Progress is Asthma:

From cytokine promotors & emerging pharmacotherapy to practical pitfals and & political barriers

Donald Kennerly, M.D., Ph.D.

Parkland Grand Rounds
Department of Internal Medicine
University of Texas Southwestern Medical Center

July 18, 1996

OVERVIEW AND RELEVANCE OF ASTHMA IN 1996

Asthma is a very common disease both in adult and pediatric populations. It affects 4-7% of adults and 6-10% of children and has a disproportionately high and increasing prevalence in urban environments. While mortality from acute asthma is low compared to many other illnesses typically treated by the internist, asthma causes frequent and substantial morbidity in patients with all but the most mild disease. An extensive study of adult managed care participants with asthma found that 17% of patients found it necessary to cancel or rearrange activities relating to work or other important activities during the past month.

Despite relatively limited mortality, exacerbations due to both controllable and uncontrollable factors has resulted in the need to expend approximately 1% of all US healthcare dollars on asthma. Because good asthma care involves very few ER visits or inpatient admissions, the frequency of acute care for asthma has been designated as a HEDIS (Health Employer Data and Information Set) 'marker' in versions 2.0, 2.5 and 3.0 used to evaluate quality of healthcare systems. For patients with mild asthma effective care is relatively straightforward. Unfortunately, management of patients with moderate or severe asthma is more difficult, particularly care that facilitates reducing to near zero the need for acute care. Moreover, while asthma represents the fifth most common illness to be treated by internists, its management takes place largely in outpatient settings, which has reduced the emphasis upon this disease in largely inpatient-based training programs in Internal Medicine and Pediatrics.

Figure 1 describes a current working definition of asthma. The clinical definition -- the presence of airway obstruction that can be reversed with treatment -- has long been recognized. Though the latter two elements of the definition of asthma, airway inflammation and airway hyperresponsiveness, are not readily accessible to the clinician to assess, recognition of their importance to the pathophysiology of asthma has had a profound effect upon the way this illness has been

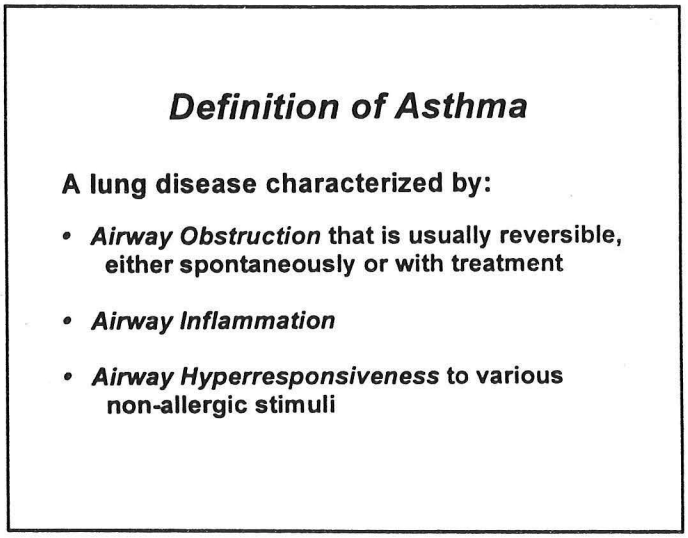

Figure 1

treated during the past 5 years.

During the 1980's asthma was primarily viewed as a disease of bronchospasm which required the use of bronchodilating medications as first line agents. Inflammation of the airways was recognized to exist but its treatment using inhaled glucocorticoids was felt to be needed only in situations when bronchospasm could not be reversed by classical bronchodilators such as inhaled or systemic β2 agonists and theophylline.

A pivotal development that generated the impetus for change in this view was a report published by an expert panel of the National Heart Blood and Lung Institute of the NIH (NHLBI) in 1991 that emphasized the role of inflammation in asthma. Figure 2 illustrates that the genesis of symptoms of asthma by bronchospasm, mucous hypersecretion and airway wall edema can be caused by a variety of mediators released not only by the mast cell, but by T cells, eosinophils, neutrophils, and platelets. Though less support existed for this view in 1987 when this slide was used in a previous Grand Rounds, the current view of asthma focuses less upon allergic triggers and the role of the mast cell than the role of a variety of important cells contributing to a rich and complex inflammatory response. Central to our current understanding of asthma is the concept that many of the mediators produced by one or another of these cells not only cause symptoms of asthma but contribute to the perpetuation of inflammation through their effects upon other cells involved in the airway inflammation associated with asthma. Though beyond the scope of this presentation, a rich array of cytokines, chemokines, peptide mediators, eicosanoids, proteases, chemotactic agents, and others are involved. The richness and complexity of this inflammatory response may serve to

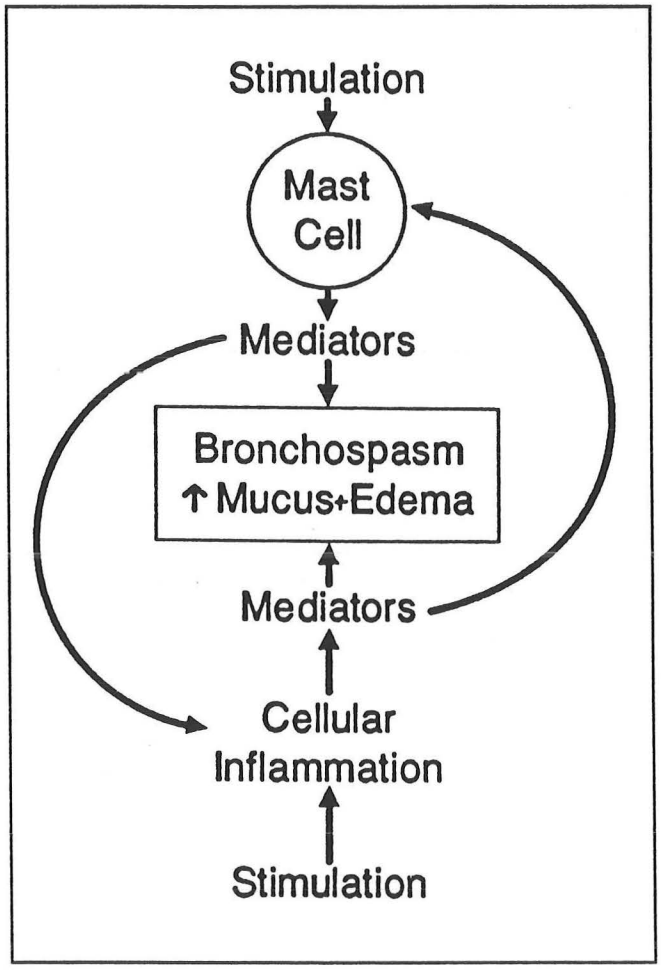

Figure 2

explain the difficulty in treating asthma with specific mediator antagonists that may have effects upon only one class of mediators. An important additional finding relates to the increasing appreciation that inflammation associated with asthma involves loss of epithelial integrity. The combination of chronic epithelial injury and airway wall inflammation results in not only the symptoms associated with acute airway obstruction, but also in clinically relevant acceleration of the normal progressive loss of airway function in many patients with moderate to severe asthma.

An additional key feature of asthma relates to the development of bronchial hyperreactivity. Though not absolutely pathognomonic of asthma, a hallmark finding in patients with asthma is the ability of short acting bronchoconstricting agents to have a disproportionately greater effect upon individuals suffering with asthma than upon individuals who are either normal or who have other atopic illnesses.

Nebulized histamine or methacholine (a short acting cholinergic agonist) can be administered in progressively higher concentrations in a challenge procedure as pulmonary function is monitored by repetitive analysis of the FEV_1. Once the FEV_1 has dropped by more than 20%, the concentration required to cause a 20% decline in FEV_1 can be estimated by interpolation, generating the parameter PC_{20} (methacholine), for example (the concentration of methacholine producing a 20% decline in FEV_1). Though this challenge procedure is typically used either in investigational settings or to diagnose individuals in whom asthma is suspected but airway obstruction has not been documented, this parameter has been found to be helpful inasmuch as it tends to correlate with the severity of the underlying inflammatory response. Another application for methacholine challenge testing is in individuals having cough variant asthma who may have cough that may limit sleep and/or exercise, but who may not have bronchospasm uncommonly. In these patients, methacholine challenge testing can help bring out airway obstruction at low concentrations of methacholine in order to confirm a suspected diagnosis. Although clinically recognized for many years to exist, bronchial hyperreactivity remains reasonably poorly understood at a molecular level. As discussed in some detail below, the development of nonspecific bronchial hyperreactivity appears to be polygenic.

The conceptual interaction between the clinical phenomena of bronchial hyperreactivity and atopy are complex, but critical to an understanding of not only the pathogenesis of asthma, but also the role of environment vs. genetic predisposition in the development of asthma. Since asthma is phenotypically quite

variable and the diagnosis used in different ways by different groups of physicians and in different age groups, these two more easily defined clinical characteristics are used to better explore in clinical and basic science studies the elements that contribute to their development. Though raised in other sections of this presentation, the critical interplay of the elements presented in Figure 3 cannot be over emphasized. A clinical diagnosis of asthma can exist for a limited number of patients who lack bronchial hyperresponsiveness, though many would argue that this diagnosis would be in error. Conversely, there are individuals who have bronchial hyperreactivity and reversible airway obstruction who do not complain of symptoms. Atopy is certainly *not* <u>required</u> for the development of either asthma or sufficient inflammation to result in nonspecific bronchial hyperreactivity, but is, particularly in children, a very important mechanism for causing inflammation that may importantly contribute to the development of bronchial hyperreactivity that is characteristic of asthma. Though genetic predisposition is very important (discussed below), the role of environment should be stressed. Urbanization and exposure level to certain aeroallergens are statistically significant risk factors for the development of asthma in children. Indeed, the prevalence of asthma is virtually zero in native villages where housing is rudimentary and air pollution scant, but high when this same population emigrates to cities. Environmental factors that are likely to be important in the development of bronchial hyperreactivity and asthma not only include indoor aeroallergens, but also air pollution (indoor and outdoor; serving important roles as both a risk factor for developing the disease and for attacks) and lower respiratory.

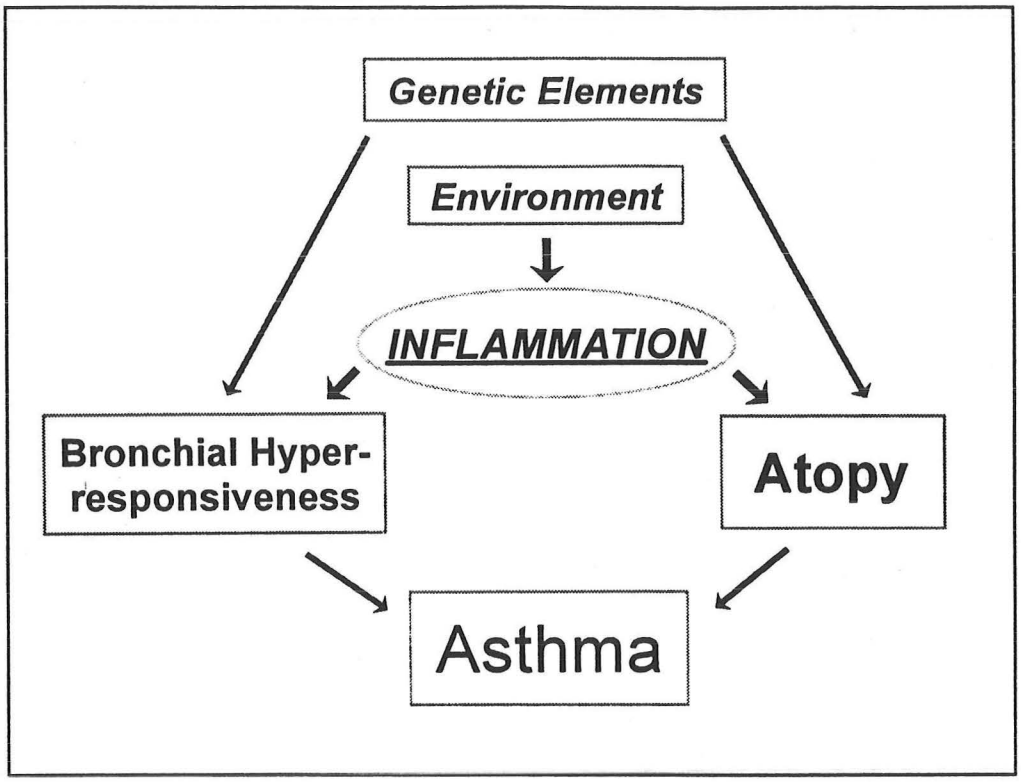

Figure 3

RELEVANT PATHOPHYSIOLOGIC CONCEPTS

A great deal of scientific and clinical knowledge has contributed to a more thorough understanding of the immunologic and inflammatory responses associated with development of allergic disorders. In the current context, however, it is important to distinguish between the forces that contribute IgE production, the development of specific IgE immune responses to environmental antigens and to the development of nonspecific bronchial hyperreactivity. This conceptual distinction is important inasmuch as a significant fraction of individuals who have reversible airway obstruction that is consistent with asthma and who have evidence of the classic inflammatory response associated with it do not necessarily demonstrate allergic sensitivity; that is, they do not have *allergic* asthma. Moreover, while the incidence of asthma is higher in the patients who are atopic and have associated IgE immune responses to environmental antigens, there are a large number of patients who have allergic rhinitis that may be quite severe but who have no evidence of lower tract disease despite regular exposure of the lower respiratory tract to antigens which can stimulate IgE-dependent mast cell activation.

Though a substantive discussion of cytokine biology and allergic inflammation is beyond the scope of the current presentation, several aspects of scientific advances relating to the regulation of IgE synthesis are worthy of mention. First, IL-4 has been identified as a pivotal cytokine in the development of IgE immune responses and, hence, the regulation of synthesis of this important cytokine has been viewed as very important to a thorough understanding of allergic disorders. Of note, however, is that even in individuals who have very significant allergic sensitivity and clinical reactivity, the vast majority of the increases in total IgE commonly observed in these patients is not antigen-specific, but rather reflects a general increase in the synthesis rate of IgE in a polyclonal fashion. Second, identification of different roles for helper T cells that fall into either T_{H1} or T_{H2} phenotypes has aided progress in understanding the development of allergic responses inasmuch as the latter, that is T_{H2} helper cells, tend to produce increased levels of cytokines that are consistent with the development of IgE immune responses and the support of eosinophil growth and survival (IL-4, IL-5, and GM-CSF). Indeed, increasing evidence suggests that antigen-driven T_{H2} cell activation may importantly contribute in an IgE-independent fashion to airway inflammation. Additionally, the recent identification of multiple splice variant forms of IgE has added to the complexity of understanding structure function relationships and regulatory pathways associated with generating allergic sensitivity.

In addition to the capacity of T cells and antigen presenting cells to elaborate significant and pathophysiologically meaningful levels of important cytokines in inflammation associated with asthma, a great deal of data now exist to implicate the mast cell as an important source of cytokines. While eosinophils are a very short lived cell, they are abundantly present in inflammatory responses associated with asthma and recent work indicates that they appear to be able to synthesize a significant amount of T_{H2} cytokines.

Risk Factors and Associated Implications

A number of risk factors for the development of either nonspecific bronchial hyperreactivity, allergic sensitization or clinical asthma have been identified for children and/or adults. While certain of these have genetic implications and appear to be beyond our ability to control (parental asthma and atopy, for example; discussed subsequently), a number of risk factors have implications for either environmental control measures in our homes and/or for public health policy. With regard to the former, the level of antigen exposure (allergen load) for indoor allergens appears to be predictive of the ultimate development of asthma. Studies involving house dust mite and cat allergen exposure are fairly clear in this regard, while quantitative associations for cockroach and dog exposure are not conclusive. The increased prevalence of asthma in children with early serious lower respiratory infection raises issues with regard to crowding of children particularly in day care settings that increases the frequency of viral infections. Epidemiologic data stunningly emphasize the relative paucity of asthma in rural environments and its near absence in aboriginal villages; findings that underscore the critical contribution of environment in genetically susceptible individuals. A variety of epidemiologic studies strongly implicate increasing pollution with both the excess urban prevalence and its increase during the mid-late 20th century. Particularly important are recent results that implicate diesel exhaust particles as an adjuvant in the genesis of allergic sensitization to aeroallergens as a result of its high content of aromatic hydrocarbons associated with these particles that can facilitate transcription of a variety of important regulatory genes. From a policy perspective, however, the mounting evidence surrounding the deleterious effects of diesel exhaust particles is important inasmuch as Federal efforts to limit air pollution have been directed toward other components of pollution (SO_2, No_x and ozone) and have largely exempted diesel engine-powered motor vehicles. These policies should be reexamined carefully in light of both the morbidity and the costs associated with the alarming rise in the prevalence of asthma in the US.

While clinical goals of therapy are quite clear, the pathophysiologic targets for therapy have not been entirely clear. In patients with either nonallergic or allergic asthma, avoidance of nonspecific triggers and viral infection remain obvious and appropriate goals. Anti-inflammatory pharmacotherapy is clearly an important and central target as well. But for patients with allergic asthma, the pathophysiologic goals add additional complexities and controversies. Agreement is readily achieved on the value of identifying sensitivity to avoidable aeroallergens so that patients can try to the best of their abilities to avoid them. Identification of the T_{H1} and T_{H2} phenotypic differences in T helper cell function, with the predominant role of the latter in asthma, raises the question as to whether it would be of value to try to engage immunomodulatory efforts seeking to convert an existing T_{H2}-predominant response to a T_{H1}-predominant response. While many investigators feel that the capability of IL-12 to accomplish this goal *in vitro* makes this approach a reasonable one to try in patients with asthma, others feel strongly that this may generate a very significant risk for patients. Indeed some fear that such a therapy might shift the clinical phenotype from asthma to something that looks more like an antigen-driven sarcoidosis.

GENETIC ASPECTS OF ASTHMA

Because 70-80% of children born to parents who both have asthma also develop asthma, a strong genetic contribution has long been assumed. That asthma has a genetic component is also indicated by a relatively high ratio of the prevalence of asthma in first degree relatives of probands versus its presence in the general population (20 to 25% versus 4 to 5%, respectively). A variety of clinical and biologic elements conspire to make genetic analysis and the identification of disease-related genes very complex in asthma. First, since neither atopy nor bronchial hyperreactivity are either consistently able to predict the existence of clinical asthma, neither can serve as the sole indicator for asthma. Efforts are underway to identify genetic elements contributing to these related clinical conditions. Second, it appears that environment contributes importantly to the development of the asthma phenotype, a situation that further complicates genetic approaches. It appears highly likely that asthma represents a quite variable clinical phenotype that results from a polygenic array of distinct molecular defects that contribute variably to the development of asthma that, in part, depend upon environmental exposures.

Twin studies have contributed significantly to our understanding of the importance of genetic predisposition to the development of asthma. In identical

twins there is a relatively high but incomplete concordance rate in the development of asthma and this rate is substantially increased when the identical twins are raised in the same environment as opposed to identical twins raised in different environments. These and other data have led to an estimate that genetic elements are of approximately equal weight as environmental elements in the pathogenesis of clinical asthma.

Contributing to the complexity of understanding the role that IgE sensitization may have in the development of asthma is the observation that there appears to be two related but distinct phenotypes: 1) increased total IgE and 2) the presence of IgE immune responses to relevant aeroallergens (measured by skin test positivity by the presence of wheal and flare skin responses to epicutaneously administered extracts of allergens). Indeed, the distribution of total IgE appears to behave as a unimodal normal distribution when it is plotted in log [IgE] terms. On the other hand, the presence in large populations of skin test responses to outdoor and indoor aeroallergens has a bimodal distribution suggestive of a more limited number of genetic elements that may be responsible for the development of the ability of an individual to develop an allergic response when exposed to environmental aeroallergens. The relevance of this distinction -- that is, between total IgE level and antigen-specific IgE sensitivity -- will be discussed subsequently.

A substantial and increasing focus of attention for investigators has been determining the molecular mechanisms associated with the development of non-specific bronchial hyperreactivity, which can occur in the presence or absence of allergic sensitization or increased total IgE. Drazen and his colleagues have developed data using breeding experiments in mice strain variations in reactivity to inhaled bronchoconstrictive agents to predict that bronchial hyperreactivity is likely due to the contribution of only a few genes. An attractive hypothesis currently receiving attention is that moderate bronchial hyperreactivity may be genetically determined, but development of severe bronchial hyperreactivity may additionally require environmental exposures that may be either immunologic (allergic sensitization and subsequent exposure to antigens) or non-immunologic inflammatory responses (severe viral infection or exposure to irritating agents).

The complexity and likely interacting elements of these two phenotypes -- that is, bronchial hyperresponsiveness and allergic sensitization -- in contributing to the development of clinical asthma makes it extremely difficult to approach the identification of causative disease genes using positional cloning as has been accomplished for cystic fibrosis, for example. As a result, identifying disease

causing or modifying genes has been pursued through the use of the candidate gene approach in which identification of important pathophysiologic pathways, receptors and agonists are evaluated for the potential to be altered as a result of genetic variation in a way that confers the disease phenotype or the susceptibility upon those who suffer with or are at risk for developing clinical asthma.

CANDIDATE DISEASE GENES

Recent attention has been focused upon the potential of variations in the β subunit of FcεR-1 (the high affinity receptor for IgE) to contribute to the development of asthma. Specifically, a leucine substitution at position 181 has been reported to be increasingly associated with asthma but the association has been weak or nonexistent in confirmatory studies. Initial enthusiasm was somewhat higher as a result of the location of this gene to 11q13, a region that appears to have genetic relevance with regard to the ability of disease markers in this region to be associated with asthma in women.

Of substantial interest has been the identification of the 5q31 area as being rich in both candidate genes as well as markers which are more highly associated with asthma. The IL-4 gene locus and a variety of other cytokine genes are found in this region. An autosomal dominant pattern of asthma in one study was mapped to the IL-4 gene locus, but only if individuals who were skin test positive to environmental aeroallergens were excluded; an interesting finding given the central role of IL-4 in IgE regulation. Some studies suggest that bronchial hyperresponsiveness may also be mapped to this region although support also exists for a contribution of an area closer to the β2 adrenergic receptor. Other candidate genes in this area include IL-5, IL-13 and a *cis*-acting element involved with interferon responsiveness.

Recent data suggests that the 14q area may be important with regard to linkage to a development of specific IgE immune responses (i.e., skin test positivity to antigens) and it is of interest that the alpha and delta subunits of the TCR map to this area. These findings have not yet been confirmed.

The β2 adrenergic receptor has been the focus of significant interest inasmuch as an early hypothesis related to the pathogenesis of asthma involved a deficient cyclic AMP response to adrenergic receptor stimulation. More recent data indicate that there appears to be an association of asthma severity (as indicated by the increased need for systemic steroid medication) mapping to this region. Unfortunately, structural abnormalities in the β2 adrenergic receptor have not been

forthcoming with regard to clearly different cyclic AMP based responses although data do indicate that there may be increased receptor down regulation in certain isoforms.

Although IL-5 was felt to represent an exciting candidate cytokine in the pathogenesis of asthma, transgenic mice that overexpress IL-5 failed to develop any clinical phenotype aside from increased levels of eosinophils.

More recently, IL-10 has shown promise as a candidate disease gene in asthma. In humans IL-10 shows broad anti-inflammatory effects. Its presence in bronchoalveolar lavage (BAL) fluid from asthmatics is lower than that found in non-asthmatic controls as is its mRNA in cells recovered in BAL from patients with asthma. In unpublished studies a mutation in the IL-10 promoter has been identified by Borish in a significant fraction of patients with asthma and its presence is associated with higher levels of IgE.

The latter studies involving genetic abnormalities that confer a deficient anti-inflammatory phenotype appear to have become increasingly attractive candidates for causing the asthma phenotype.

PRACTICAL MANAGEMENT OF ASTHMA

As introduced earlier, treating the underlying inflammation associated with asthma is now felt to be central to appropriate management. Despite aggressive efforts on the part of the NHLBI and the National Asthma Education Program (NAEP), this message has been slow to be adopted by many physicians in this country. There may be many reasons for this unfortunate circumstance. I suspect that it rests in large part as a result of 1) the relatively large number of physicians who were previously trained to believe that bronchodilator therapy should be the focus of asthma treatment, 2) the time intensive nature of patient education necessary for effective use of preventive anti-inflammatory medications, and 3) the very limited mortality associated with asthma that limits concern for suboptimal outcomes.

Figure 4 illustrates three strategies that can be employed to reduce inflammation associated with asthma. Limiting exposure to or the impact of pro-inflammatory triggers can have a marked benefit. Though important and without medical complications, this form of management is often overlooked as a result of lack of recognition of the specific set of triggers in each patient that may set an

exacerbation into motion. Failure of clinicians to identify a limited number of primary triggers for patients and instead to provide a potpourri of patient education literature that describes all potential asthma triggers limits enthusiasm on the part of the patients for investing the substantial effort required to achieve successful environmental control.

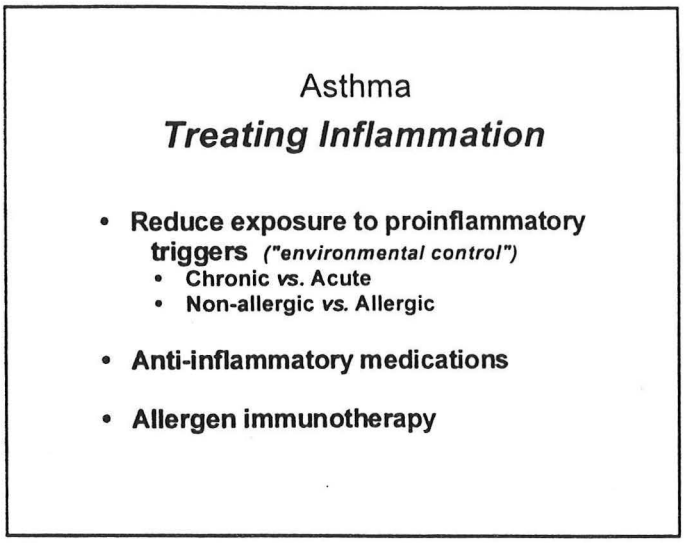

Figure 4

Use of anti-inflammatory medications has been increasing slowly but a variety of studies involving large databases of patients using pharmacy records indicate that the use of bronchodilating medications is still substantially greater than the use of anti-inflammatory medications. Of inpatients who were hospitalized for asthma at Parkland Memorial Hospital >40% were not using an inhaled anti-inflammatory medication at the time of admission. The role of allergen immunotherapy to reduce the allergic sensitivity of a patient with allergic asthma has been controversial, but carefully controlled studies indicate that in selected individuals significant improvements in symptoms and a reduced requirement for medications can be accomplished when high dose aqueous allergen immunotherapy is used. Because the latter represents a therapy primarily limited to the Allergy and Immunology subspecialty, it will not be covered in this Grand Rounds.

The fraction of patients who have an allergic component to their asthma varies depending upon age (Figure 5). In infants, allergic sensitivity is limited and a viral infection provides the most common cause for exacerbation of asthma. Cigarette smoking by mothers of asthmatic infants can also be a serious problem. In preschool and school-age children there is an increased role for allergic sensitivity in causing/triggering asthma. Initially, these agents tend to be indoor allergens to which children have the greatest exposure during their early lives and, for a few children, a modest contribution by food allergens. With increasing age, food allergy becomes progressively less important and seasonal aeroallergens (pollens and

mold spores) become the more typical cause for inflammation that underlies asthma. For reasons that are not well understood, the pattern changes with increasing age; for individuals in their fifth and sixth decades and beyond the role of allergen-induced inflammation diminishes both with regard to the impact of exposure in previously sensitized individuals as well as the fraction of individuals who have any allergic component to their asthma. In these older individuals viral infection, workplace exposures and GERD seem to be the more common sources for exacerbations.

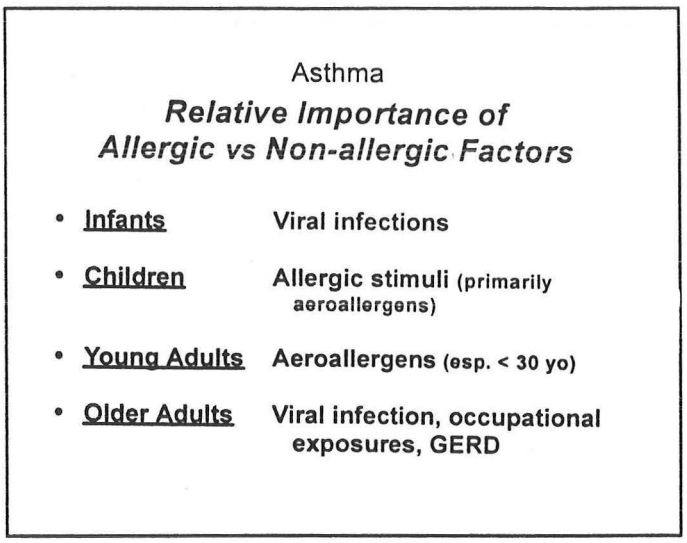

Figure 5

Identifying and Reducing Triggers

Figure 6 lists other pro-inflammatory triggers. Triggers seemingly without an inflammatory basis that cause either acute or chronic airway obstruction in patients with asthma are listed in Figure 7. The mechanism by which the latter group cause symptoms is for many highly variable and/or uncertain. Identification of reversible triggers (GERD, chronic sinusitis, allergic rhinitis, exposure to cigarette smoke, exposure to certain aeroallergens and irritants) can cause substantive clinical improvement. An all too often neglected aspect of treating asthma is meticulous care of coexistent allergic rhinitis. It is the experience of many asthma specialists and several studies that aggressive treatment of allergic rhinitis (particularly using inhaled nasal steroids) is often associated with a marked improvement in lower airway function.

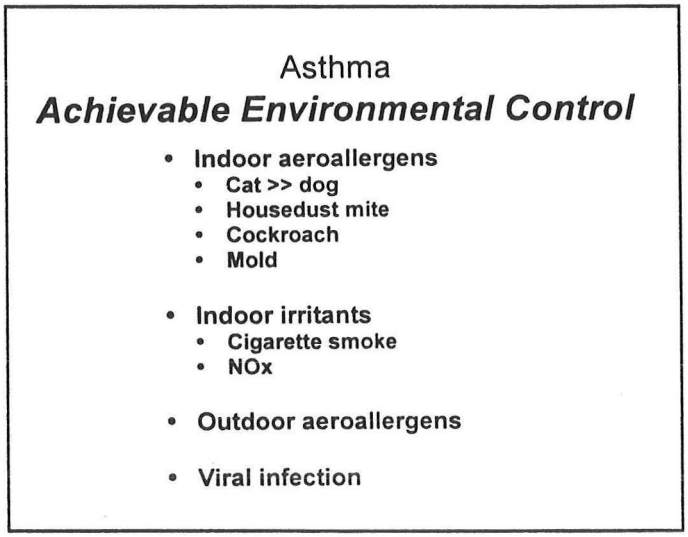

Figure 6

Though outdoor aeroallergens are difficult to avoid, identifying indoor aeroallergens as triggers for patients with asthma is of substantial importance. Exposure to indoor agents such as cat or dog dander, house dust mite, cockroach and indoor molds (in some climates) can be very substantially lowered as a result of avoidance efforts. Patients are, unfortunately, often unable to accurately convey whether exposure to any of these allergens represents a significant problem for them. Though comprehensive skin testing to a large panel of aeroallergens to identify allergen-specific IgE is not generally indicated in patients with asthma, identification of sensitivity to a limited panel of indoor aeroallergens can be extremely helpful to a highly effective and tailored environmental control intervention for patients. Unfortunately, several commercial disease state management interventions advise generic environmental control programs which request individuals to limit exposure to all of these agents rather than just the ones to which an individual is sensitive.

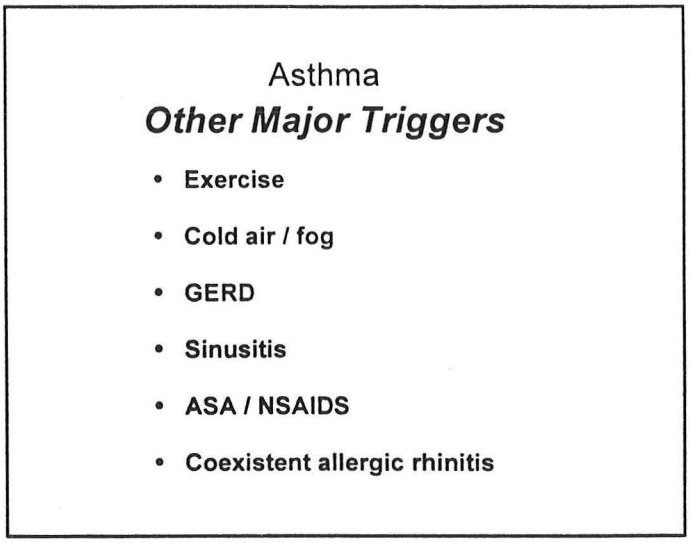

Figure 7

Though the approaches to avoiding exposure to cat or dog are relatively straightforward in the purest sense -- finding a new home for the animal -- intermediate success can often be achieved. Evidence indicates that cat-specific antigen can be reduced substantially as a result of weekly washing and efforts to generate a line of cats to fail to produce the major antigen of cat dander (Fel d I) are underway. Exposure to house dust mite can be limited to a very significant and clinically meaningful degree by efforts that involve either 1) reduction of the nutritional source for the house dust mite, Dermatophagoides (by limiting or eliminating the presence of feather-containing comforters and pillows or mattresses and reducing shed human epithelium by frequent washing of bed linens), or 2) reduced exposure to reservoirs that contain high quantities of house dust mite antigen (using mattress and pillow encasements, eliminating or reducing carpeting, upholstered furniture, and draperies in the bedroom and more frequent vacuuming by individuals not affected by exposure to house dust mite antigen). Exposure to cockroach antigen is caused by suspension in the air of micro particles of proteinaceous debris left behind after the decay of dead cockroaches. While newer

bait-poison roach traps (Combat®) have been quite effective in reducing cockroach infestation, data have not yet been developed that indicate that antigen levels in homes can decline to a sufficiently significant extent to cause reduction of symptoms in cockroach-sensitive asthmatics.

Though individuals do not have allergic sensitivity to irritants, (that is, do not have antigen-specific IgE), exposure to cigarette smoke and oxides of nitrogen (NO_x) in indoor environments can have deleterious effects upon individuals with asthma. Fortunately, increasing recognition of the health hazards associated with smoking has resulted in substantially reduced exposure of many patients to cigarette smoke. In inner city and rural populations either gas stoves/ovens or woodburning fireplaces are used for heating purposes and can result in substantial exposure of individuals to irritating oxides of nitrogen.

In patients with sensitivity to outdoor aeroallergens (typically pollen and mold spores), exposure to these agents can be reduced to only a limited extent by reducing time spent outside and efforts to keep windows and doors in the home closed. Fortunately, many commercial workplace environments offer a "friendly" environment for patients who have sensitivity to outdoor aeroallergens inasmuch as industrial air handling systems often filter and wash air in such a way that there is a marked reduction in exposure to aeroallergens during the time that individuals are at work.

Though difficult to achieve due to practical limitations, young children in daycare environments or in crowded family circumstances can have an increased frequency of viral infection which leads to markedly increased numbers of exacerbations of asthma.

Other Non-Pharmacologic Elements of Asthma Care

Effective treatment of asthma has increasingly been recognized to require much more than just pharmaceutical-based care and environmental control. Figure 8 summarizes the components identified by asthma specialists and the NHLBI to be important in achieving successful control of patients, particularly those who have moderate to severe asthma. Environmental control maneuvers have already been discussed and serve to try to limit the stimuli that tend to worsen asthma. Appropriate pharmacotherapy (described in more detail subsequently) that targets inflammation is critically important. Effective delivery of topical agents requires patient education, particularly for using metered dose inhalers (MDIs).

In order to gauge success and to adjust pharmacotherapy objective monitoring of airway function has been found to be highly valuable. Specifically, the use by patients of home peak flow meters has served to identify the degree to which treatment regimes have or have not been effective in preserving near normal or normal airway function. Though not perfect, the peak expiratory flow rate (PEFR) tends to correlate fairly well with FEV_1 in most patients and serves as a tool for monitoring and revising medical management. The role of self monitoring is made particularly important by the observation that patients with asthma are often less capable than normal individuals of recognizing moderate airway obstruction. Alternately, some individuals will perceive chest tightness and/or shortness of breath due to anxiety-based causes rather than airway obstruction and inappropriately and excessively use β2 adrenergic agents which may then exacerbate these neuropsychiatrically-based symptoms.

Components of a Successful Asthma Management Program

- **Objective measurement of lung function**
- **Environmental Control (allergic and non-allergic)**
- **Pharmacotherapy**
- **Patient Education**
- **Early intervention during acute exacerbations**
- **Frequent reassessment**

Figure 8

Peak expiratory flow rate information can guide changes in pharmacotherapy (a process termed patient self-management) but requires substantial oral and written instruction and agreement. It is critically important for all patients to understand what they need to do when they have exacerbations of asthma that will inevitably take place from time to time since early intervention can often substantially limit the level and duration of morbidity. Failure to achieve success along these lines results in unnecessary emergency room utilization and/or hospital admission which generate nearly 50% of the direct medical costs associated with managing asthma in the US. Though many of the components of a successful asthma management program can more easily be achieved in subspecialty environments in which efficient patient education can take place, many elements of a comprehensive asthma management program can be delivered in a primary care environment, especially for patients with lower levels of underlying severity. Perhaps most important (and discussed in a later section) is the effective interplay between subspecialty and primary care medicine that utilizes the subspecialist for developing and implementing a successful asthma management program coupled with a timely return to the primary care environment once success has been achieved.

Pharmacotherapy of Asthma

An impediment to successful management of patients with asthma is the difficulty in easily estimating severity. Although the expert panel report by the NHLBI and guidelines promulgated were critically important for clinicians in managing patients with asthma, the definitions of asthma severity were, to some degree, misleading. In the NHLBI guidelines, severity tended to be categorized based upon the level of symptoms an individual was sustaining at the time and, therefore, was viewed as a highly dynamic feature of a patient's asthma. A more helpful estimate of the underlying severity was lacking. At an intuitive level, most clinicians understand that asthma severity can only be understood by simultaneous consideration of 1) the level of symptoms a patient experiences and 2) the level of pharmacotherapy the patient is receiving at the time. These variables tend to be reciprocally related. Pharmacotherapy provides the context that clinicians intuitively use to understand whether the severity of the underlying asthma is mild, moderate or severe. Clearly, a patient with few symptoms of asthma who requires high dose oral steroids does not constitute a patient with only mild asthma. Similarly, an individual who is receiving no treatment but who has very substantial airway obstruction may suffer from severe symptoms, but not have severe underlying asthma inasmuch as relatively few medications markedly reduce symptoms. Many asthma specialists suggest that severity of asthma should be defined as the level of pharmacotherapy that is required to achieve control of asthma symptoms.

A detailed review of the agents used to treat asthma is beyond the scope of the current discussion, but certain key issues are important to raise in the context of changes in management strategy that have evolved during the last few years.

The use of β2 adrenergic agents has for many years been a cornerstone in successfully treating the bronchospasm associated with asthma. Increasing recognition of the central importance of inflammation, however, has resulted in diminished use of inhaled β2 agonists in chronic management as a result of increased success in achieving control using anti-inflammatory strategies. Evidence indicates that control of asthma is less successful in patients who use short acting β2 adrenergic agents on a regular (qid) basis rather than when needed only. Though still an excellent bronchodilator for acute management of airway obstruction and the preventive management of exercise induced bronchospasm, the use of β2 adrenergic agents has been discouraged except in situations of documented reduction of airflow (home monitoring using a peak flow meter). Though controversial, most clinicians now feel that anti-inflammatory therapy needs to be

intensified if patients regularly require short acting β2 adrenergic agents at a rate of 2-4 puffs per day. A substantial and still unresolved controversy surrounds whether increased use of β2 adrenergic agents is simply associated with as opposed to causative of increased mortality in patients with asthma. An important recent advance relates to the availability of Salmeterol, a long acting inhaled β2 adrenergic agent. The presence of a highly lipophilic aliphatic side chain in Salmeterol has been proposed to cause increased localization of this agent to the β adrenergic receptor of appropriate airway cells. Although somewhat counter intuitive, some data indicate that Salmeterol may have some anti-inflammatory properties despite the failure to document similar properties in short acting agents.

The NHLBI expert panel report on asthma has caused subspecialists and astute primary care physicians in this country to increasingly utilize inhaled corticosteroid agents in patients with chronic asthma. Though not felt to be indicated in mild episodic asthma and chronic mild asthma that is responsive to either Cromolyn or Nedocromil, inhaled glucocorticoids represent the most potent class of anti-inflammatory pharmacologic agent available today. These agents serve to markedly reduce allergic inflammation as a result of their broad anti-inflammatory effects on a variety of cells and pathways but exert their effect somewhat slowly; often peak effect is not achieved for 3-6 weeks. Patient education is essential to the successful use of inhaled glucocorticoid agents. First, patients must be aware of the slow onset of action and the slow dissipation of effect in order to enhance adherence to <u>daily</u> regimens which are necessary for these agents. Second, many patients at mid or above socio-economic levels will have access to and read about these agents in the PDR which may cause concern over listed side effects. Informing patients that these agents are taken in microgram quantities that have few systemic effects is essential. All too often, well meaning clinicians fail to inform their patients that these agents are in the "steroid" class of medications and recognition of this fact by consumeristic patients undermines confidence in the physician by the patient and often serves to limit adherence to medical regimens containing inhaled glucocorticoids.

The use of a spacer device is critically important in reducing oropharyngeal deposition of inhaled glucocorticoids and absorption of medication that fails to reach the lower respiratory tract but is swallowed. Hoarseness caused by a steroid myopathy of the arytenoids, irritative cough and/or a pharyngeal candidiasis are the most common complaints reported by patients but are relatively mild in most.

Though use of higher than recommended dosages of these agents has been

increasingly commonplace during the past 3 to 5 years, studies have increasingly called into question the degree to which the dose response curve for these agents is linear. An additional concern relates the view by many clinicians that these agents have equal potency on a weight basis. While conceptually absurd, the rough comparibility of these agents, coupled with the difficulty in establishing dose response curves, has contributed to this unfortunate practice.

Nedocromil is a non-steroid anti-inflammatory medication that has been used increasingly in place of Cromolyn in patients with mild to moderate asthma. It has an excellent safety profile due to minimal absorption and modest adverse effects. These medications suffer from being less effective than inhaled glucocorticoids. While use of Nedocromil is less costly than its structurally related Cromolyn, it is still more costly than most inhaled glucocorticoid preparations. Recently, Nedocromil has been used with substantial success in patients with cough associated with asthma. Nedocromil has become the anti-inflammatory drug of first choice in children and pregnant women due to safety concerns but cost and efficacy issues have typically necessitated moving on to inhaled glucocorticoid medications in the vast majority of patients.

Though use of systemic corticosteroid medications on a chronic basis is substantially limited by predictable development of a number of complications, this class of agents remains the most powerful and effective form of treatment of asthma in either the subacute or chronic settings. The ability of these agents to reduce cellular inflammatory responses is well known and only several issues need be raised in the current context. First, many patients receive these agents too late during exacerbations and, in some patients, in dosages that are suboptimal. Because systemic glucocorticoids require 12 to 24 hours to achieve substantial therapeutic benefit (although some changes can be detected as early as 4 to 8 hours) it is important for patients to either seek medical attention early or, if authorized as part of a care plan, use systemic glucocorticoids early during the course of an exacerbation of asthma. Indeed, in the pediatric setting it has been shown that the total dose of systemic glucocorticoid required for treating a viral syndrome-induced exacerbation of asthma is less in children when systemic glucocorticoids are introduced early during the exacerbation than when therapy is delayed until its use has become mandatory. Additionally, while there is no single best approach to dosing and tapering systemic glucocorticoids, it is frequent practice to use "bursts" of prednisone that are of overly brief duration in patients who are somewhat brittle and require slower tapering. Past experience for each individual patient dictates the level and duration of systemic glucocorticoid therapy during

exacerbations. No data exist that support the need for LIV systemic glucocorticoids over orally administered glucocorticoids in asthma except for individuals in whom there is a predictable absorbative defect. Orally administered agents are preferred over use of depot parenteral administration due to reduced ability to tailor the latter to individual patient needs. More recently, a number of groups have suggested that individuals requiring systemic glucocorticoid therapy should take it in the mid to late afternoon rather than in the morning. The rationale behind this strategy relates to trying to target peak action of medications to coincide with the period of greatest endogenous steroid deficiency during normal diurnal variations. Though much work needs to be done in this area, an increasing fraction of asthma experts are using systemic glucocorticoids administered at 3 to 4 pm. Rarely, steroid resistant patients are encountered. Though referral guidelines for patients vary widely depending upon the structure of the healthcare financing issues surrounding patient management, most experts agree that patients requiring regular use of systemic glucocorticoids (either daily, alternate day or frequent bursts) should be managed in a subspecialty setting. Close follow up of patients for the development of steroid-induced complications is, of course, an important aspect of managing this subset of patients.

The use of methylxanthines in asthma has declined substantially during the past 5 years. Contributing to this situation is recognition that these agents are relatively weak bronchodilators that have limiting safety profiles as a result of complex drug interactions and metabolic heterogeneity between patients. Perhaps even more importantly, Salmeterol is now used as a long acting bronchodilating agent that can facilitate uninterrupted sleep in patients who suffer from nocturnal asthma. Parenteral administration of theophylline is no longer recommended for emergency department-based management of acute asthma inasmuch as randomized controlled trials have failed to show efficacy in this setting. Despite these relatively significant concerns relating to efficacy, theophylline remains an option in individuals who have achieved an unsatisfactory level of control as a result of use of other agents.

Ipratropium bromide has been available for chronic bronchitis/COPD for a number of years. It has been recognized that its anticholinergic properties provide some modest bronchodilator effect in patients with asthma. Because of the availability of much more powerful β2 adrenergic agents, this agent has received relatively little attention in acute or chronic management of patients with asthma except in those in whom a mixed picture involving bronchitis exists typically as a result of ongoing cigarette use. Although use of β adrenergic blocking agents is

strongly discouraged in patients with asthma, some of individuals can or must use β blockers. In this limited group of patients, ipratropium bromide can be helpful as a result of the markedly reduced effectiveness of β2 adrenergic agents. An additional subset of patients in whom ipratropium bromide can be quite helpful is cough variant asthma since patients tend to respond very well to the anticholinergic treatment with of this agent.

LTD_4 receptor antagonists and inhibitors of the 5 lipoxygenase will very likely be released for use in asthma in late 1996. Experience in Europe and Japan as well as in trials in the US indicate that these agents will likely be of significant value in the management of asthma. While they target only a single class of mediators, the sulfidopeptide leukotrienes, these are important mediators and also important paracrine functions in allergic inflammation. These agents have the advantage of being orally administered and have a very limited adverse effect profile, but require fairly frequent dosing. From a clinical perspective, these agents have received attention for their capacity to be very effective in aspirin sensitive asthma and for general use in mild-moderate asthma, particularly when an allergic component exists. While relatively little published information is available comparing the efficacy of these agents to Nedocromil and inhaled glucocorticoids, it seems likely that these agents will have an intermediate position, that is less effective than inhaled glucocorticoids, but more effective than Nedocromil. Controlled trials exploring the efficacy of combinations of anti-leukotriene therapies with other anti-inflammatory therapies are lacking.

Although histamine is an important mediator released by mast cells, its relative contribution to airway obstruction in chronic asthma is modest and may be very low in nonallergic asthma. While it is now clear that initial concern over the anticholinergic drying effects of early generations of antihistamines was unjustified, the practical use of this class of medications was seriously limited by the development of intolerable sedation. The development of nonsedating H_1 antagonists has allowed exploration of the role of these agents in treating asthma. Though fairly effective in limiting airway obstruction when patients are acutely exposed to allergens to which they are sensitive (or prior to exercise in those who have exercise-induced bronchospasm), their role in chronic asthma has been uncertain. While terfenadine and astemizole cannot be used at high dose due to their capacity to increase the QTc interval loratadine and cetirizine can be used at higher doses. While the latter is burdened by mild dose-related sedation, it appears to have some additional anti-inflammatory properties and has been shown to contribute to decreased airway obstruction in chronic asthma. The role of these agents is likely to remain largely

adjunctive and particularly useful in patients who also suffer from allergic rhinitis. Indeed, more successful management of allergic rhinitis in patients with asthma may contribute significantly to improved control of lower airway disease in patients with asthma as several studies have shown and the experience of many experts supports.

INTEGRATION OF THERAPEUTIC MODALITIES

A stepwise approach to increasing pharmacotherapy in asthma has been increasingly adopted during the past decade. It is important to reiterate at this point that in Figures 9 through 12 increasing "severity" relates to the underlying disease as reflected by both the level of symptoms as well as the level of medication received.

In mild episodic asthma most experts feel that if occasional use of bronchodilating medications is all that is required, PRN β2 adrenergic agonists represent the appropriate therapy in these minimally effected individuals. If identifiable avoidable triggers can be easily targeted then avoidance can be suggested, but skin testing and/or *in vitro* testing to identify IgE sensitivity is, in general, not recommended in these patients except to confirm strongly suspected sensitivities (for example to cat allergen).

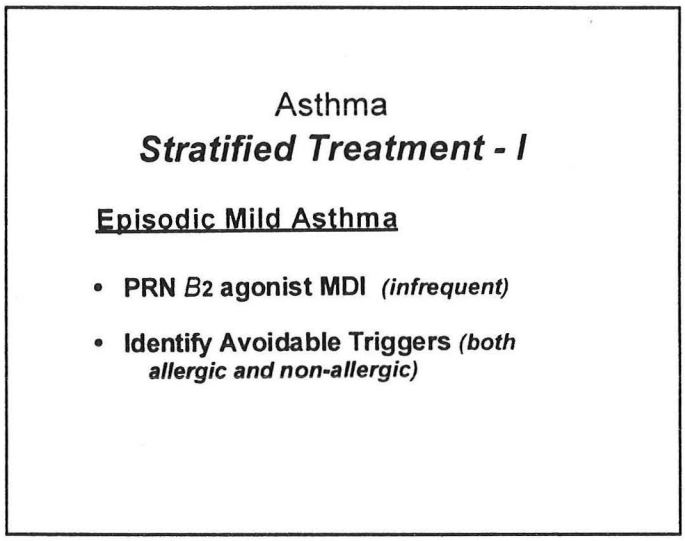

Figure 9

In patients in whom symptoms of asthma are persistent or are present for a large fraction of the year (Figure 10), asthma experts increasingly feel that treatment with topical anti-inflammatory medications is centrally important. While β2 adrenergic agents used frequently can often control patients who have this level of severity,

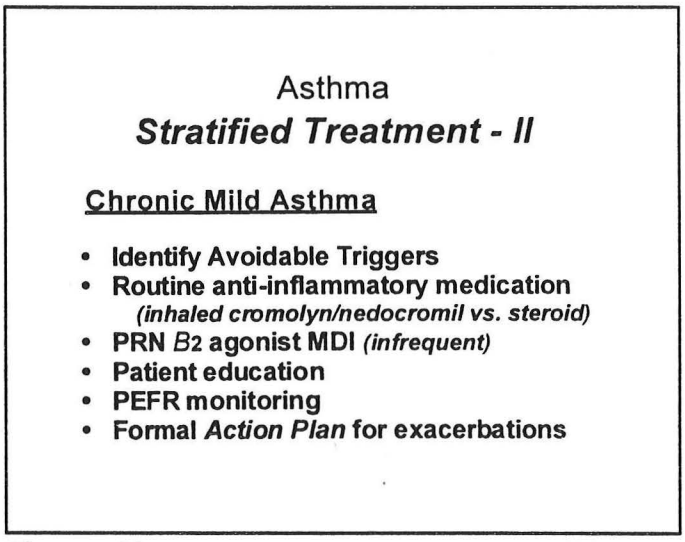

Figure 10

concerns over the inability of bronchodilating agents to exert an impact upon underlying inflammation limits enthusiasm for using only bronchodilators. More recently increasing recognition that inflammation causes permanent fibrotic and/or bronchiectatic changes of the airways have added momentum to more aggressive use of chronic anti-inflammatory medications in patients with mild asthma. If symptoms are easily controlled with Cromolyn or Nedocromil -- defined by the relatively infrequent need for inhaled β2 agonists -- then inhaled glucocorticoid medications need not be employed. Even in patients with mild chronic asthma it is increasingly felt to be important to identify allergic sensitivity to avoidable indoor aeroallergens in order to try to limit inflammatory pressure that exposure to these antigens can cause on a daily basis. Beyond pharmacotherapy, patient education and peak flow monitoring and the development of a formal action plan for exacerbations are essential to developing successful patient self-management.

Figure 11 illustrates the additional therapies that are warranted when success has not been achieved by the use of environmental control and Nedocromil or low dose inhaled glucocorticoid medications in patients who most consider to have moderate underlying severity. Specifically, higher doses of inhaled glucocorticoids are used as well as Salmeterol and, when they become available, agents capable of inhibiting the synthesis and/or effect of leukotrienes. Intensification of patient education and/or avoidance measures are critically important at this level in order to avoid the necessity of increased use of systemic glucocorticoid therapy. While the financial structure of reimbursement for medical care has dramatic effects upon decision making, most would agree that patients who require high dose inhaled glucocorticoid therapy and/or continue to have persistent symptoms requiring frequent use of inhaled β2 agonists despite high dose anti-inflammatory therapy represent good candidates for subspecialty referral, at least on a consultative basis.

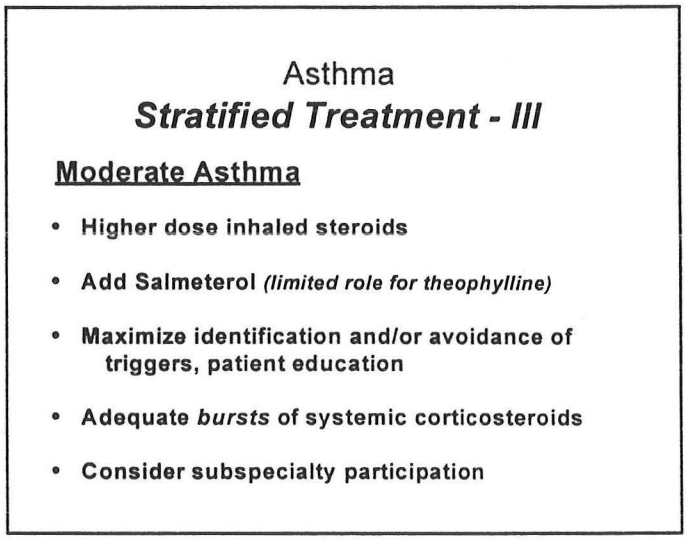

Figure 11

Finally, in patients who fail to respond to the intensive therapies mentioned above subspecialty management of patients having severe asthma involves

maximization of the therapies described previously as well as the regular use of systemic glucocorticoid agents in conjunction with steroid sparing agents (Figure 12). The latter involve a family of agents that have varying degrees of support in the literature for their effectiveness in patients with severe asthma. They include methotrexate, cyclosporin, intravenous immunoglobulin, dapsone, inhaled furosemide and inhaled lidocaine. In these patients, and selected patients with moderate asthma, it may be appropriate to consider allergen immunotherapy, a treatment which has been found to be particularly effective in those who have associated allergic rhinitis.

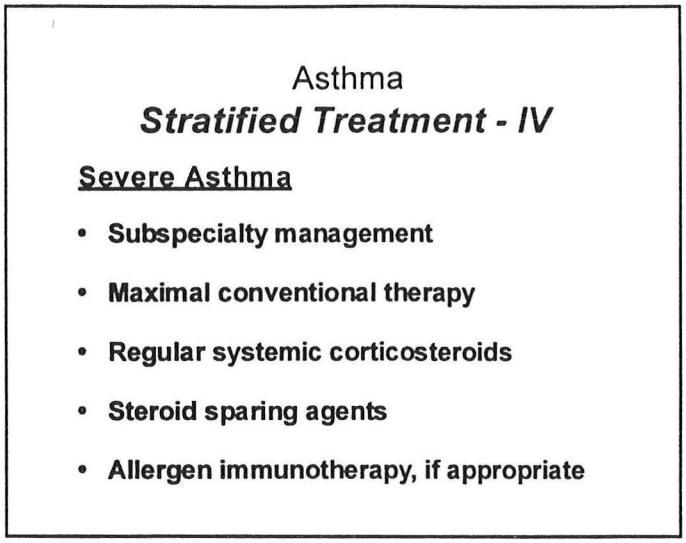

Figure 12

OTHER EDUCATIONAL / MANAGEMENT TOOLS

A widely used and highly effective approach to educating patients with regard to self-management that involves adjusting the dosage and/or frequency of their medications has been developed and uses to "traffic signal" paradigm. In this model, individuals whose peak expiratory flow rate (PEFR) is greater than 80% of their personal best (not their predicted best but the best that has been observed during the past year) represents the "being in the green". The yellow represents peak flows in the 50-80% range for PEFR while red indicates peak flows that are less than 50% of an individual's personal best. The value of this paradigm relates to guidelines presented to patients in written care plans that guide their self-management (Figure 13). So long as individuals are in the green zone they are told to continue their current therapy. When they drop into the yellow zone they should

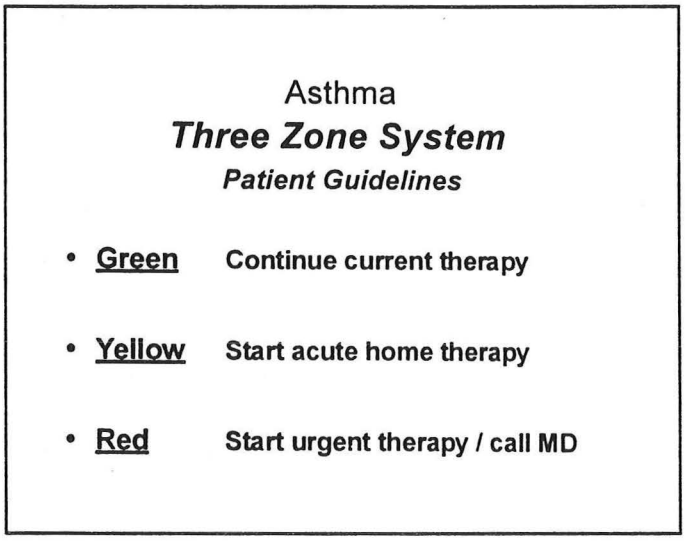

Figure 13

initiate acute home based therapy, typically involving the increased use of β2 adrenergic agents and, if needed, either increased dosages of inhaled glucocorticoids for patients with mild to moderate disease or systemic glucocorticoids for individuals with moderate to severe underlying disease. When individuals fall into the red zone they are directed to initiate urgent home therapy and to seek immediate contact with their physician or other healthcare provider. Telephone access is critically important not only to assure appropriate medical management of these patients, but also to enhance rapport and associated patient compliance.

This traffic signal system also serves to facilitate success from the physician's standpoint (Figure 14). If a patient is always in the green zone then it makes sense to consider reducing therapies usually beginning with bronchodilators (until their use is minimal) followed by anti-inflammatory medications. Patients who occasionally fall into the yellow zone are usually felt to be receiving appropriate pharmacotherapy. Patients who are frequently in the yellow zone would often benefit from intensification of anti-inflammatory therapy. Patients who are frequently in the red zone require maximization of anti-inflammatory therapy, intensification of patient education and/or subspecialty referral.

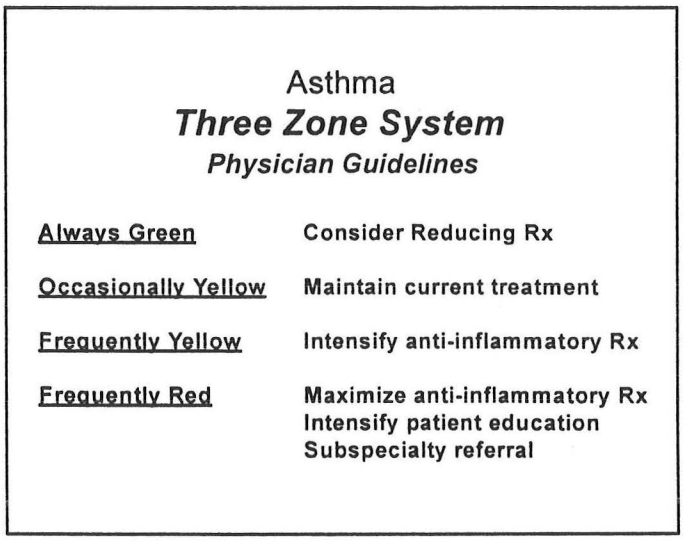

Figure 14

THE IMPACT OF HEALTHCARE FINANCING ON ASTHMA

The development of widely varying incentive-based approaches to reimbursement for healthcare has led to widely varying success in the management of asthma. Prior to the pressures associated with cost containment and development of risk-based compensation for primary care physicians, patients were referred to asthma specialists (pulmonologists and allergy and immunology specialists) based upon severity as judged by failure to achieve success using therapeutic strategies available to the primary care practitioner. A very large fraction of patients would self refer to subspecialists as a result of their perception that their goals for successful management had not been met. At this point in time (late

1980s and early 1990s) comprehensive economic studies indicated that the cost of asthma on a national basis was approximately $4 billion in direct medical costs and approximately $2 billion in indirect costs to employers and society.

Efforts seeking to reduce healthcare costs have had a variety of effects upon treatment strategies associated with asthma. First, patients who choose or are required to use an HMO-based system that involves a "gatekeeper" have found themselves frequently unable to seek out care in the subspecialty environment. Second, incentives provided to primary care practitioners in this environment often involve withhold pools for subspecialty referral which reduce enthusiasm to refer patients to asthma specialists. As intended, these plan features achieve reduced subspecialty participation. An additional effort at cost constraint involves formulary restriction to more costly medications (particularly Cromolyn, Nedocromil, Salmeterol and some medications for allergic rhinitis). Though documentation of the economic impact of these changes in the delivery system relating to asthma have been limited, data from a managed care consortium show that greater formulary restriction was associated with increased <u>total</u> costs of asthma care; presumably the result of increases in acute care costs associated with unscheduled physician visits, emergency room utilization and inpatient management. Excess ER utilization by patients with asthma has continued to be a significant problem despite the existence of powerful agents and approaches to control asthma.

Also unfortunate is the struggle between subspecialists and primary care physicians that has mirrored patterns in a variety of disciplines. Excessive productivity demands placed upon primary care providers limit their capacity to engage in patient education activities related to asthma. Additionally, the diversity of illnesses that must be cared for in the primary care setting limits the capacity of support personnel to be able to effectively deliver patient-specific educational interventions since the latter services do not qualify for reimbursement in virtually any healthcare financing system in place in the United States and few punitive economic systems discourage continuing ED utilization. Although data has previously been sparse, increasing evidence indicates that despite the existence of NHLBI guidelines in the National Education Program, relatively little progress has been made in reducing the costs associated with asthma on a nationwide basis.

Because it has been well known for some time that acute care costs are virtually nonexistent in the subspecialy environment, the lack of reducing acute care costs in asthma during the past 5 years has resulted in the development of a number of commercial interventions that seek to overcome ineffective or counterproductive

financing systems. Specifically, disease state management programs that receive compensation based upon either achieving successful economic goals of reduced inpatient and emergency room and/or providing case management services on a fee for service basis have proliferated. Approximately 60 cents PMPM (per member per month healthcare costs) are expended for acute care of asthma resulting in the existence of approximately $0.6 to $0.8 million per year in acute care costs to be at risk for a pool of 100,000 covered lives. The managed care industry has identified the potential savings that can be achieved by bringing into control a relatively small number of patients who cause these costs as "low hanging fruit".

Though it is entirely appropriate to enhance the quality of care patients receive and reap the benefits of reduced acute care costs, a concern that many asthma specialists share is that patients with less severe disease and/or the need for few, if any, acute care services may not receive optimal services and indeed suffer from unnecessary morbidity as a result of the failure of disease state management programs to target these patients in whom economic incentives are limited. Perhaps providing some degree of optimism for this patient group, however, is that while they will not yield substantial direct medical cost reductions through improved care, they may incur frequent indirect costs that may be of substantial interest to employers (the ultimate purchasers of healthcare coverage). Specifically, reduced worker productivity as a result of lost days from work and/or school absences (that reduce per diem school district compensation) provide a significant and largely unrecognized target for improvement in patients who are less severely effected than those targeted by disease state management programs.

THE PARKLAND EXPERIENCE

History of Parkland Asthma Task Force - In late 1992 a multi-disciplinary committee was established to study perceived excessive utilization of emergency services by patients with asthma. Chart review and a novel computer-based search strategy indicated the existence of ~3,000 adult visits and nearly $3 million in charges associated with care in the Emergency Department. In studyin patterns of care for patients at Parkland, it was found that a significant "recycling" of patients through the Emergency Room took place as a result of delays in scheduling for the Chest Medicine Clinic which was heavily burdened by its commitment to provide care for those with COPD and other lung diseases. Moreover, a significant number of these patients also had no or only intermittent primary care. In early 1993 the Parkland Asthma Task Force proposed a new comprehensive and integrated system for patients with asthma shown in Figure 14. This system proposed to generate a new Asthma Clinic that would provide subspecialty medical evaluation, patient education related to preventive self-management and enhanced patient access. Additionally, this

clinic was viewed as a "conduit" for care since it was hoped that patients who achieved successful patient self-management would return to a primary care setting and an improved primary care/subspecialtyt interface could be developed. In response to the likely capacity to enhance the quality of care, improve outcomes and reduce costs, this proposal was approved for phased implementation and the Asthma Clinic was opened late in 1993.

Nearly three years since its inception, the Parkland Asthma Task Force has fully or partially implemented a number of interventions seeking to achieve the model of care illustrated in Figure 15 and summarized in the following sections:

Asthma Clinic - At the request of the Parkland Asthma Task Force, the Asthma Clinic was opened in the fall of 1993. This half day asthma clinic currently provides: 1) subspecialty medical care by the faculty and fellows of the Division of Allergy and Immunology; 2) extensive education in preventive self-management provided by the Asthma Nurse Coordinator, the Emergency Department Asthma Nurse Specialist, the Asthma and Allergy Pharmacist and Respiratory Therapist 3) routine spirometric evaluation of airway function by a Respiratory Therapist; and 4) evaluation of allergic sensitivity to avoidable aeroallergens by skin testing. The effectiveness of the clinic has been formally demonstrated in a case controlled study of the first 69 enrolled patients in whom a statistically and clinically significant reduction in ED utilization was shown (3.79 → 1.79 ED visits/year/patient; $p<0.005$).

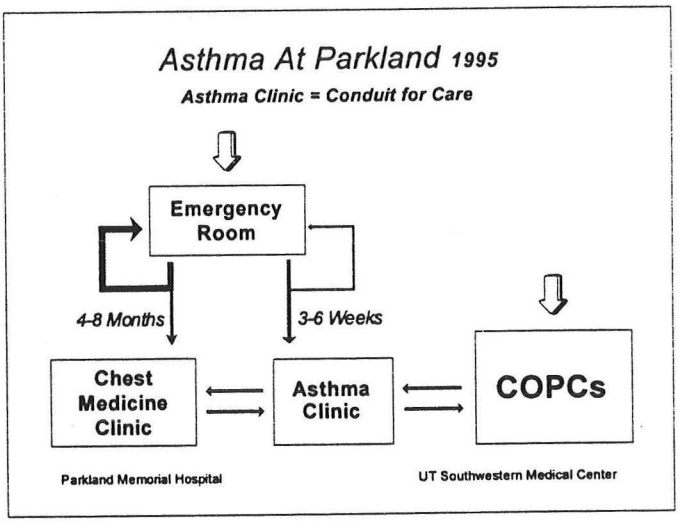

Figure 15

Emergency Department - Both retrospective and prospective studies in 1993 and early 1994 indicated the existence of ~3,000 ED visits annually, incurring an average charge of $944/ED visit ($2.8 million annually). Care has been provided in a ~200 square foot "Asthma Booth" in which 8 chairs are available to those who do not require more intensive ED treatment. Evaluation and management of triaged patients has been provided by Respiratory Therapists, ED nursing staff and Internal Medicine Residents under the supervision of the ED faculty. At the request of the Asthma Task Force an ED-based Asthma nurse specialist was recruited to: 1) assist with acute evaluation and management, 2) initiate patient education related to changing the pattern of care from recurrent use of ED services to that of preventive self-management; and 3) evaluate the suitability of patients for referral to the Asthma Clinic.

COPCs - Care of both adult and pediatric patients with asthma is provided for those who utilize the COPCs as their source of primary care. The need to generate continuing and timely access to new patient appointments in the Asthma Clinic has motivated the development of a pilot project to "graduate" patients from the Asthma Clinic (those who have achieved their maximum benefit from this clinic) to the appropriate COPC. A pilot project being refined at this time seeks to facilitate a smooth transition between the subspecialty environment of the Asthma Clinic and a primary care model in the COPC as well as to develop community outreach programs to facilitate identification an improved primary care-based management of patients with asthma.

Research Projects - As one of Parkland's CQI projects, the effectiveness of several components of this intervention are being evaluated and both major and minor processes have been targeted for improvement efforts. Under the auspices of the Research Committee of the Asthma Task Force, a major interest in health services research has spawned the development of several important research projects that have resulted in Federal and private foundation funding of 4 different health services research projects.

SUGGESTED ADDITIONAL READING

In addition to the guidelines developed by the NHLBI and the NAEP, the Joint Council of Allergy and Immunology (a joint organization representing the two major national organizations in allergy and immunology) has developed and released a useful compendium relating to practice parameters in asthma. This 160 page document was published in the November issue of the *Journal of Allergy and Clinical Immunology* primarily to represent a description of the standard of care for asthma for this subspecialty; a very useful 14 page compilation of the summary statements has been included as an appendix to this Grand Rounds protocol. It has been reprinted with permission (Susan Patterson) from Mosby-Year Book, Inc., St. Louis, MO and the American Academy of Allergy, Asthma and Immunology. This is a highly distilled and well-referenced guide to important points relating to the diagnosis and management of asthma.

Additionally, an updated set of guidelines is under development by the NHLBI and is expected to be released in late November, 1996 and published and distributed in early 1997.