted.

THERAPEUTIC ISSUES IN REFRACTORY ASTHMA

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As outlined in the Expert Panel 2 report (108), the cornerstone of management for patients with severe persistent asthma is high-dose inhaled CS (*see* Table 1). Although a preferred inhaled CS has not been defined, studies suggest that subjects with refractory asthma should be treated with a high-potency inhaled CS (budesonide, fluticasone propionate, or mometasone) to minimize the number of actuations administered by the patient, and to potentially improve outcomes (108–111). Generally, this treatment is combined with a long-acting bronchodilator (long acting inhaled or oral β_2-agonist and/or sustained release theophylline). Although not currently in the Expert Panel 2 report, more recent data would also support the trial of a leukotriene modifier in this population (112). However, patients with "refractory asthma" often will not improve with these combinations. The "best" therapeutic step to undertake in this population at this point is not at all clear.

Before a patient is termed "refractory," it is extremely important that adherence to the treatment program be monitored. Simple methods to assess medication adherence include direct questioning of the patient for medication recall in the last several days. Adherence should be further pursued in patients who appear hesitant on specifics of their medication use. Pharmacy records can also provide information on the amount of medication used by the patient. Finally, devices that monitor the time and date of medication administration have also been developed. While none of these are perfect, they can be used in selected patients to provide an estimate of medication adherence. Even with these efforts, an accurate assessment of adherence is often difficult.

The clinician should also be sure that an action plan has been developed and that the patient is carefully following this plan. This, along with frequent visits to review asthma control, are key elements to reducing the oral and inhaled CS requirements in many patients. It is recommended that repeated attempts be made to reduce systemic CS and maintain control with high-dose inhaled CS therapy (108). However, in contrast to patients who are under- or poorly treated, patients with truly refractory asthma often pose considerable challenges to the successful reduction in systemic CS.

Beyond high-dose inhaled CSs combined with one or two other long-term controllers, it is not clear what the preferred "next step" medication should be. Although there are several studies that show the benefits of combination therapy with an inhaled CS and a long-acting inhaled β_2-agonist, such as salmeterol, or oral theophylline, no studies have evaluated the benefits of multiple combinations of these alternative controllers. In addition, although modest data now exist with the leukotriene modifiers in this situation, no studies have evaluated the combination with the further addition of a long-acting β-agonist or theophylline. Therefore, it is not known what combination is most likely to enhance asthma control, assist in resolving inflammation, and perhaps contribute to normalization of the airway. In the absence of this information, the clinician should carefully monitor clinical parameters to assess the best combination of medications. The physician should be encouraged to try an assortment of combinations of long-term controllers with high-dose CS in a controlled and stepwise fashion. While environmental control can be helpful in improving clinical control in the sensitized patient, there are few data to support immunotherapy in the treatment of patients with refractory asthma and these patients may be at risk for adverse effects to immunotherapy (113).

If a patient fails to respond or is unable to tolerate CS doses lower than 20 mg every other day with either prednisone or methylprednisolone, evaluation of CS pharmacokinetics can identify patients with incomplete CS absorption, failure to convert an inactive form (prednisone) to an active form (prednisolone), or rapid elimination (114, 115). However, less than 25% of patients with severe asthma show clinically significant increased clearance of either prednisolone or methylprednisolone. Most of these patients have a specific reason for rapid elimination, such as a drug interaction with a medication that induces CS metabolism, including rifampin and the anticonvulsants phenytoin, carbamazepine, and phenobarbital.

Markers of inflammation, for example, plasma or sputum eosinophils/eosinophil cationic protein and exhaled nitric oxide, may be helpful in examining medication response in those patients in whom they are detectable (88). In these patients, the marker can be measured before and after a 1- to 2-wk course of oral CS therapy, but no studies have demonstrated the long-term efficacy of this approach. Although tissue biopsies have not generally been used to guide therapy, better understanding of the underlying pathology has the potential to lead to more rational approaches to therapy. These studies should be done only in centers with experience in performing and interpreting biopsies from asthma patients, and ideally in the context of a clinical trial (90).

Several observations help to explain the limitations in response to conventional therapy in subjects with refractory asthma. Certain patients with asthma have been termed "steroid resistant" or "steroid insensitive." These patients are characterized by a prebronchodilator FEV_1 of less than 70% predicted with a maintained bronchodilator response. Steroid resistance is defined by administering a course of oral prednisone, for example, 40 mg/d (divided doses) for 7 d, or preferably 2 wk, and observing the effect on morning pre-bronchodilator FEV_1 (116). This type of trial can also assess the possibility of poor adherence to the maintenance regimen. If the FEV_1 fails to increase by 15% (and 200 ml), the patient is considered steroid resistant. It is not clear what dose should be administered to patients who are already receiving high-dose oral CS therapy. If the patient fails to respond, the dose is generally doubled and the patient is monitored for an additional 2 wk. If the patient responds to this high dose, then the dose is gradually decreased to determine a threshold dose. Many patients with severe asthma will not meet the criteria for steroid resistance, but rather will demonstrate a response at a "higher than expected" dose, suggestive of altered,

but not absent, steroid responsiveness. The relation of this condition to "steroid resistance" is not clear.

Multiple explanations for CS resistance exist. These include decreased numbers or binding affinity of the CS receptor in association with increased glucocorticoid receptor β concentrations, altered suppression of transcription factors, the presence of relatively steroid resistant neutrophils, or extensive airway structural changes (85–87, 117). In some individuals, it appears that reduced CS receptor binding affinity may be improved with a course of high-dose CS (88). The clinician must, however, keep in mind the complicating effects of CS, specifically high-dose systemic CS therapy, on neuromuscular function and general conditioning. These complications may interfere with assessment of the beneficial effects of these medications on airway inflammation and lung function.

In patients with refractory asthma who remain symptomatic despite optimal application of conventional therapy and management of concomitant disorders, some studies have demonstrated modest, but inconsistent, efficacy of alternative antiinflammatory and immunomodulating drugs, such as methotrexate, gold, cyclosporine, intravenous gamma globulin, and macrolide antibiotics (118, 119). Although some studies indicate an ability to reduce oral CS requirements by approximately 50%, concurrent improvement in pulmonary function is limited. Most of the studies were not conducted at a time when it was customary to utilize high-dose inhaled CS. In the presence of this form of treatment and especially in combination with other long-term controllers, the use of these immunomodulator and alternative antiinflammatory treatments has not been impressive. Although intravenous gamma globulin may be effective in some patients, its high cost is prohibitive. Methotrexate has limited efficacy and carries a risk for liver toxicity and immunosuppression. Cyclosporine has been utilized only in a limited study population and carries a significant risk for hypertension. Oral gold has limited efficacy and gastrointestinal adverse effects can limit its use. None of these medications have demonstrated a significant improvement in airway hyperresponsiveness. More studies are needed with all of these agents to carefully define their benefits and risks, as well as which patients are most likely to respond to the selected treatment.

SUMMARY OF RECOMMENDATIONS

In approaching a patient with refractory asthma, it is important to: (*1*) confirm the diagnosis of asthma, (*2*) evaluate and treat confounding or exacerbating factors, and (*3*) optimize the "standard" asthma pharmacotherapy. The workshop group believed that certain testing should be fairly routine to address points 1 and 2. These are outlined in Table 2.

Confirmation of Diagnosis

Beyond an extensive history and physical, an in-depth assessment of pulmonary function testing, including pre- and postbronchodilator spirometry, flow-volume loops, lung volumes, and diffusing capacity, total eosinophil count, allergy skin testing and evaluation, serum IgE, and chest X-ray should be part of any initial evaluation. This combination of studies should suggest whether more detailed studies are required to confirm alternative diagnoses, such as chronic obstructive pulmonary disease (COPD), vocal cord dysfunction, eosinophilic syndromes, and allergic bronchopulmonary aspergillosis. Depending on these initial results, further testing could include high-resolution chest computed tomography (CT) scans (primarily for bronchiectasis or hypersensitivity pneumonitis), genetic testing for cystic fibrosis or α_1 anti-trypsin deficiency, and allergy skin testing and/or evaluation of specific IgE antibodies for aspergillus.

Evaluation for Exacerbating Factors

There was general consensus by the workshop participants that an evaluation for level of compliance (history, pharmaceutical records, morning cortisol), allergic factors (history, allergy [prick] skin testing), sinus disease (sinus CT), gastroesophageal reflux disease (GERD) (24-h pH probe monitoring), and psychiatric issues, such as anxiety, external stress factors, and secondary gain issues should be pursued. Obese patients with asthma should be evaluated for sleep disorders, as well. It was pointed out that vocal cord dysfunction (VCD) can coexist with asthma and may be an "exacerbating factor" as well as an alternative diagnosis. These potential exacerbating factors should then be managed as effectively as possible. While this may be "relatively easy" for some of these exacerbating factors (removing a cat from the home, treating GERD), therapy is often difficult or inadequate for others (sinus disease, psychiatric issues).

Pharmacotherapy of Refractory Asthma

The consensus of the workshop group was that all patients with refractory asthma should be treated, as a starting point, as outlined in the Expert Panel 2 report (108). This includes high-dose/high-potency inhaled CS, oral CS at as low a dose as possible, and one to three additional controller agents. These patients should be recording peak flows on a daily basis, and should be provided with an "asthma action plan" with appropriate rescue plans outlined. Most of these patients will require frequent clinic visits to monitor their condition. If these steps do not lead to an improvement in their condition, these patients should be referred to an asthma center. These asthma centers should have extensive experience in evaluating and treating these patients, as well as research protocols available to address the unanswered questions outlined in the next section.

UNANSWERED QUESTIONS

Many questions remain regarding refractory asthma, and will require extensive further study.

1. Little is known regarding the natural history of refractory asthma, or even the prevalence of this subgroup of patients. Do some individual with refractory asthma have a much more rapid decline in pulmonary function than others? The long-term prognosis of these patients is not clear.
2. Clinically, there is considerable heterogeneity among patients with refractory asthma, and it is not known whether refractory asthma is one disease or multiple different diseases.
3. While certain genetic polymorphisms have been loosely associated with asthma, are certain genetic polymorphisms more closely associated with refractory disease?
4. It is not clear whether certain physiologic properties characterize patients with refractory asthma in general, or a particular subgroup. Could certain physiologic abnormalities predispose patients with refractory asthma to "near fatal events"? What are the mechanisms involved in the poor perception of dyspnea?
5. Although allergen exposure and sensitization, viral illnesses, and stress are clearly linked to asthma, how do they influence the development of refractory asthma?
6. Can reversal of sinusitis or GERD improve outcomes in patients with refractory asthma?
7. The pathologic processes of refractory asthma are poorly understood. Similar to the clinical pattern, there may be more than one pathologic process associated with the development of refractory asthma. Is there a classic Th2 pattern for some patients with refractory asthma, with other less well-defined processes driving refractory disease in other patients? What role do

abnormalities at the level of the small airway and parenchymal/airway interface play in refractory asthma? Is "irreversibility" a hallmark of fixed fibrotic disease, or is it a potentially reversible process? What is the association of persistent inflammation with irreversible disease and/or airway remodeling?

8. Treatment beyond that outlined by the Expert Panel 2 remains problematic. Future studies should address the following questions: Are there novel nonspecific or specific antiinflammatory medications that will consistently impact the course of the disease? Can treatment be customized on the basis of pathologic subtype, as ascertained by tissue specimens or biologic markers from other sources? Does early treatment with antiinflammatory agents prevent progression to refractory disease?

PROPOSED APPROACH

It was proposed that a working group be assembled to efficiently design and conduct clinical trials at a small number of sites. This group should be represented by allergy/immunology, pulmonary, pharmacology, pathology, molecular biology, epidemiology, and biostatistics. The workshop group believed that a national registry of subjects with refractory asthma coupled with a national database of information on the clinical and pathologic features of the disease should be developed to aid in the conduct of epidemiologic studies and assist in recruitment for clinical trials. Such a registry should include both children and adults. Longitudinal studies of children in particular may be useful in determining the changing patterns of pediatric and adult refractory asthma. The utility of this database will be greatly increased by having a bank of tissue and blood from these patients that could be used to advance knowledge of the immunopathologic and genetic characteristics of the disease. More specific epidemiologic studies aimed at determining prevalence of refractory disease and distribution of subtypes of patients with asthma is greatly needed. The incorporation of genetic testing in these epidemiologic studies would be desirable. Similar studies are currently being undertaken by the European Network for Understanding the Mechanisms of Severe Asthma (ENFUMOSA). As the approach recommended here varies somewhat from the ENFUMOSA approach, it is hoped that the results will be complementary.

As so little is understood regarding the pathophysiology of asthma in these patients, clinical trials should be initiated at a small number of sites that incorporate an extensive evaluation of clinical symptomatology, environmental and genetic factors, pulmonary physiology, and lung inflammation and structure. Concurrent evaluation of noninvasive measures of inflammation, such as sputum and exhaled gases, should be included. Unfortunately, understanding the pathologic/structural processes involving the small airways and parenchyma are more problematic, but consideration should be given to pathologic approaches such as transbronchial biopsies and thoracoscopic or open lung biopsy procedures in patients with refractory asthma. Concurrent with these studies, physiologic and radiologic measures of small airway function and appearance should also be undertaken. These studies should determine if multiple subtypes of disease exist under the umbrella term of "refractory asthma."

Pharmacologic trials either with nonspecific antiinflammatory agents or novel specific agents should also be undertaken in a multicenter, placebo-controlled design. An approach that customizes therapy on the basis of pathologic features should be entertained. Objective measures of response should include physiologic readouts (including, but not limited to FEV_1), tissue measurements of inflammation and structural elements, and changes in exacerbations/need for systemic CS.

The committee believed that until these far-reaching approaches are initiated, most of the understanding of refractory asthma will remain anecdotal and the treatment will continue to be "by consensus opinion."

References

1. Weiss KB. Breathing better or wheezing worse? The changing epidemiology of asthma morbidity and mortality. *Annu Rev Publ Health* 1993; 14:491–513.
2. Burney PGL. Epidemiology of asthma. *Allergy* 1993;48:17–21.
3. Auerbach I, Springer C, Godfrey S. Total population survey of the frequency and severity of asthma in 17 year old boys in an urban area in Israel. *Thorax* 1993;48:139–141.
4. Woolcock AJ. Worldwide differences in asthma prevalence and mortality. *Chest* 1986;90:40s–45s.
5. Weiss KB, Gergen PJ, Hodgson TA. An economic evaluation of asthma in the United States. *N Engl J Med* 1992;326:862–866.
6. Smith DH, Malone DC, Lawson KA, Okamoto LJ, Battista C, Saunders WB. A national estimate of the economic costs of asthma. *Am J Respir Crit Care Med* 1997;156:787–793.
7. Serra-Batlles J, Plaza V, Morejon E, Comella A, Brugues J. Costs of asthma according to the degree of severity. *Eur Respir J* 1998;12: 1322–1326.
8. Ayres JG, Miles JF, Barnes PJ. Brittle asthma. *Thorax* 1998;53:315–321.
9. Chan MTS, Leung DYM, Szefler SJ, Spahn JD. Difficult-to-control asthma: clinical characteristics of steroid-insensitive asthma. *J Allergy Clin Immun* 1998;101:594–601.
10. Cockcroft DW, Swystun VA. Asthma control versus asthma severity. *J Allergy Clin Immunol* 1996;98:1016–1018.
11. Redington AE, Howarth PH. Airway wall remodeling in asthma. *Thorax* 1997;52:310–312.
12. Lange P, Parner J, Vestbo J, Schnohr P, Jensen G. A 15-year followup study of ventilatory function in adults with asthma. *N Engl J Med* 1998;339:1194–1200.
13. Panhuysen CIM, Vonk JM, Koeter GH, Schouten JP, Van Altena R, Bleecker ER, Postma DS. Adult patients may outgrow their asthma. A 25-year followup study. *Am J Respir Crit Care Med* 1997;155:1267–1272.
14. Roorda RJ, Gerritsen J, Van Aalderen WMC, Schouten JP, Veltman JC, Weiss ST, Knol K. Followup of asthma from childhood to adulthood: influence of potential childhood risk factors on the outcome of pulmonary function and bronchial responsiveness in adulthood. *J Allergy Clin Immunol* 1994;93:575–584.
15. Blair H. Natural history of childhood asthma. *Arch Dis Child* 1977;52: 613–619.
16. Ulrik CS, Backer V, Dirksen A. Mortality and decline in lung function in 213 adults with bronchial asthma: a ten-year followup. *J Asthma* 1992;29:29–38.
17. Ulrik CS, Lange P. Decline of lung function in adults with bronchial asthma. *Am J Respir Crit Care Med* 1994;150:629–634.
18. Boushey HA. Clinical diagnosis in adults. In: Barnes PJ, Grunstein MJ, Leff AR, Woolcock AJ, editors. Asthma. Baltimore, MD: Lippincott-Raven; 1997. p. 1391–1403.
19. Irwin RS, Curley FJ, French CL. Difficult-to-control asthma: contributing factors and outcome of a systematic management protocol. *Chest* 1993;103:1662–1669.
20. Larsen GL, Cherniack RM, Irvin CG. Pulmonary physiology of severe asthma in children and adults. In: Szefler SJ, Leung DYM, editors. Severe asthma: pathogenesis and clinical management. New York: Marcel Dekker; 1996.
21. Wasserfallen J-B, Schaller M-D, Feihl F, Perret CH. Sudden asphyxic asthma: a distinct entity? *Am Rev Respir Dis* 1990;142:108–111.
22. Cho SH, Seo JY, Choi DC, Yoon HJ, Cho YJ, Min KU, Lee GK, Seo JW, Kim YY. Pathological changes according to the severity of asthma. *Clin Exp Allergy* 1996;26:1210–1219.
23. Chetta A, Foresi A, Donno MD, Bertorelli G, Pesci A, Olivieri D. Airway remodeling is a distinctive feature of asthma and is related to severity of asthma. *Chest* 1997;111:852–857.
24. Chu HW, Halliday JL, Martin RJ, Leung DYM, Szefler SJ, Wenzel SE. Collagen deposition in large airways does not appear to differentiate severe asthma from milder forms of the disease. *Am J Respir Crit Care Med* 1998;158:1936–1944.
25. Fish JE, Peters SP. Airway remodeling and persistent airway obstruction is asthma. *J Allergy Clin Immunol* 1999;104:509–516.
26. Peat JK, Woolcock AJ, Collen K. Rate of decline of lung function in subjects with asthma. *Eur J Respir Dis* 1987;70:171–179.

27. Brown PJ, Greville HW, Finucane KE. Asthma and irreversible airflow limitation. *Thorax* 1984;39:131–136.
28. Agertoft L, Pedersen S. Effects of long-term treatment with an inhaled corticosteroid on growth and pulmonary function in asthmatic children. *Respir Med* 1994;88:373–381.
29. Postma DS, Bleecker ER, Amelung PJ, Holroyd KJ, Xu J, Panhuysen CIMA, Levitt RC. Genetic susceptibility to asthma—bronchial hyperresponsiveness coinherited with a major gene for atopy. *N Engl J Med* 1995;333:894–900.
30. Gerritsen J, Koater GW, Postma DS, Schouten JP, Van Aalderen WMC, Knol K. Airways responsiveness in childhood as a predictor of the outcome of asthma in adulthood. *Am Rev Respir Dis* 1991;143: 1468–1469.
31. Kokkonen J, Linna O. The state of childhood asthma in young adulthood. *Eur Respir J* 1993;6:657–661.
32. Martin AJ, Landau LI, Phelan PD. Lung function in young adults who had asthma in childhood. *Am Rev Respir Dis* 1980;122:609–616.
33. Irvin CG, Eidelman D. Airway mechanics in asthma. In: Holgate S, Busse W, editors. Rhinitis and asthma. Boston: Blackwell Scientific Publications; 1995. p. 1033–1043.
34. Society ER. Airways responsiveness standardized challenge testing with pharmacological, physical and sensitizing stimuli in adults. *Eur Respir J* 1993;16:53–83.
35. Hargreave FE, Dolovich J, O'Byrne PM, Ransdale EH, Daniel EE. The origin of airways hyperresponsiveness. *J Allergy Clin Immunol* 1986; 78:825–832.
36. Cockcroft DW, Murdock KY, Berchoid BA, Gore BP. Sensitivity and specificity of histamine PC_{20} determination in a random selection of young college students. *J Allergy Clin Immunol* 1992;89:23–30.
37. Cockcroft DW, Killian DN, Mellon JA, Hargreave FE. Bronchial reactivity to inhaled histamines: a method of clinical survey. *Clin Allergy* 1977;7:235–239.
38. Ding DC, Martin JG, Macklem PT. Effect of lung volume on maximal methacholine involved bronchoconstriction in normal humans. *J Appl Physiol* 1987;62:1324–1330.
39. Haahtela T, Jarvinen M, Kava T, Kiviranta K, Koskinen S, Lehtonen K, Nikande K, Persson T, Selroos O, Sovijarvi A, *et al.* Effects of reducing or discontinuing inhaled budesonide in patients with mild asthma. *N Engl J Med* 1994;331:700–705.
40. Brand PLP, Postma DS, Kerstjans HAM, Koeter GH. Relationship and airway hyperresponsiveness to respiratory symptoms and diurnal peak flow variation in patients with obstructive lung disease. *Am Rev Respir Dis* 1991;143:916–921.
41. Selroos O, Pietinalho, Lofroos AB, Riska H. Effect of early versus late intervention with inhaled corticosteroids in asthma. *Chest* 1995;108: 1228–1239.
42. Hetzel MR, Clark TJH, Branthwaite MA. Asthma: analysis of sudden deaths and ventilatory arrest in hospital. *Br Med J* 1977;1:808–811.
43. Rubinfeld AR, Pain MCE. Perception of asthma. *Lancet* 1976;1:882–887.
44. Irvin CG. Throwing the baby out with the bath water. *J Asthma* 1996; 33:275–276.
45. Wagner EM, Liu MC, Weinmann GG, Permutt S, Bleecker ER. Peripheral lung resistance in normal and asthmatic subjects. *Am Rev Respir Dis* 1990;141:584–588.
46. KaminskyDA, Wenzel SE, Carcano C and colleagues Hyperpnea-induced changes in parenchymal lung mechanics in normal subjects and in asthmatics. *Am J Respir Crit Care Med* 1997;155:1260–1266.
47. Chan CS, Woolcock AJ, Sullivan CE. Nocturnal asthma: role of snoring and obstructive sleep apnea. *Am Rev Respir Dis* 1988;137:1502–1504.
48. Kikuchi Y, Okabe S, Tamura G, Hida W, Homma M, Shirato K, Takishima T. Chemosensitivity and perception of dyspnea in patients with a history of near-fatal asthma. *N Engl J Med* 1994;330:1329–1334.
49. in't Veen JCCM, Smits HH, Ravensberg AJJ, Hiemstra PS, Sterk PJ, Bel EH. Impaired perception of dyspnea in patients with severe asthma: relation to sputum eosinophils. *Am J Respir Crit Care Med* 1998;158:1134–1141.
50. Hanrahan JP, Tager IB, Segal MR, Tosteson TD, Castile RG, Van Vunakis H, Weiss ST, Spitzer FE. The effect of maternal smoking during pregnancy on early infant lung function. *Am Rev Respir Dis* 1992;145:1129–1135.
51. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. *N Engl J Med* 1995;332:133–138.
52. Weiss ST, Tager IB, Speizer FE, Rosner B. Persistent wheeze: 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.
53. Martinez FD, Cline M, Burrows B. Increased incidence of asthma in children of smoking mothers. *Pediatrics* 1992;89:21–26.
54. Lewis S, Richards D, Bynner J, Butler N, Britton J. Prospective study of risk factors for early and persistent wheezing in childhood. *Eur Respir J* 1995;8:349–356.
55. Doull IJM, Holgate ST. Asthma: early predisposing factors. *Br Med Bull* 1997;53:71–80.
56. Taylor B, Wadsworth J. Maternal smoking during pregnancy and lower respiratory tract illness in early life. *Arch Dis Child* 1987;62:786–791.
57. Jin C, Rossignol AM. Effects of passive smoking on respiratory illness from birth to age eighteen months, in Shanghai, People's Republic of China. *J Pediatr* 1993;123:553–558.
58. von Mutius E, Martinez FD, Fritzsch C, Nicolai T, Roll G, Thiemann H-H. Prevalence of asthma and atopy in two areas of West and East Germany. *Am J Respir Crit Care Med* 1994;149:358–364.
59. Sears M, Burrows B, Flannery EM, Herbison GP, Hewitt CJ, Holdaway MD. Relationship between airway responsiveness and serum IgE in children with asthma and apparently normal children. *N Engl J Med* 1991;325:1067–1071.
60. Burrows B, Barbee RA, Cline MG, Knudson RJ, Lebowitz MD. Characteristics of asthma among elderly adults in a sample of the general population. *Chest* 1991;100:935–942.
61. Marsh DG, Neely JD, Breazeale DR, Ghosh B, Freidhoff LR, Ehrlich-Kautzky E, Schou C, Krishnaswamy G, Beaty TH. Linkage analysis of IL-4 and other chromosome 5q31.1 markers and total serum IgE concentrations. *Science* 1994;264:1152–1156.
62. Meyers DA, Postma DS, Panhuysen CIM, Siu J, Amelung PJ, Levitt RC, Bleecker ER. Evidence for a locus regulating total serum IgE levels mapping to chromosome 5. *Genomics* 1994;23:464–470.
63. Halonen M, Stern DA, Wright AL, Taussig LM, Martinez FD. *Alternaria* as a major allergen for asthma in children raised in a desert environment. *Am J Respir Crit Care Med* 1997;155:1356–1361.
64. Aquillace SP, Sporik RB, Rakes G, Couture N, Lawrence A, Merriam S, Zhang J, Platts-Mills TAE. Sensitization to dust mites as a dominant risk factor for asthma among adolescents living in central Virginia: multiple regression analysis of a population-based study. *Am J Respir Crit Care Med* 1997;156:1760–1764.
65. Litonjua AA, Sparrow D, Weiss ST, O'Connor GT, Long AA, Ohman JL Jr. Sensitization to cat allergen is associated with asthma in older men and predicts new-onset airway hyperresponsiveness: the normative aging study. *Am J Respir Crit Care Med* 1997;156:23–27.
66. Laitinen T, Rasanen M, Kaprio J, Koskenvuo M, Laitinen LA. Importance of genetic factors in adolescent asthma: a population-based twin study. *Am J Respir Crit Care Med* 1998;157:1073–1078.
67. Duffy DL, Mitchell CA, Martin NG. Genetic and environmental risk factors for asthma: a cotwin–control study. *Am J Respir Crit Care Med* 1998;157:840–845.
68. Burchard EG, Silverman EK, Rosenwasser LJ, Borish L, Yandava C, Pillari A, Weiss ST, Hasday J, Lilly CM, Ford JG, Drazen JM. Association between a sequence variant in the IL-4 gene promoter and FEV_1 in asthma. *Am J Respir Crit Care Med* 1999;160:919–922.
69. Neukirch C, Henry C, Leynaert B, Liard R, Bousquet J, Neukirch F. Is sensitization to *Alternaria alternata* a risk factor for severe asthma? A population-based study. *J Allergy Clin Immunol* 1999;103:709–711.
70. Targonski PV, Persky VW, Ramekrishnan V. Effect of environmental molds on risk of death from asthma during the pollen season. *J Allergy Clin Immunol* 1995;95:955–961.
71. Rosenstreich DL, Eggleston P, Kattan M, Baker D, Slavin RG, Gergen P, Mitchell H, McNiff-Mortimer K, Lynn H, Ownby D, Malveaux F. The role of cockroach allergy and exposure to cockroach allergen in causing morbidity among inner-city children with asthma. *N Engl J Med* 1997;336:1356–1363.
72. Platts-Mills TAE, Tovey ER, Mitchell EB, Moszoro H, Nock P, Wilkins SR. Reduction of bronchial hyperreactivity during prolonged allergen avoidance. *Lancet* 1982;2:675–678.
73. Nicholson KG, Kent J, Ireland DC. Respiratory viruses and exacerbations of asthma in adults. *Br Med J* 1993;307:982–986.
74. Johnston SL,Pattemore PK, Sanderson G, Smith S, Lampe F, Josephs L, Symington P, O'Toole S, Myint SH, Tyrrell DA, Holgate ST. Community study of role of viral infections in exacerbations of asthma in 9–11 year old children. *Br Med J* 1995;310:1225–1229.
75. Busse WW. Respiratory infections: their role in airway responsiveness and the pathogenesis of asthma. *J Allergy Clin Immunol* 1990;85:671–683.
76. Folkerts G, Busse WW, Nijkamp FP, Sorkness R, Gern JE. Virus-induced airway hyperresponsiveness and asthma. *Am J Respir Crit Care Med* 1998;157:1708–1720.
77. Calhoun WJ, Dick EC, Schwartz LB, Busse WW. A common cold vi-

rus, rhinovirus 16, potentiates airway inflammation after segmental antigen bronchoprovocation in allergic subjects. *J Clin Invest* 1994;94: 2200–2208.
78. Schwarze J, Hamelmann E, Bradley KL, Takeda K, Gelfand EW. Respiratory syncytial virus infection results in airway hyperresponsiveness and enhanced airway sensitization to allergen. *J Clin Invest* 1997; 99:226–233.
79. Peebles RS Jr, Sheller JR, Johnson JE, Mitchell DB, Graham BS. Respiratory syncytial virus infection prolongs methacholine-induced airway hyperresponsiveness in ovalbumin–sensitized mice. *J Med Virol* 1999;57:186–192.
80. Chan-Yeung M, Malo J-L. Occupational asthma. *N Engl J Med* 1995;333: 107–112.
81. Isenberg SA, Lehrer PM, Hochron S. The effects of suggestion and emotional arousal on pulmonary function in asthma: a review and a hypothesis regarding vagal mediation. *Psychosom Med* 1992;54:192–216.
82. Busse WW, Kiecolt-Glaser JK, Coe C, Martin RJ, Weiss ST, Parker SR. NHLBI workshop summary: stress and asthma. *Am J Respir Crit Care Med* 1995;151:249–252.
83. Sher E, Leung DYM, Surs W, Kam JC, Zieg G, Kamada AK, Szefler SJ. Steroid-resistant asthma. Cellular mechanisms contributing to inadequate response to glucocorticoid therapy. *J Clin Invest* 1994;93:33–39.
84. Leung DYM, Martin RJ, Szefler SJ, Sher ER, Ying S, Kay AB, Hamid Q. Dysregulation of interleukin 4, interleukin 5, and interferon gamma gene expression in steroid-resistant asthma. *J Exp Med* 1995; 181:33–40.
85. Adcock IM, Lane SJ, Brown CR, Lee TH, Barnes PJ. Abnormal glucocorticoid receptor-activator protein 1 interaction in steroid-resistant asthma. *J Exp Med* 1995;182:1951–1958.
86. Hamid QA, Wenzel SE, Hauk PJ, Tsicopoulos A, Wallaert B, Lafitte JJ, Chrousos GP, Szefler SJ, Leung DY. Increased glucocorticoid receptor beta in airway cells of glucocorticoid-insensitive asthma. *Am J Respir Crit Care Med* 1999;159:1600–1604.
87. Sousa AR, Lane SJ, Soh C, Lee TH. In vivo resistance of glucocorticoids in bronchial asthma is associated with enhanced phosphrylation of JUN N-terminal kinase and failure of prednisolone to inhibit JUN N-terminal kinase phosphorylation. *J Allergy Clin Immunol* 1999;104:565–574.
88. Spahn JD, Leung DYM, Surs W, Harbeck RJ, Nimmagadda S, Szefler SJ. Reduced glucocorticoid binding affinity in asthma is related to ongoing allergic inflammation. *Am J Respir Crit Care Med* 1995;151: 1709–1714.
89. Wenzel SE, Schwartz LB, Langmack EL, Halliday JL, Trudeau JB, Gibbs RL, Chu HW. Evidence that severe asthma can be divided pathologically into two inflammatory subtypes with distinct physiologic and clinical characteristics. *Am J Respir Crit Care Med* 1999;160: 1001–1008.
90. Wenzel SE, Szefler SJ, Leung DYM, Sloan SI, Rex MD, Martin RJ. Bronchoscopic evaluation of severe asthma: persistent inflammation associated with high dose glucocorticoids. *Am J Respir Crit Care Med* 1997;156:737–743.
91. Jatakanon A, Uasuf C, Maziak W, Lim S, Chung KF, Barnes PJ. Neutrophilic inflammation in severe persistent asthma. *Am J Respir Crit Care Med* 1999;160:1532–1539.
92. Sur S, Crotty TB, Kephart GM, Hyma BA, Colby TV, Reed CE, Hunt LW, Gleich GJ. Sudden-onset fatal asthma—a distinct entity with few eosinophils and relatively more neutrophils in the airway submucosa? *Am Rev Respir Dis* 1993;148:713–719.
93. Fahy JV, Kim KW, Liu J. Prominent neutrophilic inflammation in sputum from subjects with asthma exacerbation. *J Allergy Clin Immunol* 1995;95:843–852.
94. Lamblin C, Gosset P, Tillie-Leblond I, Saulnier F, Marquette C-H, Wallaert B, Tonnel AB. Bronchial neutrophilia in patients with noninfectious status asthmaticus. *Am J Respir Crit Care Med* 1998;157:394–402.
95. Gibson PA, Norzila MZ, Fakes K, Simpson J, Henry RL. Pattern of airway inflammation and its determinants in children with acute severe asthma. *Pediatr Pulmonol* 1999;28:261–270.
96. Cox G. Glucocorticoid treatment inhibits apoptosis in human neutrophils: separation of survival and activation outcomes. *J Immunol* 1995; 154:4719–4725.
97. Busse W, Elias J, Sheppard D, Banks-Schlegel S. Airway remodeling and repair. *Am J Respir Crit Care Med* 1999;160:1035–1042.
98. Jeffery PK, Godfrey RW, Adelroth E, Nelson F, Rogers A, Johansson SA. Effects of treatment on airway inflammation and thickening of basement membrane reticular collagen in asthma. *Am Rev Respir Dis* 1992;145:89–99.
99. Minshall EM, Leung DYM, Martin RJ, Song YL, Cameron L, Ernst P, Hamid Q. Eosinophil-associated TGF-β1 mRNA expression and airway fibrosis in bronchial asthma. *Am J Respir Cell Mol Biol* 1997;17: 326–333.
100. Minshall E, Chakir J, Laviolette M, Molet S, Zhu Z, Olivenstein R, Elias JA, Hamid Q. Interleukin-11 expression is increased in severe asthma: association with epithelial cells and eosinophils. *J Allergy Clin Immunol* 2000;105:232–238.
101. Carroll N, Elliot J, Morton A, James A. The structure of large and small airways in nonfatal and fatal asthma. *Am Rev Respir Dis* 1993;147: 405–410.
102. Li X, Wilson JW. Increased vascularity of the bronchial mucosa in mild asthma. *Am J Respir Crit Care Med* 1997;156:229–233.
103. Bousquet J, Lacost J-Y, Chanez P, Vic P, Godard P, Francois-Bernard M. Bronchial elastic fibers in normal subjects and asthmatic patients. *Am J Respir Crit Care Med* 1996;153:1648–1654.
104. Laitinen A, Altraja A, Kampe M, Linden M, Virtanen I, Laitinen LA. Tenascin is increased in airway basement membrane of asthmatics and decreased by an inhaled steroid. *Am J Respir Crit Care Med* 1997; 156:951–958.
105. Saetta M, DiStefano A, Rosina C, Thiene G, Fabbri LM. Quantitative structural analysis of peripheral airways and arteries in sudden fatal asthma. *Am Rev Respir Dis* 1991;143:138–143.
106. Haley KJ, Sunday ME, Wiggs BR, Kosakewich HP, Reilly JJ, Mentzer SJ, Sugarbaker DJ, Doerschuk CM, Drazen JM. Inflammatory cell distribution within and along asthmatic airways. *Am J Respir Crit Care Med* 1998;158:565–572.
107. Kraft M, Djukanovic R, Wilson S, Holgate ST, Martin RJ. Alveolar tissue inflammation in asthma. *Am J Respir Crit Care Med* 1996;154: 1505–1510.
108. National Asthma Education and Prevention Program Expert Panel. Report 2: Guidelines for the diagnosis and management of asthma. Washington DC: U.S. Government Printing Office; 1997. NIH–NHLBI Publication No. 97-4051.
109. Noonan M, Chervinsky P, Busse WW, Weisberg SC, Pinnas J, de Boisblanc BP, Boltansky H, Pearlman D, Repsher L, Kellerman D. Fluticasone propionate reduces oral prednisone use while it improves asthma control and quality of life. *Am J Respir Crit Care Med* 1995; 152:1467–1473.
110. Wenzel S, Morgan K, Griffin R, Rogenes P, Goodwin B, Edwards L, Wamboldt F. Improvement in health care utilization and pulmonary function in very severe asthmatics one year following initiation of fluticasone propionate (FP) therapy concurrent with evaluation at a national asthma referral center. *Am J Respir Crit Care Med* 1998;157: A874.
111. Nelson HS, Bernstein IL, Fink J, Edwards TB, Spector SL, Storms WW, Tashkin DP. Oral glucocorticosteroid-sparing effect of budesonide administered by Turbuhaler: a double-blind, placebo-controlled study in adults with moderate-to-severe chronic asthma. Pulmicort Turbuhaler Study Group. *Chest* 1998;113:1264–1271.
112. Lofdahl C-G, Reiss TF, Leff JA, Israel E, Noonan MJ, Finn AF, Seidenberg BC, Capizzi T, Kundu S, Godard P. Randomized, placebo controlled trial of effect of a leukotriene receptor antagonist, montelukast, on tapering inhaled corticosteroids in asthmatic patients. *Br Med J* 1999;319:87–90.
113. Bousquet J, Michael FB. Specific immunotherapy in asthma. *J Allergy Clin Immunol* 1994;94:1–11.
114. Spahn JD, Leung DYM, Szefler SJ. Difficult to control asthma: new insights and implications for management. In: Szefler SJ, Leung DYM, editors. Severe asthma: pathogenesis and clinical management, vol. 86: Lung bology in health and disease. New York: Marcel Dekker; 1996. p. 497–535.
115. Hill MR, Szefler SJ, Ball BD, Bartoszek M, Brenner M. Monitoring glucocorticoid therapy: a pharmacokinetic approach. *Clin Pharmacol Ther* 1990;48:390–398.
116. Lee TH, Brattsand R, Leung DYM, editors. Corticosteroid action and resistance in asthma. *Am J Respir Cell Mol Biol* 1996;154(Suppl): S1–S79.
117. Szefler SJ, Spahn JD, Wenzel SE, Leung DYM. Glucocorticoid insensitive asthma: lessons for future asthma management. In: Lenfant C, editor. Lung biology in health and diseases, vol. 115: fatal asthma. New York: Marcel Dekker; 1998. p. 307–333.
118. Jarjour N, McGill K, Busse WW, Gelfand E. Alternative anti-inflammatory and immunomodulatory therapy. In: Szefler SJ, Leung DYM, editors. Lung Biology in health and disease, vol. 86: Severe asthma: pathogenesis and clinical management. New York: Marcel Dekker; 1996. p. 333–339.
119. Spector SL. Treatment of the unusually difficult asthmatic patient. *Allergy Asthma Proc* 1997;18:153–155.