

# INFLAMMATION IN ASTHMA

Sally Wenzel, M.D.

## INTRODUCTION

Asthma is associated with a wide range of symptoms and signs, including wheezing, cough, chest tightness, shortness of breath and sputum production.

The symptoms and signs evolve from three basic characteristics that underlie the disease and its exacerbations: airway obstruction, airway hyperresponsiveness and airway inflammation.

Airway obstruction and hyperresponsiveness represent the classic physiology of asthma, and their contribution to the disease process and symptomatology have been well recognized for some time. Appreciation of the role of airway inflammation in asthma has evolved more recently.

Today asthma experts consider airway inflammation a central feature of asthma pathogenesis and its clinical manifestations. In fact, airway inflammation plays a critical role in airway obstruction and hyperresponsiveness.

In recent years, clinical and scientific knowledge of asthma has evolved from a model of episodic constriction of bronchial smooth muscle to a model of chronic airway inflammation. Evidence of inflammation may appear very soon after the onset of symptoms in newly diagnosed asthmatic patients.

Accordingly, treatment algorithms for asthma have emphasized treatment of the underlying inflammation, as well as the bronchoconstrictive symptoms. By

acquiring a better understanding and appreciation of the inflammatory process, physicians can employ treatments to inhibit specific steps in the process and improve control over asthma and its symptoms.

## INFLAMMATORY CASCADE

Inflammatory disorders involve a potentially wide range of cell types and cellular mediators, which will be discussed briefly later on. The multiplicity of cellular factors make inflammation and inflammatory disorders quite complex.

A number of models have been developed to explain inflammation. One that seems especially pertinent to asthma is the

inflammatory cascade, outlined below. The model suggests that asthma-associated inflammation occurs as a seven-step process:

1. Sensitization
2. Stimulation
3. Cell signaling
4. Inflammatory cell migration
5. Activation of inflammatory cells
6. Tissue stimulation and/or damage
7. Resolution

### Sensitization

Although in some patients, allergic processes are difficult or impossible to find, experts believe that a large percentage of asthma is allergy driven. An

**Airway obstruction and hyperresponsiveness represent the classic physiology of asthma.**

**UPDATE**

MEDICAL SCIENTIFIC

Vol. 14 No. 3, Fall 1996

**INFLAMMATION IN  
ASTHMA**

---

**An allergic clinical state must evolve from sensitization to a particular allergen. Sensitization must occur before the cellular triggering phase can begin.**

---

Sensitization occurs as a result of presentation of an antigen to a T-lymphocyte. At this point, no one knows for sure which cell or cells are involved in antigen presentation. Several candidate cells have been postulated, including monocytes, macrophages, B-lymphocytes and dendritic cells. Regardless of the specific cell type, an antigen is processed and delivered to a T-lymphocyte, which responds by changing from a naive lymphocyte to an allergic type of cell (T-Helper 2, or T-H2), emitting signals through the cytokine networks. The cytokines find their way to B-lymphocytes, which react by producing IgE specific for the antigen. The IgE then attaches to mast cells, thereby completing the sensitization or antigen presentation phase, the first step in the inflammatory cascade.

### **Stimulation**

Genetically predisposed individuals exposed at an early age to indoor aeroallergens, occupational antigens and respiratory viral infections become sensitized to certain allergens. Any number of factors may stimulate an exacerbation of the disease, including allergens and

---

**Allergens are the most extensively studied of the asthma stimuli.**

---

environmental agents, through triggering of mast cells. Allergens are the most extensively studied of the asthma stimuli. The issue of whether all cases of asthma require a specific stimulus remains unresolved and controversial. However, recent studies have provided evidence that most, if not all, asthma does have an allergic basis that may revolve around IgE.

allergic clinical state must evolve from sensitization to a particular allergen. Sensitization must occur before the cellular triggering phase can begin.

Especially persuasive evidence has come from research showing a high prevalence of asthma in association with early-age exposure to specific allergens and from the finding that asthma probability rises with an individual's serum IgE level and is almost non-existent in individuals with low IgE levels.

At this point, no one can say with certainty whether IgE and the triggered mast cells cause asthmatic inflammation or merely have an association with the inflammation. Additionally, studies have yet to exclude the possibility that some cases of asthma occur with little or no IgE involvement.

### **Cell signaling**

Within the conceptual framework of the inflammatory cascade, stimulation activates a complex communication network. Signaling cells issue biological commands that lead to recruitment of inflammatory cells into the airways.

T-lymphocytes, macrophages and monocytes are activated in symptomatic asthma, as indicated by the expression activation markers, such as IL-2 receptor, TNF-alpha and other activation markers. Expression of these markers appears to correlate with disease activity, and, perhaps more importantly, steroid therapy decreases expression of the markers. Research at National Jewish and other centers currently focuses on defining the role of specific T-cell subsets in asthma.

### **Migration**

During the triggering and signaling processes, substances are produced that induce leukocyte migration into the airways. At various times after allergen challenge, migration may involve eosinophils, neutrophils, lymphocytes and monocytes. The migration begins within two hours and may continue for up to 48 hours.

One possible explanation for migration of inflammatory cells is the release of chemoattractant mediators by signaling cells. Alternatively, signaling cells may release cytokines that upregulate adhesion molecules that stimulate cellular

migration into a focus of inflammation. The upregulation correlates with the size of the eosinophil population in the airways

### Activation of inflammatory cells

Following migration into the airways, inflammatory cells require activation to produce the physiologic changes associated with asthma symptomatology. Activation probably occurs after the cells' exposure to cytokines and other potential activators found in inflamed lungs. Potential activating substances include inter-

leukin-1, interleukin-5, tumor necrosis factor-alpha and granulocyte macrophage-colony stimulating factor (GM-CSF).

Considerable evidence exists to indicate

**Considerable evidence exists to indicate that eosinophils are activated in the lungs of asthmatic patients.**

that eosinophils are activated in the lungs of asthmatic patients. Levels of major basic protein have been shown to be elevated in biopsy specimens, broncho-alveolar lavage fluid and sputum. In sputum, levels of the protein rise with increasing disease activity and decline with anti-inflammatory treatment.

A limited amount of data suggest that monocyte-macrophage activation occurs during the late asthmatic response (LAR) to allergen exposure or other challenges. The data include evidence of increased expression of low-affinity IgE receptor and increased macrophage production of IL-6 and TNF-alpha following allergen exposure.

### Tissue stimulation and/or damage

Evidence continues to accumulate to suggest that the inflammatory processes of asthma lead to tissue alterations (including stimulation and damage) at the level of the epithelium, basement membrane, smooth muscle and nerves.

**Epithelium.** The airways of asthmatic patients exhibit abnormal epithelium, possibly a result of exposure to enzymes, growth factors and other proteins released by inflammatory cells. The damage may intensify the effects of bronchoconstricting stimuli to transform the

stimuli into major factors in airway reactivity.

Studies in animal models of asthma suggest a possible role for the nonadrenergic, noncholinergic system in the airway epithelial damage. A number of neuropeptides have been linked to bronchoconstriction and response to allergen challenge.

**Basement membrane.** Evidence suggests that the basement membrane or associated connective tissue is altered in asthmatic patients. For example, connective tissue adjacent to the basement membrane exhibits a different collagen composition and increased collagen deposition.

**Smooth muscle and nerves.** Pathologic studies indicate that asthmatic smooth muscle may be both hyperplastic and hypertrophied. In vivo, a thickened airway structure could be more reactive or exhibit more constriction. This evidence remains especially controversial among asthma researchers, particularly in light of studies showing that smooth muscle from asthmatic patients does not behave differently in comparison to normal tissue.

### Resolution

The discovery that asthma involves chronic underlying inflammation has given rise to the hypothesis that abnormal or incomplete resolution of inflammation may play a role in the disease and its exacerbations. Particularly compelling evidence of abnormal resolution has come from investigations of occupational asthma, wherein removing an individual from the workplace does not lead to resolution of inflammation or symptoms.

Reasons for the abnormal (or absent) resolution remain largely unknown. Potential clues may come from improved understanding of the wide variability of asthma patients' response to allergen exposure. Wide variations in the type, intensity and duration of response have been observed.

For reasons that are not entirely understood, some asthma patients have an immediate allergic response (IAR) and no LAR. Some evidence suggests that a lymphocyte-mediated

process inhibits the development of LARs in people who have IARs. Among people who develop LARs, considerable variation exists in the duration and intensity, suggesting possible inhibition of resolution signaling processes in association with a prolonged, severe LAR. Evidence also exists for impairment of alveolar macrophages' suppresser activity on lymphocytes, possibly leading to uncontrolled lymphocyte proliferation and inflammatory response.

More research is needed to confirm the lack of resolution in the inflammatory process and to identify associated underlying mechanisms. Better understanding of the resolution process could help explain the differences among mild, moderate and severe asthma and lead to the development of more effective therapies.

## INFLAMMATORY CELLS AND MEDIATORS

Ongoing research has identified numerous cells and mediators that may be involved in the airway inflammation associated with asthma. The multiplicity of these cells and substances points to the complexity of the disease and to the many unanswered clinical and research questions that await clarification in further research. Key inflammatory cells and mediators identified thus far include:

- Mast cells. Possibly a primary triggering mechanism for the IAR.
- Macrophages. Implicated in the IAR and in the antigen processing and presentation associated with later stages of the asthmatic response.
- Eosinophils. Migration into lungs is associated with inflammation and bronchoconstriction. The cells directly or indirectly produce a host of enzymes, proteins and mediators linked to tissue alteration and injury in asthma. Closely associated with the LAR.
- Lymphocytes. Possibly the overall cellular coordinator of the varied processes and interactions that constitute the inflammatory response in asthma.
- Products of the arachidonic acid cascade: leukotrienes, prostaglandins and throm-

boxane, all of which are known mediators of inflammation.

- Cytokines and growth factors, including the interleukins and GM-CSF, implicated in activities ranging from mast cell production and growth to inflammation-associated eosinophil migration to activation of various inflammatory cells and proteins.

- Preformed inflammatory mediators, such as histamine, proteases and eosinophil major basic protein.

## Implications for therapy

Controlling inflammation has become a central objective of asthma therapy. Better control of inflammation is essential to better control of the disease and may open the door to alteration of the disease course. Control of inflammation can occur at several levels. In allergy-driven asthma, environmental measures are very important, as they eliminate disease "triggers." Specifically, in humid regions, removing all unnecessary carpeting and upholstery (especially in bedrooms) diminishes dust mites' ability to thrive.

The allergen burden can be further minimized by encasing pillows and mattresses in plastic and washing all bedding in very hot water.

Individuals allergic to animal dander should keep pets out of the house.

Pharmacologically, inflammation control has been accomplished primarily by use of corticosteroids. Inhaled or oral steroids have been shown to decrease populations of inflammatory cells and cytokines in the airways of asthmatics. Improvement in inflammation is associated with improvement in pulmonary symptoms. The effect likely relates to an interruption in the inflammatory cascade. Certain other drugs (such as nedocromil, cromolyn and theophylline) may have anti-inflammatory effects as well, but the effects are milder. Improvement in the understanding of asthmatic inflammation

---

**Controlling inflammation has become a central objective of asthma therapy.**

---

has enhanced the ability to design drugs that target specific components of the inflammatory process. Researchers at National Jewish are actively involved in the study of these new therapies. Examples include drugs that modulate leukotrienes, such as LTD 4 receptor antagonist, zafirlukast and the 5-lipoxygenase inhibitor zileuton. These drugs have become available recently or should become available in the near future. Ongoing studies are evaluating drugs that inhibit cytokine activity, including IL-4 and IL-5, as well as drugs that prevent IgE binding to mast cells. These specific drugs should improve our understanding of inflammation and hopefully lead to its improved treatment.

## References

1. Henderson WR Jr. *The role of leukotrienes in inflammation*. Ann Intern Med 1994; 121:684-97
2. Wenzel SE. *Asthma as an inflammatory disease*. Ann Allergy 1994; 72:261-71.
3. Wenzel SE, Trudeau JB, Kaminsky DA, Cohn J, Martin RJ, Westcott JY. *Effect of 5-lipoxygenase inhibition on bronchoconstriction and airway inflammation in nocturnal asthma*. Am J Respir Crit Care Med 1995; 152:897-905
4. Robinson, DS et al. *Evidence for a predominant TH2-type bronchoalveolar lavage T lymphocyte population in atopic asthma*. New Engl J Med 1991; 326:298-304.
5. Diaz P, Gonzalez M, Galleguillos F, et al. *Leukocytes and mediators in bronchoalveolar lavage during allergen-induced late-phase asthmatic reactions*. Am Rev Respir Dis 1989; 139:1383-9.

## Author:- Inflammation in Asthma

Sally Wenzel, M.D.

Associate Faculty Member, Department of Medicine, National Jewish;  
Associate Professor of Medicine, UCHSC

## Faculty:

Robert Bethel, MD

Faculty Member, Department of Medicine, National Jewish; Associate Professor of Medicine, UCHSC

Mark Boguniewicz, M.D.  
Faculty Member, Pediatric Allergy/Immunology and Atopic Dermatitis Program; Associate Professor of Pediatrics, UCHSC

Richard Martin, M.D.  
Head Division of Pulmonary Medicine, National Jewish; Professor of Medicine, UCHSC

## 19th Annual Update on Allergy and Clinical Immunology



FEBRUARY 5-9, 1997  
KEYSTONE RESORT  
KEYSTONE COLORADO

- Inflammation and the development of fixed airflow obstruction
- Corticosteroid action and their role in asthma therapy
- Controversies surrounding the treatment of sinusitis
- New pharmacotherapeutic agents for the treatment of asthma
- How immunotherapy impacts the treatment of asthma
- Impact of managed care on office management of the asthmatic patient

For registration information, call the Office of Professional Education at 800-423-8891 x1000. Visit our web site to review the conference program: <http://www.njc.org>

## Upcoming CME Programs

### 19th Annual Update on Allergy and Clinical Immunology

February 5-9, 1997  
Keystone, Resort, Keystone, CO  
Tel: 800-258-0437

### 4th Comprehensive Review in Adult & Pediatric Allergy/Immunology

June 11-15, 1997  
The Marriott Southeast, Denver, CO  
Tel: 800-228-9290

### Frontiers in Mycobacteriology: TB at the Millenium - Debating the Controversies

October 15-19, 1997  
Vail Cascade Hotel & Club, Vail, CO  
Tel: 800-420-2424

For further information on CME programs,  
at National Jewish, call 303-398-1000

#### Medical Advisory Board:

Mark Boguniewicz, M.D., Willi Born, Ph.D.,  
Larry Borish, M.D., Barry Make, M.D.,  
and Uwe Staerz, M.D., Ph.D.

#### Important Phone Numbers:

Patient referrals/appointments  
Tel: 303-398-1355 or 800-222-5864 X 1355  
Fax: 303-398-1183

#### Home Page on World Wide Web:

<http://www.njc.org>

# UPDATE

National Jewish Medical and Research Center  
1400 Jackson Street  
Denver, CO 80206-2762

Address Correction Requested

## Weekly Education Listings

All sessions are held in Heitler Hall. For more information, call Peggy Hammond at 303-398-1436 or e-mail [hammondp@njc.org](mailto:hammondp@njc.org)

**Monday:** Immunology Course

**Tuesday:** Research in Progress

**Wednesday:** Denver Allergy Rounds

**Thursday:** Pediatric Grand Rounds

**Friday:** Pulmonary Research in Progress

**Medical Scientific Update**, a publication of the continuing medical education office at National Jewish, provides information to physicians about our clinical and research programs in allergic, respiratory and immune system disorders.

Please send any comments or requests for topics to Adele Gelfand, Manager of Professional Education, National Jewish Center for Immunology and Respiratory Medicine, 1400 Jackson Street, Rm M-222, Denver, CO 80206. We'd like to hear from you.

Moving?

Please forward change of address form to us to maintain your free subscription to Medical Scientific Update.

Copyright ©1996, National Jewish Center for Immunology and Respiratory Medicine

#### Lung Line® 800-222-LUNG. 355-LUNG (Denver only)

This free information service, staffed by highly qualified registered nurses, answers patients' questions about respiratory, allergic and immunologic diseases. Callers are encouraged to discuss information received with their physicians.

The Physician Line at 1-800-NJC-9555, exclusively for physician use is a toll free service that connects you with a highly experienced representative who can provide information on National Jewish programs, laboratory tests and referrals.

Non-Profit Org.  
U.S. Postage  
**PAID**  
Permit No. 1541  
Denver, CO