Future Directions in Asthma Therapy*

Is a Cure Possible?

Alan R. Leff, MD, FCCP

Asthma correctly is characterized as a syndrome rather than a disease, because a single causative mechanism has not yet been defined. This lack of definition makes the search for a cure extremely complex. Until a common pathogenetic link is identified, the possibility of a cure is remote. The precise nature of the inflammatory response in asthma has not been defined, and current concepts of the pathogenesis of asthma represent, to some extent, a reductionistic approach to a process that has been seen variously as an allergic reaction, autonomic hyperresponsiveness, or both. Additional evidence of the polygenomic nature of the disease and the inability to define a specific pathogenetic process linked to a final common pathway suggest that gene therapies probably will not be feasible, at least for the near future. As expected, most approaches now being developed are directed toward improved therapies, and optimal treatment may obviate the need to develop complex therapies effecting a cure. Under any circumstance, the notion of a cure will have to await a more comprehensive understanding of the syndrome known as human asthma. This article is intended to provide provocative insights into the reasons why a cure remains elusive.

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Key words: asthma; asthma cure; asthma gene; asthma mortality; bronchoconstriction; eosinophil; leukotriene; leukotriene receptor antagonist

Asthma is a complex condition for which new therapeutic approaches have been recently developed. Although these approaches offer encouragement that better treatments for asthma may be available soon to the general population, the vexing issue of a cure for asthma remains unsolved. For the purpose of this discussion, cure is defined as the permanent restoration of normal or very nearly normal pulmonary function as a result of a single treatment or series of treatments. This article considers the likelihood that a curative treatment will be developed in the foreseeable future in light of four major obstacles (Table 1).

Asthma Is Not a Disease

Correctly defined, a disease has a specific cause, pathologic process, and prognosis. A syndrome, however, is defined as a series of symptoms that have a final common pathway. According to these definitions, asthma is categorized more accurately as a syndrome. Its cause(s) has (have) not been elucidated. Bronchoconstriction can be caused by a number of factors, and a unified theory of the pathogenesis of asthmatic bronchoconstriction still has not been advanced.

Hypotheses About the Pathogenesis of Asthma

Three very different approaches to the pathogenesis of asthma have been suggested during the past three decades (Fig 1).1,2 The first hypothesis is that asthma is a fundamentally allergic process, in which the bivalent linkage of antigen E causes degranulation of mast cells that are located in direct proximity to the airway smooth muscle.1,2 The resultant release of bronchoactive substances triggers the bronchospasm and mucosal edema that are characteristic of bronchial asthma. According to this hypothesis, histamine and slow-reacting substance of anaphylaxis (leukotrienes C4 and D4) are the important pathogenetic factors. However, a substantial number of patients who have allergy do not have asthma, and many patients who have asthma do not have allergy.2

The second hypothesis is the "neurogenic hypothesis" of the pathogenesis of asthma. This was derived originally from Osler's conceptualization of asthma as a nervous disease. Subsequent related hypotheses included β-adrenoceptor deficiency, parasympathetic hyperresponsiveness, or both (Fig 1). In physiologic models, β-adrenoceptor stimulation has been
shown to inhibit degranulation of mast cells and thus to block the effects of the acute antigen challenge; however, this acute phase of the asthmatic response is seen now as relatively unimportant. The role of parasympathetic stimulation in augmenting secretion from mast cells was explored approximately 20 years ago and has not been defined further. The fact that the asthmatic response is not blocked readily by parasympatholytic drugs suggests a minor role for parasympathomimetic involvement.

The third hypothesis of the pathogenesis of asthma is the “myogenic hypothesis.” This is the current conceptualization in the era of cell biology. According to this view, the conversion of normally reactive airway smooth muscle to a hyperreactive state is the result of the migration of nonresident cells into the airway, where they interact directly with airway smooth muscle, epithelium, or both, to cause up-regulation of airway responsiveness and possible hypersensitization to the subsequent release of mediator. Although this hypothesis offers some explanation for how a broad variety of stimuli may cause airway hyperresponsiveness consistent with that of human asthma, many of its aspects remain poorly defined. Considerable controversy exists, for example, in defining the specific cells that are involved in the process.

Because the migration of eosinophils from the parenchyma of the airway to the lumen is a transient and unique event in airway hyperresponsiveness (Fig 2), this process may play a role in the genesis of asthmatic hyperresponsiveness. Eosinophilic infiltration of airways has been recognized for decades. Identification of these cells as important contributors to asthmatic inflammation, however, does not constitute direct physiologic evidence of a causal role in bronchoconstriction.

Numerous investigations have indicated that eosinophils are capable of causing direct bronchoconstriction of the human airway in isolated cell systems ex vivo (Fig 3). After exposure to fibronectin, eosinophils are primed during the process of transmigration. Exogenous stimulation of eosinophils has been shown to cause substantial contraction of explanted human bronchi. Nevertheless, the pathophysiologic trigger for the asthmatic bronchoconstrictor response has yet to be defined; thus, whether this exogenous stimulation of eosinophils does, in fact, represent an important event in the actual pathogenesis of asthmatic inflammation remains unknown.

**Table 1—Obstacles to a Cure for Asthma**

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<tr>
<td>1. Asthma is not a disease</td>
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<td>2. There is no single asthma gene</td>
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<tr>
<td>3. The causes of asthma likely are varied</td>
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<td>4. Different asthmatics may require different therapies</td>
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**Figure 1.** Three hypotheses of the pathogenesis of asthma: allergenic, neurogenic, and myogenic. IgE=immunoglobulin E; Ab=antibody; SRS-A=slow-reacting substance of anaphylaxis; SM=smooth muscle; ASM=airway smooth muscle (reprinted with permission).
Figure 2. Effect of eosinophil infiltration into human airways. At later stages, a cytotoxic effect likely accounts for the epithelial denudation found in human asthma. *Top left* (A): histologic section from an airway of a human who had asthma (hematoxylin-eosin; original magnification ×160). *Top right* (B): the same section if stained by fluorescent monoclonal antibody for the eosinophil major basic protein (MBP). Virtually the entire cellular infiltrate is eosinophils (immunofluorescent antibody stain; original magnification ×160). *Bottom left* (C): higher-power view of the desquamated epithelium in A. A basal layer of epithelial cells remains in one area (arrow). Two eosinophils are marked (arrowheads; original magnification ×400). *Bottom right* (D): localization of MBP in cells (arrowheads); these cells correspond directly to the cells marked in C. MBP is also localized outside cells in association with epithelial desquamation (arrow; original transformation ×400). C and D illustrate the identical area; this section was first stained for MBP by immunofluorescence and subsequently stained with hematoxylin-eosin (reprinted with permission from Gleich et al").

**There Is No Single Gene for Asthma (The Problematic Genetic Approach)**

The most promising and obvious approach to a cure for asthma would be the identification of a correctable genetic defect. Even if this were possible, however, the expense and potential therapeutic toxicity of genetic manipulation in a condition like asthma would have to be justified. Asthma is both prevalent and (except in very rare cases) nonfatal. Furthermore, although it is known to be inherited, its mode of inheritance remains poorly defined.1,10

At first blush, asthma might appear to be a relatively simple inherited mode of airway hyperresponsiveness. When students at the University of Chicago, who were asked to identify themselves as either having asthma or not having asthma, were given methacholine challenges, their dose-response curves were consistently different (Fig 4).11 When airway responsiveness in the general population is examined, no similar bimodal distribution (Fig 5) is revealed.1 Instead, that distribution is more bell shaped, with a slight skew to the right. Thus, even the definition of airway responsiveness requires the establishment of an arbitrary threshold (ie, a specific dose of methacholine that causes a specific degree of bronchoconstriction); because this threshold is derived from a continuum of airway hyperresponsiveness, no adequate physiologic definition remains for the underlying defect—airway hyperreactivity—that characterizes human asthma.

Other aspects of human asthma remain enigmatic as well. The apparent differences in prevalence and...
mortality throughout the world are largely unexplained. This suggests not only the difficulty of characterizing asthma genetically but also the difficulty of defining its various causes on the basis of population by geographic location. It is unclear, for example, why deaths from asthma occur so much more frequently in New Zealand than in the rest of the world (Fig 6). Similarly, there is no apparent explanation of why deaths from asthma in Germany, where health care is readily available to all, are double those in the United States, where health care is unavailable to a substantial percentage of the population.

**THE CAUSES OF ASTHMA ARE LIKELY VARIED**

Pathophysiologically, asthma may be regarded as a disease of the Th2 lymphocyte. The somewhat oversimplified approach illustrated in Figure 7 suggests that processes leading to the conversion or activation of Th2 cells result in the production of cytokines and other mediators, some of which are selective for the activation of human eosinophils. The specific interactions remain to be identified, and this hypothetical concept remains unproved.

However, even if this hypothesis should prove to be correct, it has some fundamental obstacles to the achievement of a cure. First, the human T cell does not differentiate as clearly into Th1 and Th2 cell types as in other species. Second, the T-cell abnormality, the specific trigger for airway hyperresponsiveness, or T-cell factors that specifically activate the human eosinophil have never been identified. This approach also raises concerns about interventions directed at the T cell, unless they specifically could be focused on and restricted to those levels of Th2-cell function that relate to eosinophil hematopoiesis and activation. Because alterations made in T-cell function could be permanent and irreversible, this approach to a cure would require careful consideration.

Furthermore, isolated interventions may not be universally applicable. The factors that lead to bronchoconstriction are so varied that they suggest multiple causes (Table 2). Even within these general categories are apparently unrelated causes. It is unclear, for example, why only a minority of the population of individuals who have asthma are extremely reactive to prostaglandin-synthetase inhibitors. Similarly, the degree of reactivity that is required to achieve β-adrenoceptor blockade is highly variable in patients who have asthma, and the specific defect that causes this response remains undefined.

Exercise-induced bronchoconstriction, as well as that caused by prostaglandin-synthetase inhibitors, can be blocked at least in part by leukotriene-receptor antagonists. Yet it appears that the causes of these processes are substantially different. Leukotrienes may play a different role in exercise-induced bronchospasm than they do in bronchospasm caused by aspirin or other nonsteroidal anti-inflammatory drugs. Although both disorders may respond well to

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**FIGURE 3.** Effect of A63162, a 5-I-O inhibitor, and indomethacin (INDO), a cycloxygenase inhibitor, on airway narrowing and wall thickness. Top: increasing concentrations of A63162 inhibited a decrease in luminal diameter in a concentration-dependent manner. Indomethacin caused a lesser, but statistically significantly different, effect in blocking luminal narrowing generated by activated eosinophils. Bottom: platelet-activating factor (PAF)-activated cells caused substantial change in wall thickness vs nonactivated cells (cells only). This effect is attenuated by A63162 but not by indomethacin. M=molarity. Asterisk indicates p<0.05—p<0.001 vs cells+PAF; two asterisks, p<0.001 vs untreated eosinophils (cells only) (reprinted with permission from Rabe et al).
the same drug, treatments that would be curative may have to be substantially different.

**DIFFERENT ASTHMAS MAY REQUIRE DIFFERENT THERAPIES**

Because asthma is actually a syndrome of bronchoconstrictive disorders caused by a variety of stimuli, and because its genetic components are highly complex, a number of different treatments probably will be required to resolve the condition in variously affected patients. No currently available therapy is adequate to the achievement of a cure.

**Therapeutic Directions**

Future avenues of approach to the treatment of human asthma are listed in Table 3. Some encour-
aging data suggest that T lymphocytes play an important role in regulating the asthmatic bronchoconstrictor response, but treatment with cyclosporine is currently expensive and problematic. Because the factor that triggers T-cell hyperresponsiveness remains unidentified—and in light of the danger of
Table 2—Some Factors That Cause Bronchoconstriction

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<td>1. Mediator release</td>
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<td>Allergic</td>
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<tr>
<td>Nonallergic</td>
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<tr>
<td>2. Autonomic imbalance?</td>
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<tr>
<td>Viral infections</td>
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<tr>
<td>Environmental</td>
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<tr>
<td>Idiopathic</td>
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<tr>
<td>3. Inflammation</td>
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<tr>
<td>Viral infections</td>
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<tr>
<td>Environmental</td>
</tr>
<tr>
<td>Idiopathic</td>
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<tr>
<td>4. Latrogenic</td>
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<tr>
<td>β-Adrenoceptor blockade</td>
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<tr>
<td>Prostaglandin-synthetase inhibitors</td>
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<tr>
<td>5. Psychological</td>
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<td>6. Exercise</td>
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Table 3—Therapeutic Directions

| T lymphocytes | Eosinophils | Pathway antagonists | Adhesion molecules | Gene therapy |

Global suppression of T-cell function—specific therapies cannot be directed against T cells at this time. Hence, this is not an avenue for cure.

Therapies directed against eosinophils have not been attempted in humans. Animal models suggest that interleukin 5 is an essential factor in the development of hyperresponsiveness that correlates with eosinophilic migration. Because eosinophils derive from initially uncommitted myeloid stem cells, it is theoretically possible that therapeutic interventions could be directed at inhibiting eosinophilopoiesis. However, development of such therapy would require a convincing demonstration that the elimination of eosinophilic function would not constitute a risk of infection to the host (i.e., an inability to deal with parasitic infections) and that it would be effective in the treatment of human asthma. A selective means for long-term suppression of eosinophilopoiesis has not been developed. Hence, there is no possibility of cure by this mechanism at present.

Currently, the main focus of therapeutic interventions is on identifying antagonists of specific pathways (e.g., 5-lipoxygenase [5-LO] and its products). This novel approach has resulted in the first new classes of drugs to be developed in more than 20 years (i.e., 5-LO-inhibiting drugs and leukotriene receptor antagonists). Pathway antagonists are only therapeutic, however; currently, there is no suggestion that these agents could lead to an enduring remission of asthma after discontinuation of treatment.

Another area of research that is directed toward the treatment of asthma is the development of products that inhibit molecular adhesion. Presumably, products that focus on the appropriate inflammatory cell could prevent its entry into the airway, thus aborting asthmatic hyperresponsiveness even in the presence of active chemotactic stimuli. This approach is potentially a double-edged sword. Because eosinophils and neutrophils share some of the same adhesion molecules, an intervention that prevents substantial migration of neutrophils could mimic syndromes associated with infection and death from neutropenia. Therefore, even though the eosinophilic granulocyte may not be necessary to human daily life, the neutrophils and lymphocytes that share its adhesion molecules are essential. Finally, antiadhesion therapies also would be a treatment rather than a cure, since their antiasthmatic effects would not be expected to remain after discontinuation of treatment.

The future for gene therapy for asthma is complex and somewhat discouraging, given the lack of significant success in identifying candidate genes that have a high correlation with the process, although this approach is being investigated aggressively by both the pharmaceutical industry and the National Institutes of Health. Because multiple genes are involved, the results so far have found only weak correlations or associations, and the likelihood that gene therapy per se can be used to treat human asthma remains a low theoretical probability. For these reasons, such therapy, which is both expensive and potentially hazardous, is an unlikely approach to treatment or cure of a moderate, relatively benign disease that affects millions of individuals.

Conclusions

The information discussed herein presents a somewhat pessimistic view of how far we are from a cure for human asthma. The disease itself is poorly defined and continues to defy description. If asthma is correctly characterized as a syndrome rather than a disease, then the search for a cure becomes even more complex. The causes of the component disorders of the asthma syndrome may result in the need for multiple therapies, thus obviating the possibility of cure through identification of a single, final common pathway.

Asthma also is unlikely to be amenable to gene therapy, even after advances are made with less complex disorders. The polygenomic nature of the
syndrome and our inability to define a specific pathogenetic process linked to a final common pathway suggest that gene therapies probably will not be feasible in the near future.

Perhaps the most vexing barrier to finding a cure for asthma is the inability to identify a unifying triggering event at the pathophysiologic level. It may be worth considering that the nature of the inflammatory response in asthma has not been defined adequately. Inflammatory cells are ubiquitous in human asthma, whereas the specific secretagogues that direct their migration and individual roles in asthmatic hyperresponsiveness remain unidentified.

Novel approaches that theoretically could effect a cure, although exciting, are associated with a number of potential risks. The double-edged sword of therapy that suppresses stem-cell function or inflammatory-cell migration must be weighed carefully when being considered for the treatment of what is usually a benign disease. Finally, most approaches are now being directed appropriately toward improved therapies, and the notion of a cure will have to await a more comprehensive understanding of the syndrome known as human asthma.

References