# IS ASTHMA CURABLE?

## An Inflammatory Perspective

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# INDEX

# BRONCHIAL ASTHMA

- A Case Report -

This 8 year old male developed asthma and perennial allergic rhinitis at 2 years of age. Between the ages of 2 and 4 years, he required four emergency room visits and three hospitalizations for the treatment of asthma. Beginning at age three, he received three years of aeroallergen immunotherapy. His current therapy for asthma includes cromolyn sodium inhalation three times daily, supplemented with a beta-adrenergic agonist by metered dose inhaler as needed. On average, he requires inhaled bronchodilator therapy at least once daily, and additional inhalations during the night in the spring because of nocturnal exacerbations that disrupt sleep.

## INTRODUCTION

Bronchial asthma is a disease characterized by dyspnea, wheezing, and cough; reversible airway obstruction; and airway hyperreactivity to nonspecific stimuli such as methacholine or histamine. Estimates of the incidence of asthma in this country range from 10% to 20%. Active disease within the past year is estimated at 1% to 5% of the population. Asthma accounts for 4% to 6% of emergency room visits, causes approximately 500,000 admissions to hospitals in this country each year, and is the leading cause of admission of children to many urban hospitals (1-4).

These rounds have repeatedly focused on the rapidly changing concepts of the pathophysiology and management of asthma. In my Internal Medicine Grand Rounds in 1984, I reviewed emerging evidence that asthma is the clinical manifestation of a characteristic form of pulmonary inflammation rather than a sustained change in tissue function resulting from sustained mediator release. On August 13, 1987, Dr. Kennerly presented an updated view of the pathophysiology and management of asthma with emphasis on

anti-inflammatory drugs to treat asthma and bronchodilators to treat the symptoms of asthma. Dr. Robert Haddox reviewed the morbidity, mortality, and conventional medical care of asthma in detail at these rounds on February 9, 1989.

This Grand Rounds presentation represents a somewhat radical departure from these earlier reviews. Traditional wisdom holds that susceptible individuals are subject to an unavoidable, incurable illness. Traditional goals of therapy for asthmatic patients (in decreasing order of importance) include suppression of symptoms to a degree sufficient to avoid death, respiratory failure, hospitalizations, urgent medical visits, days lost from work or school, disturbed sleep, limitations on physical exertion, and the symptoms of asthma. The physician's role has been seen as palliative, reacting to the disease in proportion to the degree of impairment. Symptomatic relief has been seen as the only feasible goal. Systematic attempts to prevent the establishment of chronic asthma or to induce complete, durable remission of the underlying disease are not conventional goals of therapy. Indeed, the concept of actively "curing" asthma has been regarded as an entirely theoretical consideration (5-11).

Exciting new data, particularly data emerging over the past two years, have challenged the very foundations of these traditional views. New concepts of the pathophysiology of asthma and new clinical data have raised critical questions about asthma:

Do complete, long-lasting remissions of asthma occur in response to any existing therapeutic strategies?

Are the known pathogenic mechanisms, essential for the establishment of chronic asthma, vulnerable to new pharmacologic approaches?

What is optimal care of asthma today in the context of current knowledge?

## IS ASTHMA CURABLE?

# RECENT INSIGHTS INTO THE PATHOPHYSIOLOGY OF ASTHMA RELEVANT TO THE ISSUE OF POSSIBLE INDUCTION OF REMISSION OF ASTHMA

## IgE, IgE Receptors, and Regulation of IgE synthesis.

(References 12-19)

In 1918 Rackemann introduced the concepts of "extrinsic" asthma (arising from allergy to exogenous antigens), and "intrinsic" asthma (arising from allergy to intrabronchial microorganisms). With the passage of time "intrinsic" asthma came to be seen as unrelated to specific IgE-mediated reactions. Recent data have challenged this concept. Asthma is virtually nonexistent among patients with low total serum IgE levels (16). When corrected for age, sex, and smoking habits, there is a linear relationship of the prevalence of asthma to the total serum IgE. The validity and usefulness of the intrinsic and extrinsic asthma classification appear questionable. The specific targets and roles of IgE in patients with no known aeroallergen sensitivities are not yet clear. This antibody has unquestioned roles in asthma associated with allergy to aeroallergens.

Mapping of IgE receptor binding sites - Marsh 1988

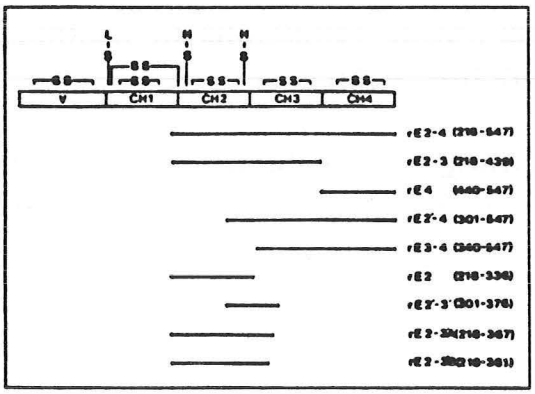



Figure 1. Recombinant IgE fragments used in mapping the high- and low-affinity receptor binding sites on the human epsilon chain.

Table 1

| | rE2-4 | rE2'-4 | rE3-4 | rE4 | rE2 | rE2-3 | rE2'-3' | rE2-3'A | rE2-3'B |
|---|---|---|---|---|---|---|---|---|---|
| $Fc_\epsilon R_I$ | + | + | – | – | – | + | + | + | – |
| $Fc_\epsilon R_{II}$ | + | + | + | – | – | – | – | – | – |

Summary of binding of recombinant IgE peptides to the human high-affinity ($Fc_\epsilon R_I$) and low-affinity ($Fc_\epsilon R_{II}$) receptors. The precise boundaries of the peptides are shown in Fig. 1.

**IgE receptor binding site.** Recently Gould and coworkers (19), using recombinant DNA techniques, traced the mast cell IgE receptor binding site on human IgE to a 76 amino acid residue linear sequence at the $C_e2/C_e3$ junction (Gln 301 - Arg 376). Recombinant peptides containing this sequence can block the binding of intact IgE to the mast cell high affinity $Fc_eR_I$ receptor. In vivo experiments in humans have proven that recombinant 301-376 peptide can inhibit IgE binding to mast cells.

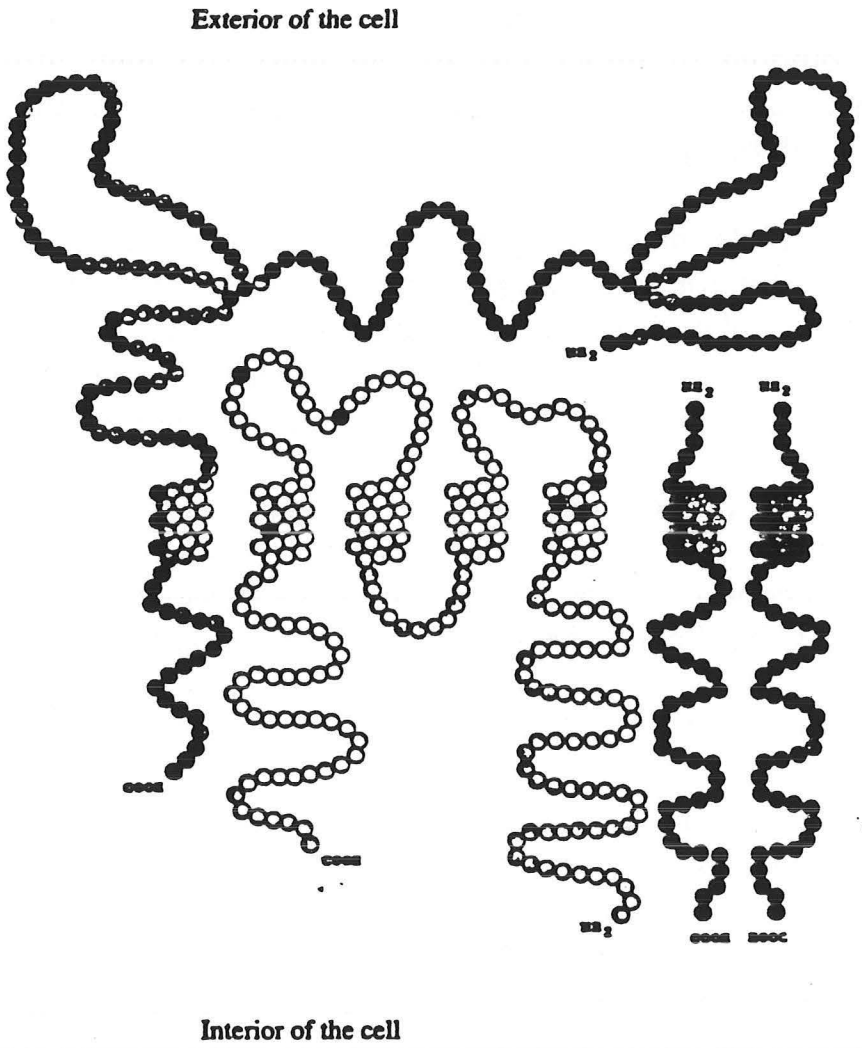
Some eosinophils, macrophages, platelets, and lymphocytes express a lower affinity receptor for IgE, designated $Fc_eR_{II}$ (CD23), that is thought to play a role in chronic allergic reactions. Based upon studies with recombinant peptides, the region of IgE that binds $Fc_eR_{II}$, a linear sequence in the $C_e3/C_e4$ region is different from that involved in binding the high affinity receptor.

**IgE receptor.** Kinet and Metzger (17,18) have cloned and expressed the alpha (human and rat), beta (rat), and gamma (rat) subunits of the high affinity mast cell receptor for IgE ($Fc_eR_I$) and have successfully expressed the entire complex in COS 7 cells. Many interesting insights have emerged from these studies. Species specificity is dictated by the alpha chains, but all three chains must be expressed for effective high affinity binding.

The clinical implications of knowing the structures of the IgE sites that bind to receptors and the structure of the high affinity mast cell receptor for IgE, and having a cell line available that expresses the high affinity receptor for human IgE are considerable. Systematic studies of approaches to blocking IgE binding are now feasible and are in progress. Success in blocking IgE binding in vivo obviously could have major impact on asthma, but clinical application of this approach is not imminent.

**Regulation of IgE synthesis.** Recent studies of murine and human IgE synthesis in vitro have provided strong evidence that IL4 is a critical positive regulatory force (12-15). IL4 has a variety of effects on B lymphocytes, T lymphocytes, macrophages, and mast cells that are beyond the scope of this presentation. Recent unpublished experiments indicate that when a neutralizing dose of monoclonal antibody to IL4 is given to mice, IgE responses to antigen can be completely suppressed. These experiments raise

Diagram of the three subunit structure of the high affinity Ige receptor (Ref 17)




the possibility that pharmacologic approaches to blocking the effects of IL4, and perhaps modulation of other forces involved in the regulation of IgE synthesis, can provide powerful clinical control of IgE expression.

**Histopathology and Bronchoalveolar Lavage Studies in Asthma.**

(References 20-37)

Postmortem studies, open lung biopsies, and very recent transbronchial biopsy studies have produced a consensus on the visible changes present in "allergic" and "nonallergic" patients' pulmonary tissues. No differences have been noted between "allergic" and "nonallergic" asthmatics. Surprisingly, mild chronic asthmatic patients (suitable for transbronchial biopsy) showed changes similar in kind and degree to those found in patients dying of asthma (36).

The subepithelial thickening long known to be characteristic of asthma, and thought to be basement membrane thickening, is now felt to be subepithelial collagen deposition (35).

## HISTOPATHOLOGIC FEATURES OF CHRONIC ASTHMA

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**Increased numbers of mast cells in airway tissues**

**Prominent mast cell degranulation**

**Eosinophils, monocytes, and platelets adherent to the vascular endothelium**

**Emigration of eosinophils and monocytes**

**Mucosal infiltration by eosinophils and eosinophils within the bronchial lumens**

**Desquamation of respiratory epithelial cells**

**Goblet cell hyperplasia**

**Smooth muscle hypertrophy and hyperplasia**

**Subepithelial fibrosis in the bronchi**

**Thickened bronchial wall area**

Bronchoalveolar lavage of mild chronic asthmatics has revealed significantly increased numbers of eosinophils, mast cells, and desquamated epithelial cells. Eosinophil granule major basic protein levels are markedly elevated in asthmatic patients' lavage fluids. Peripheral blood eosinophil counts decrease during late phase responses to antigen challenge at the time eosinophil levels in the pulmonary tissues increases, presumably because of margination and emigration in the lungs.

Evidence of peripheral blood T lymphocyte, macrophage, platelet, and neutrophil activation during acute and experimentally induced asthma has been presented, raising the possibility that they play roles in asthma. These cell types are present in asthmatic pulmonary tissues in small numbers, and could have significant impact, but little direct evidence has been presented to date to support these hypotheses.

The histologic data are consistent with the concept that activation of mast cells, infiltration of the tissues by eosinophils and other inflammatory cells, and tissue damage as well as dysfunction induced by this amalgam of cells and mediators is the source of clinical manifestations of asthma.

**Airway Hyperreactivity and Chronic Pulmonary Inflammation.**

(References 38-46)

Airway hyperreactivity can be induced or worsened by antigen inhalation, exposure to some irritating chemicals, and by respiratory tract infections. The degree of hyperreactivity to histamine or methacholine is directly correlated with the number of mast cells, eosinophils, desquamated epithelial cells, and the MBP levels detected by lavage. Thus, there is reason to believe that to a considerable extent, airway hyperreactivity is an index of the characteristic asthmatic airway inflammation.

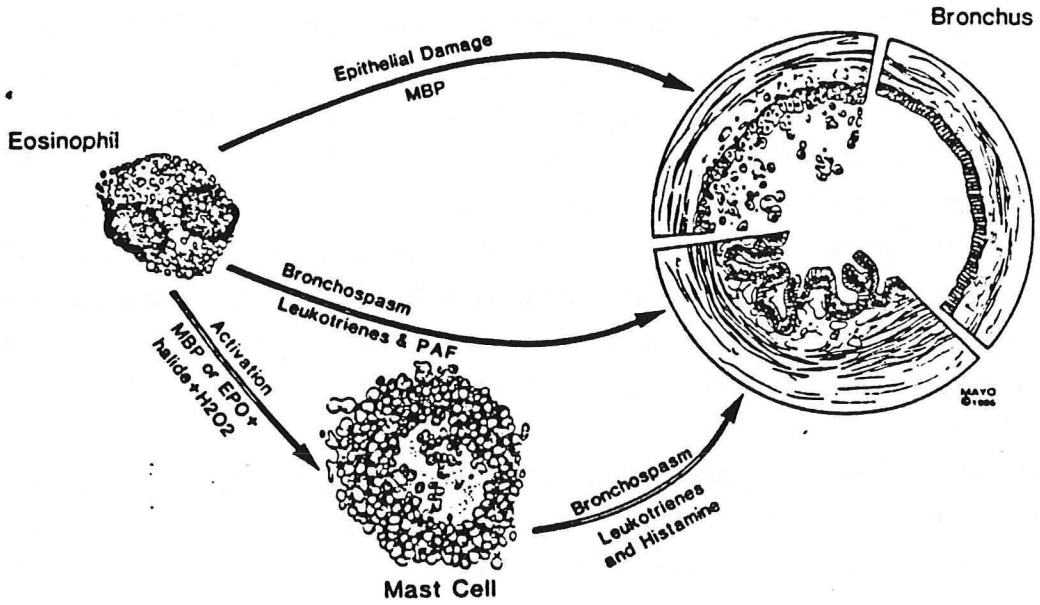
**Eosinophils and Asthma**

(References 47-67)

Eosinophils are specialized immune effector cells capable of killing infective larvae of helminths. These cells also have been implicated in the pathogenesis of asthma, as noted above, and some other inflammatory diseases. PAF, mast cell derived chemotactic factors, IL5, and a variety of other chemotactic factors attract eosinophils into areas of inflammation. IL5, in combination with IL3 and other factors, lead to increased bone marrow production of eosinophils.

A substantial fraction of the eosinophils in the peripheral blood of asthmatics and in the BAL fluids of asthmatics are of lower than normal density, they are **hypodense**. The hypodense state can be induced by chemotactic factors such as PAF, histamine, ECF-A, IL5, and other cytokines. Hypodense eosinophils are activated in several ways: they express increased numbers of complement, IgG, and IgE $Fc_eR_{II}$ receptors; they are markedly more cytotoxic and release inflammatory mediators more readily and in larger quantities.

Roles of eosinophils in asthma (Ref 47)



Eosinophil survival in tissues after recruitment is brief unless IL5 is present. Other cytokines appear to contribute to the eosinophil survival as well. This multifaceted dependence on IL5 (proliferation of precursors, terminal differentiation, activation of diverse functions, support of tissue survival) provides several new lines of attack to eliminate the eosinophil contribution to asthma.

**Mast Cells as Potent Sources of Interleukins.**

Until recently T lymphocytes have been regarded as the principal, often the sole source of the interleukins IL3, IL4, IL5, and IL6. Very recent studies indicate that a second source of these molecules has been identified - the mast cell (12,15,72). Normal rodent mast cells as well as cell culture lines of mast cells secrete these molecules within 1 to 2 hours after antigen-IgE interactions. Activated mast cells also make GM-CSF, but do not express IL2 or INFgamma. The amounts of IL3-6 produced are comparable to those made by activated T lymphocytes on a per cell basis. To date, screens of other cell types using probes for mRNA indicate that the expression of interleukins 3-5 is restricted to mast cells and T lymphocytes.

The implications of this unexpected discovery are just being clarified. Antigen can trigger the mast cell to express molecules that can initiate mast cell proliferation (IL3 and IL4), support mast cell differentiation (IL3 and IL4), and support mast cell survival in tissues (IL3 and IL4). These molecules appear to act as autocoid stimuli for proliferation and differentiation similar to IL2 for T lymphocytes. Mast cells express receptors for IL3 and IL4 - antigen can initiate expression of IL3 and IL4 by mast cells - self activation of these receptors then occurs. The mast cell hyperplasia noted in asthma may at least in part be related to this autocoid loop.

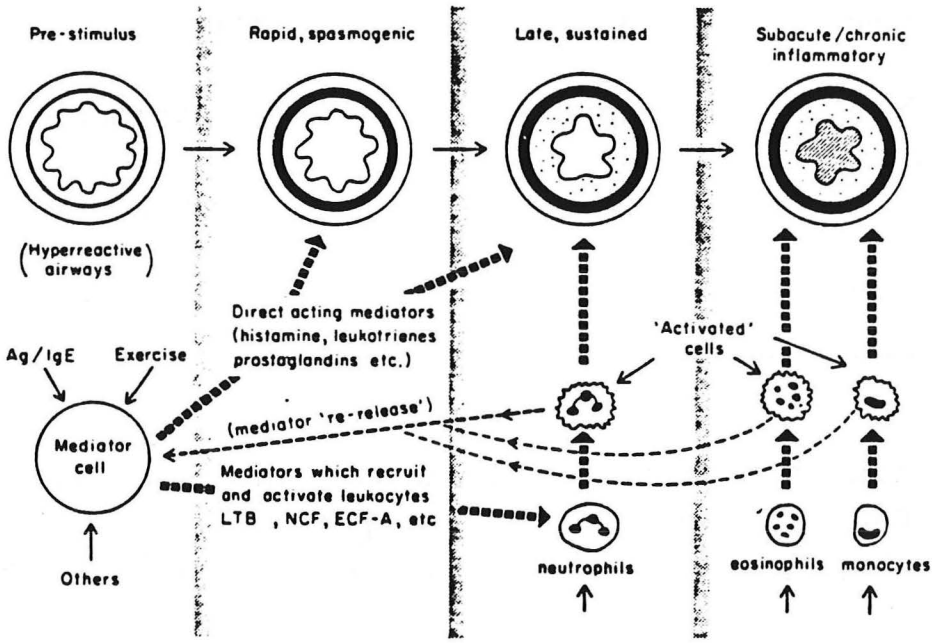
Production of large amounts of IL5 by antigen activated mast cells would be expected to create a local environment that would potently attract and activate eosinophils, and markedly extend the life span of the infiltrating eosinophils.

**Cell-Cell Interactions that may Perpetuate Asthma.**

(References 73-80)

Several forms of cell-cell interactions are now known that are thought to contribute to progressive worsening of asthma, to the chronicity of the disease, and to the perpetuation of asthma when the initiating force (antigen, infection, irritant) no longer is present. Mast cell-eosinophil interactions were the first recognized: mast cells can recruit and activate eosinophils, eosinophil secretion products can trigger mast cell secretion, which in turn .... Interactions among mast cells, eosinophils, T lymphocytes, macrophages, neutrophils, and perhaps platelets may play critical roles in the pathophysiology of asthma.

Cell-cell interactions and asthma (Ref 5)



## CELL-CELL INTERACTIONS IN ASTHMA

| ACTIVATING CELL | STIMULUS | TARGET CELL |
|---|---|---|
| Mast cell | IL5, PAF, Others | Eosinophil |
| T lymphocyte | IL5 | Eosinophil |
| Eosinophil | MBP, Others | Mast cell |
| T lymphocyte | IL3&4, HRF | Mast cell |
| Neutrophil | Peptides | Mast cell |
| Macrophage | Peptides | Mast cell |
| Eosinophil | Peptides | T lymphocyte |
| Mast cell | IL4 | B lymphocyte |
| T lymphocyte | IL4 | B lymphocyte |

Antigen can activate several components of this system through IgE activation of mast cells through $Fc_eR_{II}$ receptors; and the activation of eosinophils, macrophages, platelets, and lymphocytes through $Fc_eR_{II}$ receptors.

**Recapitulation.**

A consideration of what is known of the pathophysiology of asthma leads to the perception that clinical asthma is the result of the establishment of a dynamic, highly interactive and interdependent form of cellular inflammation in the lung.

Is this complicated form of chronic inflammation irreversible?

If the chronic inflammation could be eradicated, would asthma inexorably return?

## EVIDENCE THAT ASTHMA IS A REVERSIBLE PROCESS

**Spontaneous remission of asthma.**

Approximately one-half of children with asthma experience spontaneous remissions during the second and third decades of life (1,81-83). Remission is most frequent in those with late onset, intermittent, mild disease. Of those who experience spontaneous remission, approximately half have recurrences of asthma at some time in later years. Published studies and our own experience (see below) indicate that bronchial hyperreactivity to methacholine or exercise is present in 73% to 82% of patients in stable, long-term spontaneous remission from clinical asthma (81-83). Spontaneous, complete, long term remissions also occur in adults with asthma: estimates of frequency range from 16% to 29% (1). These observations unambiguously demonstrate that at least some forms of asthma are completely reversible, without intervention of any kind or obvious change in environmental factors.

A second form of spontaneous remission occurs in the context of seasonal or situational antigen exposure. Seasonal asthma associated with airborne antigen exposure is well documented (2,3). Complete clinical remission occurs between seasonal antigen exposures. Intercurrent

aeroallergen exposures, for example animal or occupational exposures, can cause asthma that completely remits following cessation of antigen exposure. Complete remission can occur in as many as 47% of patients following relocation to a region that does not have sources of relevant aeroallergens (1). Asthma initiated by respiratory tract viral infections also may remit, indicating that spontaneous remissions are not restricted to IgE mediated mechanisms. Many patients, particularly those with mild asthma, appear to experience a series of active asthma - complete clinical remission cycles.

Clearly, spontaneous remissions of asthma are common occurrences. These observations suggest that while a propensity to express asthma may persist, complete clinical remission can be achieved through the actions of endogenous control mechanisms. The data are consistent with the broader hypothesis that chronic asthma is reversible, if asthmatic inflammation could be eradicated and if endogenous control mechanisms could be activated.

**Remissions of asthma induced by antigen removal or specific antigen immunotherapy.**

Identification of an antigen responsible for causing asthma in a specific patient permits introduction of **avoidance measures** and specific immunotherapy. The best studied example of the impact of antigen avoidance is asthma induced by Dermatophagoides mite antigens. Effective avoidance of mite antigens in patients with perennial asthma, caused solely by mite antigen hypersensitivity, has been associated with clinical remission of asthma, normalization of pulmonary functions, and normalization of airway responses to histamine or methacholine in most patients (84).

Interestingly, the removal of antigen had no immediate effect. Recovery began several weeks after antigen removal and then progressed gradually to normal over a period of several months. The pulmonary inflammation and consequent clinical asthma can have remarkable momentum after the inciting antigen is removed. Indeed, some patients experience perennial asthma despite removal of the antigen that initiated the process.

Effect of withdrawl from exposure to mite antigens on asthma (Ref 84)

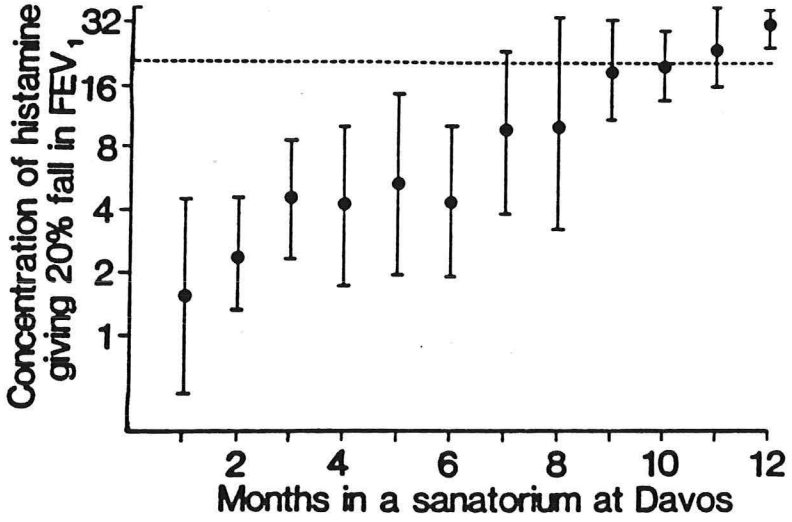



FIG. 6A. Study demonstrating progressive reduction in bronchial sensitivity in mite-allergic patients with asthma who moved from home to a relatively mite-free environment. Results on a group of 10 children studied in a sanatorium in Davos, Switzerland, altitude 2000 m. Values are the geometric mean and 95% confidence limits for the group. (Results calculated from Table 24 of reference 93 by permission of the author.)

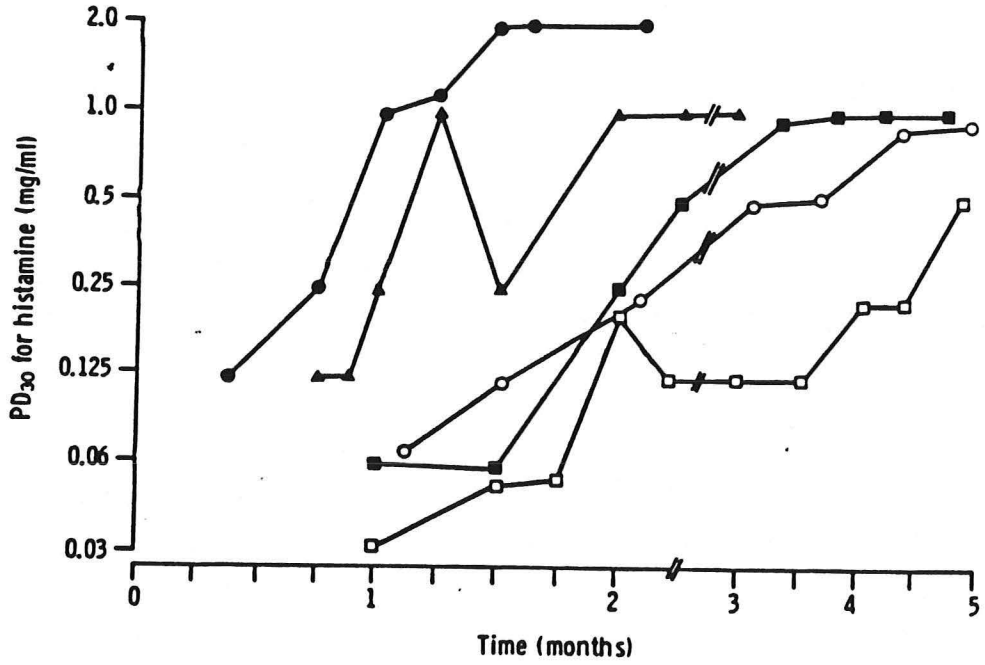



FIG. 6B. Results on five individual adults who used a hospital room in London as their home.[95] The conditions for histamine challenge in the two studies, Figs. 6A and 6B, were different. Normal levels for Fig. 6A were about 20 mg/ml, whereas for Fig. 6B, normal values are ≥2 mg/ml of histamine.[93, 95]

Studies of **occupational asthma**, resulting from immunologic or nonspecific inflammatory reactions, have provided important insights into the transition from specific "cause and effect asthma" to "self-perpetuating asthma" no longer completely dependent upon the original inciting agent. Studies of occupational asthma induced by western red cedar dust, in previously non-asthmatic subjects, indicated that only 40% of workers who stopped exposure to cedar dust recovered completely (88). Despite the absence of a history of prior asthma, 60% of the workers remained asthmatic indefinitely despite cessation of dust exposure. All who continued exposure continued to have asthma. Subsequently, the pattern of perennial asthma continuing despite cessation of occupational exposure has been detected in other occupational settings, particularly the plastics industry (99). At a practical level these observations indicate that early diagnosis and removal from exposure are critical to achieving complete remission of occupational asthma.

The observation that antigen or irritant induced asthma can become to some degree self-sustaining and independent of the original cause is in keeping with recent studies of the pathophysiology of chronic asthma. The characteristic cellular arrays in the lungs of asthmatics and the development of reverberating cell-cell interactions and activations appear to be capable of becoming partially or completely self-perpetuating.

**Specific antigen immunotherapy**, long known to be capable of diminishing the severity of allergic rhinitis, recently has been shown to be capable of inducing complete remissions in some patients with pure mite antigen induced asthma (85-87). While these data provide strong evidence that immunotherapy can induce remission of clinical asthma, and therefore that perennial allergic asthma may be curable, complete remissions only occurred in a subpopulation of this selected population treated with immunotherapy.

These studies indicate that identification and then removal of causal antigens, or specific immunotherapy, can lead to durable remission of asthma. This is in accord with the hypothesis that chronic asthma is reversible. In general, however, complete antigen avoidance often is not feasible and therefore of varying effectiveness. While immunotherapy appears to be

capable of inducing remission of asthma, complete remission is rare.

**Remission of asthma associated with respiratory tract infection.**

Acute, and in some instances persistent asthma can be induced in susceptible patients by respiratory tract infections with RSV, parainfluenza virus types 1 and 3, influenza virus, adenoviruses, rhinoviruses, and mycoplasma. In addition to direct airway inflammation, these infections agents variably alter IgE immunoregulation, induce IgE to microbial antigens, enhance mediator release from inflammatory cells, enhance cholinergic responsiveness, diminish beta-adrenergic responsiveness, and induce a state of heightened propensity to develop chronic airway inflammation and hyperreactivity (89-92). While acute, self-limited respiratory tract infections can initiate perennial asthma, often the asthma remits spontaneously within weeks.

Recent studies of Parainfluenza type 1 bronchiolitis in rats have revealed that infection of newborn rats results in a transient respiratory infection that is followed by a chronic, progressively severe pulmonary inflammatory disease in the absence of persistent virus (93-95). This chronic process is characterized by progressive accumulation of degranulating mast cells, eosinophils, airway dysfunction, and airway hyperreactivity over 3 months. Infection of older animals results in self-limited airway infection and no chronic airway inflammation or dysfunction. This model system, very similar to postinfectious asthma in humans, demonstrates that a transient airway insult can consistently be followed by progressive, chronic mast cell and eosinophil inflammation of the airways in susceptible individuals.

Experimental rhinovirus infection of patients with allergic rhinitis, but no history of asthma or evidence of asthma, resulted in acquisition of expression of late phase pulmonary responses to antigen inhalation and increased airway hyperreactivity. Both the late phase responsiveness and hyperreactivity gradually subsided after resolution of the rhinovirus infection. Clearly the viral infection rendered the patients susceptible to acquisition or exacerbation of asthma, and potentially to the establishment of chronic asthma (90).

**Prevention of asthma associated with respiratory tract infections.**

The impact of corticosteroid bursts on asthma exacerbations triggered by viral respiratory tract infections was investigated in non-steroid dependent asthmatic children who had been hospitalized at least two times a year because of asthma triggered by asthma (96). One group received conventional therapy, the other group also received bursts of prednisone initiated at the onset of a respiratory tract infection. Significant reductions in morbidity were observed in the group receiving bursts of prednisone: **90% reduction in hospitalization rate, 61% reduction in ER visits, 56% reduction in episodes of clinical asthma, and a 65% reduction in days of wheezing.** Because high dose corticosteroid therapy was used in hospitalized patients and the rate of hospitalization was 10 times more frequent in patients not receiving bursts of steroids, comparable total doses of corticosteroids were given to both groups.

These data suggest that asthma initiated by respiratory tract infections often can be prevented by early intervention with corticosteroids. The reported impact on morbidity and need for emergent or inpatient care is extraordinary and must be studied in detail.

**Remission of asthma following treatment of chronic infections of the paranasal sinuses.**

In an uncontrolled study of 48 children with chronic daily asthma requiring bronchodilators who were discovered to have associated sinusitis, marked improvement was noted after treatment of the sinusitis. Prior to therapy for sinusitis all patients experienced daily wheezing and cough, required bronchodilators, and had abnormal pulmonary functions. After treatment only 15% noted any wheezing, 29% noted cough, 21% used any bronchodilators, and 33% had abnormal PFT (98). While considerable work deserves to be done to explore this issue, the data suggest that sinusitis can be an important factor in the perpetuation of chronic asthma. Complete remissions of chronic asthma may be attainable in some patients with chronic sinusitis.

Studies in adults also have described marked improvement in asthma after resolution of sinusitis, but no controlled studies have been reported and no complete remissions have been reported in adults (97). Unpublished data from this medical center do support the concept that complete remissions of chronic asthma, lasting for several months, can occur immediately after eradication of sinusitis.

**Recapitulation**

Significant numbers of chronic asthmatic patients experience spontaneous remissions of asthma. Avoidance of specific antigens, and specific antigen immunotherapy can induce complete remissions of perennial asthma in a subpopulation of patients. Asthma triggered by respiratory tract infections can be suppressed by early therapy with systemic corticosteroids. Complete remissions of chronic asthma can occur when chronic sinusitis is cured.

These observations strongly support the concept that chronic asthma is not an irreversible disease. Remission of chronic asthma is not inexorably followed by recurrence of asthma. While the propensity to have asthma may remain, clinical disease clearly can go into long-lasting, complete remission.

## EXAMPLES OF REVERSIBILITY OF ASTHMA

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**Spontaneous remissions in children and adults**
**Seasonal asthma**
**Occupational asthma**
**Antigen avoidance**
**Specific immunotherapy**
**Asthma and infections**
**Asthma and sinusitis**

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## PHARMACOLOGIC INTERVENTIONS AND REMISSION OF ASTHMA

Can existing anti-inflammatory drug regimens induce complete durable remissions of asthma? If so, what proportion of patients can be put into remission? Which patients are candidates for this approach? Are interventions more effective at the onset of asthma than after chronic, severe disease is established? These crucial questions can not yet be answered completely, but pharmacologically induced remissions appear to have occurred. Most of the patients to be described had mild to moderately severe asthma. Experimental data support the notion that complete remission may be achieved more readily at the onset than after full development of chronic disease.

### Chrysotherapy and asthma.

(References 100-106)

Chrysotherapy has a multitude of known anti-inflammatory effects. The potential for improving the inflammation associated with asthma is clear. Interestingly, gold therapy has been used for asthma in Japan for many years. At Tokyo University Hospital from 1962-1968 chrysotherapy was used in 59 patients: 15 (25%) went into complete remission. A double blind, placebo controlled study reported in 1978 demonstrated significant effects of gold therapy. A followup controlled study reported in 1981 described beneficial effects of gold on airway hyperreactivity in moderately severe asthmatics, compared to immunotherapy or placebo. More striking was the observation that **5 of 14 gold treated patients (36%) became symptom free and required no medication for asthma for 3 years or more** (102). An as yet unpublished followup at an international congress in the fall of 1988, stated that these patients remain in remission. Studies in this country have demonstrated that gold can suppress mediator release from human mast cells and basophils, can reduce airway hyperreactivity, and can have a steroid sparing effect in severe asthma. No other reported studies have addressed the issue of the impact of chrysotherapy on moderately severe asthma. Nevertheless, complete, durable remission of asthma induced by chrysotherapy has been reported in a one

controlled study, and beneficial effects on asthma has been reported by several groups.

**Impact of Cancer Chemotherapy on Asthma.**

(References 107-117)

If cellular inflammation is central to the existence of chronic asthma, therapy that eradicates production of inflammatory cells, that interferes with localization of inflammatory cells, and that interferes with function of activated inflammatory cells should cause remission of asthma. Chemotherapy for a variety of neoplasms achieves just those effects, providing an opportunity to observe the impact of extraordinarily effective anti-inflammatory conditions on concurrent asthma. Chemotherapy with such drugs should eradicate the sustained pulmonary inflammation. Inflammatory cell-cell interactions should be disrupted. Once the inflammation dissipates, asthma should remit. Once the inflammation has resolved, and chemotherapy has ended, an opportunity to observe the propensity to have recurrences of asthma is presented.

In a study organized and performed by our own Dr. Elisa B. Lange, we studied asthmatic children receiving chemotherapy (CT) for cancer to assess the course of asthma after CT-induced suppression of normal inflammatory cell numbers and functions. Eleven of 727 oncology clinic patients (1.5%) had active asthma at the time of the diagnosis of cancer. Prior to CT, chronic asthma was present in 8, moderately severe in 1 and mild in 7, and mild episodic asthma in 3 subjects.

All patients developed markedly reduced levels of eosinophils, neutrophils, monocytes, and lymphocytes during CT. Eight of 11 patients (73%) became asymptomatic during the first month of CT and required no medication for asthma. Six of 8 patients with chronic asthma (75%) had complete remissions of asthma; one experienced partial improvement. Two of the 3 patients with episodic asthma had no recurrences during CT. One of the 8 patients who had remission of asthma has not completed CT.

# INDICATIONS FOR CANCER CHEMOTHERAPY IN ASTHMATIC PATIENTS

| Pt. | Age (yr)/ Sex | Age* at Ca Dx | Diagnosis | Duration of Chemotherapy** |
|---|---|---|---|---|
| 1. | 9 M | 8 y | Acute lymphocytic leukemia | 6 m |
| 2. | 23 M | 7 y | Acute lymphocytic leukemia | 2 y |
| 3. | 20 M | 13 y | Hodgkins disease | 9 m |
| 4. | 17 M | 15 y | Hodgkins disease | 2 y |
| 5. | 14 M | 13 y | Malignant Histiocytosis | 1 y |
| 6. | 10 F | 3 y | Yolk sac carcinoma | 6 y |
| 7. | 8 M | 4 y | Acute lymphocytic leukemia | 2 y |
| 8. | 9 M | 2 y | Acute lymphocytic leukemia | 3 y |
| 9. | 14 F | 12 y | Acute lymphocytic leukemia | 2 y |
| 10. | 9 M | 8 y | Sarcoma | 6 m |
| 11. | 4 M | 9 m | Wilms tumor | 1 y |

* Age in years or months (m).

** Chemotherapy regimens presented in Results

**IMPACT OF CANCER CHEMOTHERAPY ON ASTHMA**

| Pt. | Asthma* Duration | Asthma** Severity | Remission during Chemotherapy | Remission after Chemotherapy | Asthma Recurrence |
|---|---|---|---|---|---|
| 1. | 6 y | Chr/Mod | Complete | 18 m | No |
| 2. | 3 y | Chr/Mild | Complete | 13 y | No |
| 3. | 6 y | Chr/Mild | Complete | 6 y | Yes |
| 4. | 2 y | Chr/Mild | Complete | 18 m | No |
| 5. | 7 y | Chr/Mild | Complete | In progress | No |
| 6. | 2 y | Chr/Mild | Complete | 10 m | Yes |
| 7. | 2 y | Chr/Mild | Partial | - | - |
| 8. | 3 m | Chr/Mild | None | - | - |
| 9. | 9 y | Epi/Mild | Complete | 1 y | No |
| 10. | 6 y | Epi/Mild | Complete | In progress | No |
| 11. | 3 m | Epi/Mild | None | - | - |

* Duration of asthma before diagnosis of neoplasia.
** Chronic, Chr; Episodic, Epi; Moderate, Mod.

# CYTOPENIAS INDUCED BY CANCER CHEMOTHERAPY IN ASTHMATIC PATIENTS

Lowest Absolute Number / $mm^3$

| Pt. | WBC | NEU | EOS | LYM | MON |
|---|---|---|---|---|---|
| 1. | 100 | 2 | 0 | 0 | 2 |
| 2. | 990 | 0 | 0 | 770 | 0 |
| 3. | 1100 | 253 | 0 | 152 | 120 |
| 4. | 2800 | 1204 | 32 | 98 | 37 |
| 5. | 1300 | 52 | 13 | 750 | 32 |
| 6. | 2400 | 408 | 0 | 360 | 105 |
| 7. | 700 | 12 | 0 | 143 | 0 |
| 8. | 1000 | 170 | 0 | 437 | 150 |
| 9. | 400 | 0 | 0 | 48 | 0 |
| 10. | 100 | 0 | 0 | 85 | 3 |
| 11. | 3300 | 429 | 0 | 2052 | 0 |

# METHACHOLINE CHALLENGE

## Baseline Pulmonary Function Tests

| Pt. | FVC (%PRED) | $FEV_1$ (%PRED) | PD20 ($FEV_1$)* |
|---|---|---|---|
| 1. | 101% | 85% | 1.4 |
| 2. | 105% | 112% | 17 |
| 3. | 79% | 67% | 114 |
| 4. | 90% | 90% | 24 |
| 5. | 107% | 82% | 6 |
| 6. | 120% | 111% | 41 |
| 7. | 112% | 112% | NR |
| 8. | 107% | 86% | 23 |
| 9. | 115% | 104% | NR |
| 10. | 91% | 85% | NR |
| 11. | 97% | 88% | 35 |

* cumulative breath units (1 bu = 1 inhalation of 1 mg/cc of methacholine)

Remissions have continued in 5 of the 7 patients who have completed CT (71%) for 2 months to 13 years after CT (median 1.5 years). Two patients who remitted during CT experienced recurrences of asthma after asymptomatic intervals of 10 months and 6 years. Pulmonary functions were normal in 10 of the 11, including all in apparent clinical remission. Methacholine challenges were positive in 8 of the 11, and 5 of the 6 patients in sustained clinical remission.

The results of this study suggest that a brief course of therapy with CT agents possessing potent anti-inflammatory effects can induce complete, durable remissions of asthma in a high proportion of patients, consistent with the theory that airway inflammation is an important factor in the expression and perpetuation of asthma.

Remission of chronic asthma during chemotherapy was not surprising. Nor was the appearance of short, self-limited episodes of asthma despite chemotherapy a surprise. The high frequency of long term complete remissions of chronic asthma, without any form of suppressive therapy, was unexpected. The persistence of airway hyperreactivity despite clinical remission suggests the propensity to asthma remains. While much work remains to be done to clarify this issue, these data are consistent with the concept that once chronic asthmatic inflammation is eradicated, clinical asthma does not readily recur in many patients.

**Weekly Low Dose Methotrexate and Chronic Asthma.**

(References 118-147)

Numerous inflammatory diseases of children and adults are benefitted by weekly low dose methotrexate. The drug is known to suppress granulocyte chemotaxis and to have a variety of effects on lymphocytes, but the important sites of action and mechanisms of anti-inflammatory effects are unknown. In light of the discussion to this point, a potent anti-inflammatory drug with actions on a variety of immune and nonimmune forms of inflammation should be considered for use in chronic asthma. While this regimen is not without

adverse effects, irreversible damage is extremely rare. Compared to chronic systemic corticosteroid therapy, methotrexate is markedly less toxic.

Mullarkey has presented evidence, in a double-blind, placebo controlled, crossover study with 3 month treatment cycles, that low dose methotrexate is indeed effective in reducing or eradicating the need for systemic corticosteroids in severe asthmatics(118). In a followup study (In press:JAMA), Mullarkey reports that of 25 patients on weekly methotrexate for over 18 months, 15 (60%) require no systemic corticosteroid. Of the remaining 10, 9 require lower doses of steroid. One of the 25 failed to respond.

The 15 patients no longer requiring corticosteroids are being weaned from bronchodilators and topical steroids to assess the total degree of reduction in symptoms and medication needs.

To date no studies of the impact of methotrexate on moderately severe asthma have been published, and no complete remission has been described. In light of the data reviewed above, particularly the remissions induced by gold, a study of non-steroid dependent asthma, with assessment of possible remission, would be very desireable.

**Timing of Attempts to Induce Remission of Asthma.**

(References 148-151)

As described above, aggressive use of systemic corticosteroids at the onset of respiratory tract viral infection, in asthma prone children, was associated with a dramatic reduction in clinical asthma exacerbations. Yet high dose systemic corticosteroid therapy does not induce remission of chronic asthma. Systemic steroids have only suppressive effects at that stage of the illness.

A closely analogous animal model of chronic inflammation has been described. Intraperitoneal injection of streptococcal cell walls into Lewis rats

results in an acute and then chronic arthritis. The acute arthritis is associated with streptococcal antigens in the inflamed joints, while the succeeding months of arthritis are less clearly related to the antigen.

Closely related Fisher rats do not express the acute or the chronic arthritis following the same challenge. Recently, the difference in the two strains has been traced to a Lewis rat defect in HPA axis response to acute inflammation. When replacement doses of corticosteroid (to mimic physiologic levels achieved in Fisher rats) were given at the time of streptococcal antigen injection into Lewis rats, neither the acute nor the chronic arthritis appeared. Administration of systemic corticosteroids during the chronic arthritis had only suppressive, not remittive effects.

The concept that the manner in which an acute inflammatory reaction is handled can be decisive in the establishment of a chronic, more refractory inflammatory process has huge implications for studies of the fundamental susceptibility to asthma. Is a critical difference between asthma prone and not prone individuals a variation in adrenal or other suppressive responses to acute inflammation? Is the presence and severity of asthma decided at the outset more than during chronic or repeated antigen exposures, infections, and irritant exposures?

The animal model data indicate that a prompt and vigorous endogenous corticosteroid response can result in suppression of acute inflammation and avoidance of chronic inflammation. To the degree that this is true of acute asthma progressing to chronic asthma, vigorous attempts to suppress acute asthma may be very effective in avoiding chronic asthma. Indeed, the only study addressing this issue did indicate that prompt corticosteroid therapy at the time of insult did suppress progression to asthma.

## WHAT ROLE SHOULD ANTI-INFLAMMATORY THERAPY PLAY IN CURRENT THERAPY OF ASTHMA?

(References 152-163)

How, if at all, should these new insights into the pathophysiology and experimental anti-inflammatory drug therapy influence current therapy of asthma? Potentially, early aggressive therapy with corticosteroids or other agents could prevent progression to chronic asthma, but the efficacy and relative safety of these approaches are obscure. Systemic corticosteroids are not remittive in chronic asthma. Potentially, chrysotherapy should be considered for remittive therapy, but a relatively high incidence of adverse effects is certain while the likelihood of success is not yet completely clear.

Two relatively benign, well known anti-inflammatory therapies deserve consideration in this context: topical corticosteroids and topical cromolyn sodium. Chronic use of topical corticosteroids is useful for the suppression of the symptoms of asthma. In high doses (e.g. 250 ug b.i.d.) topical steroids can cause progressive reduction in airway hyperreactivity to methacholine or histamine. When systemic steroid therapy is compared to topical steroid therapy, topical therapy can reduce airway hyperreactivity while systemic therapy can not. This is true when comparing doses of each required to achieve a comparable effect on symptoms or when comparing bioequivalent doses. Thus months of topical steroid therapy can normalize airway reactivity in many mild and moderately severe asthmatics. Unfortunately, hyperreactivity appears to return promptly when topical therapy is halted.

Topical cromolyn sodium also can gradually reduce airway hyperreactivity, and prevent seasonal antigen exposure-induced increases in hyperreactivity. In both children and adults with moderately severe asthma, institution of chronic cromolyn therapy can significantly reduce the symptoms of asthma and spirometric abnormalities, while permitting a significant reduction or discontinuation of chronic bronchodilator therapy.

Should therapy of chronic asthma begin with a topical anti-inflammatory drug, using bronchodilators as supplemental symptomatic medication as

needed? Would the anti-inflammatory therapy reduce vulnerability to acute exacerbations from irritants, exercise, antigens and infections? Would this strategy reduce hospitalizations, emergency visits, nocturnal awakening, days lost from school or work, limitations on exercise, and the chronic symptoms of asthma? If so which patients should be selected and persuaded to comply? The answers to these questions are not unambiguously agreed upon, but existing data favor this approach for many patients.

## SUMMARY

The patient described at the beginning of this protocol developed acute lymphocytic leukemia at 8 years of age. He received chemotherapy for 6 months with apparent cure of his leukemia. Within the first month of chemotherapy his asthma remitted - no symptoms and no medications for asthma. He has remained free of asthma for 18 months (patient #1 in Dr. Lange's study).

The information reviewed in this presentation supports the concept that asthma is potentially curable. Reports of complete, durable remission of asthma can no longer be regarded as fortuitous occurrences, unrepresentative of asthma in general. Systematic studies of anti-inflammatory drug therapy designed to explore possible induction of remission of asthma clearly are warranted. Studies of aggressive anti-inflammatory drug therapy of asthma at the onset, to avoid establishment of chronic asthma, also are very desireable.

Pathophysiologic mechanisms apparently essential to the establishment and perpetuation of chronic asthma have been identified. These processes may be vulnerable to eradication by existing pharmacologic agents such as cyclosporin A (to suppress cytokine production), gold, methotrexate, and other anti-inflammatory drugs, alone or in combination. Equally important, the vigorous anti-inflammatory therapy may be necessary only long enough to

achieve a resolution of the chronic pulmonary inflammation. The use of these agents should be studied carefully.

Serious thought must be given to revising the current goals of therapy of asthma to include reduction of airway hyperreactivity, with topical anti-inflammatory drugs, in addition to relief of current symptoms. "Treat asthma with anti-inflammatory drugs. Treat the symptoms of asthma with bronchodilating drugs."

In the past, remissions of asthma in children with neoplasia and the other patients presented herein were complete, durable, and welcome, but they were largely unexpected and unpredictable. For the future, there is increasing reason to believe that predictable pharmacologically induced remission of asthma will feasible.

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**Topical anti-inflammatory therapy**

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