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**Managing Asthma: Past, Present, and Future**

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Asthma has been recognized in the medical literature for almost 2000 years. Modern pharmacotherapy for asthma began with the commencement of the 20<sup>th</sup> century following the development of epinephrine and the demonstration of its effectiveness for acute symptoms of asthma. Progressive development of this class of bronchodilator medication has provided greater  $\beta_2$  specificity and longer duration of action. Corticosteroids were introduced about 50 years ago. As a systemic medication, they provided anti-inflammatory activity that continues to be essential for exacerbations of symptoms that are unresponsive to a bronchodilator. Corticosteroids were subsequently developed as inhaled agents for long-term maintenance therapy. The availability of corticosteroids with high topical effect has permitted the use of smaller doses with minimal systemic effect; therefore, the inhaled corticosteroids have become the most effective monotherapeutic agents for chronic asthma.

Both theophylline and long-acting  $\beta_2$  agonists (e.g., salmeterol) provide additive clinical effect to small doses of inhaled corticosteroids. This effect is greater than that achieved with larger doses of the inhaled steroid used alone. A new approach to managing allergic asthma is now available in the form of a monoclonal antibody directed against immunoglobulin E (IgE). This agent, omalizumab, binds to circulating IgE, thereby preventing IgE from binding to mast cells. This subsequently prevents the release of mediators for bronchospasm and inflammation. Under investigation are monoclonal antibodies to modify the effects of interleukins involved in the inflammatory process of asthma. Phosphodiesterase inhibitors that are more specific than theophylline and monoclonal antibodies that prevent the attachment of rhinovirus to respiratory mucosa are being studied. Since rhinoviruses are major causes of acute exacerbations of asthma, these and other measures to prevent or modify the common cold provide great potential for further improvement in the outcome of asthma.

**KEYWORDS:** asthma

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**ASTHMA: THE DISEASE**

*"If from running, gymnastic exercises, or any other work the breathing becomes difficult, it is called Asthma. The symptoms are heaviness of the chest, sluggishness to one's accustomed work; they are hoarse and troubled with cough; and if these symptoms increase they sometimes produce suffocation."* [Aretaeus (c.A.D.120-180): On the causes and symptoms of chronic diseases]

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*"This disorder starts with a common cold, and the patient is forced to gasp for breath day and night, until the phlegm is expelled, the flow completed and the lung well cleared."* [Moses Maimonides (A.D. 1135-1204): Treatise on Asthma]

These quotations from the ancient medical literature demonstrate the duration of our awareness for the clinical entity known as asthma. The above descriptions are consistent with a pragmatic definition of asthma arrived at by a committee of the American Thoracic Society in 1962: *"Asthma is a disease characterized by an increased responsiveness of the trachea and bronchi to various stimuli and manifested by a widespread narrowing of the airways that changes in severity either spontaneously or as a result of therapy."*<sup>1</sup> Berkart first de-

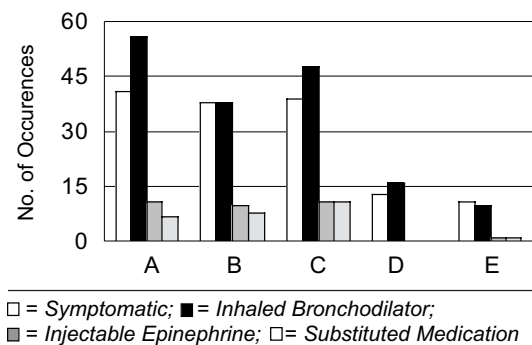
scribed the importance of what we now recognize as the inflammatory component of asthma with the description “*The desquamation of the epithelium is followed by a copious emigration of leukocytes. In contact with the fibrinoplastic substances, which exude at the same time, the white corpuscles disintegrate.*” (Asthma: its pathology and treatment. London: Churchill, 1889).

### EVOLUTION OF EFFECTIVE PHARMACOTHERAPY

Modern treatment of asthma can be dated to the observations of Solis-Cohen who described an “adrenal substance” that provided benefit for asthma.<sup>2</sup> Benefit from injected epinephrine was noted in 1903.<sup>3</sup> Ephedrine, an oral agent with epinephrine-like properties, was identified in 1925 as an active ingredient in the Chinese herb, Ma Huang.<sup>4</sup> Further development of this class of drugs led to agents with more specific  $\beta_2$  adrenergic effect and longer duration of action (Table). Although anecdotal descriptions of the benefit from coffee date back to at least the middle of the 19<sup>th</sup> century, the medical use of the most effective of the xanthines, theophylline, was not documented until 1937.<sup>5</sup> A subsequent publication three years later described the use of oral theophylline in combination with ephedrine.<sup>6</sup> That was followed by the marketing of multiple pharmaceutical preparations containing fixed dose combinations of ephedrine and theophylline; these formulations remained the most common medications used to treat asthma for the next 35 years.

The use of these combination products declined precipitously following controlled clinical trials demonstrating that ephedrine increased adverse effects without adding clinically impor-

**Figure 1.** Number of symptomatic 8 hour patient observation periods. Twelve children with acute symptoms of asthma received five drug regimens in a randomized double-blind study. Each child received a week-long trial of: placebo (Intervention A); ephedrine and aminophylline in “small” dose combinations that were customary for the time (Intervention B); “large” dose ephedrine (Intervention C); “large” dose theophylline (Intervention D); and “large” dose ephedrine and theophylline (Intervention E). With or without ephedrine, “large” doses of theophylline that maintained serum theophylline concentrations between 10 and 20  $\mu\text{g}/\text{mL}$  was highly effective. Conventional doses for the time were not more effective than placebo in these patients. Adverse effects differed from placebo only when ephedrine was added to the theophylline.<sup>7</sup>



tant benefit.<sup>7,8</sup> Theophylline alone in larger doses than had been used previously was highly effective in controlling symptoms of chronic asthma (Figure 1). These findings led to the use of theophylline as a maintenance preventative medication that was more effective than alternatives proposed for that purpose.<sup>9-11</sup>

However, the effective and safe use of theophylline required characterization of both its pharmacodynamics and its pharmacokinetics. The initial studies demonstrated that serum theophylline concentrations of 10–20  $\mu\text{g}/\text{mL}$  provided optimal therapeutic benefit.<sup>7,8</sup> These findings were consistent with reports by others.<sup>12</sup> The variable rate of elimination required individualization of dosage to attain those optimal concentrations.<sup>13-16</sup> The rapid rate of absorption and elimination from plain tablets resulted in fluctuations in serum concentration. This variability in theophylline concentrations had the potential to cause unacceptable degrees of therapeutic effect. This led to the development of slow-release theophylline formulations that produced more stable serum concentrations and clinical effect with the advantage of twice daily dosing.<sup>17,18</sup> Serum theophylline concentrations that exceeded 20  $\mu\text{g}/\text{mL}$  were associated with progressively increasing risk of toxicity;<sup>19</sup> however,

**Table 1.** Development of Sympathomimetic Bronchodilator Medications Arranged Generally from the Oldest to the Most Recently Marketed

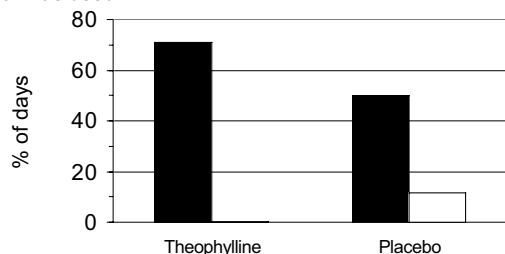
Parenteral and inhaled	Oral
Epinephrine (adrenalin)	Ephedrine
Isoproterenol (isoprenaline)	Metaproterenol (orciprenaline)
Isoetharine	Terbutaline
Metaproterenol (orciprenaline)	Albuterol (salbutamol)
Bitolterol	
Terbutaline	
Pirbuterol	
Albuterol (salbutamol)	
Formoterol	
Salmeterol	

doses that maintained the concentrations within the 10–20 µg/mL reference range were generally devoid of even concerns about behavior and learning effects.<sup>20,21</sup>

Adrenal corticosteroid hormones were demonstrated to be of value for asthma in the 1950s.<sup>22</sup> Although controversies concerning their use have persisted, the value of these agents, given orally or parenterally for acute exacerbations of asthma, is now well established.<sup>23,24</sup> However, doses that were safe and effective for the short-term treatment of exacerbations were not safe for prolonged use. This led to the development of corticosteroids dosage strategies that were safe as maintenance therapy for the management of persistent symptoms. Alternate-morning use of prednisolone, prednisone (the inactive pro-drug of prednisolone), and methylprednisolone were used to control chronic asthma with acceptable safety.<sup>25</sup> Inhaled corticosteroids were introduced in the late 1970s. Inhalation therapy allowed the administration of medication with potent topical effect in sufficiently small enough doses to minimize systemic effects. A small degree of depressed hypothalamic-pituitary-adrenal axis function could be demonstrated for both the inhaled and alternate-morning oral regimen.<sup>25,26</sup> No difference in growth was apparent between these regimens. The inhaled corticosteroid appeared to be effective for those individuals who were not optimally controlled with the alternate-morning oral regimen.

Low doses of inhaled corticosteroids were somewhat more effective than theophylline for controlling chronic asthma.<sup>27,28</sup> Moreover, they were easier to use because they didn't require serum concentration monitoring and had no po-

**Figure 2.** Percent of symptom free days and excessive inhaled bronchodilator usage among 21 children receiving theophylline or placebo as additive medication with inhaled corticosteroids. Theophylline added to an inhaled steroid was associated with significantly more symptom-free days and virtually eliminated days when excessive inhaled bronchodilator was used.<sup>29</sup>

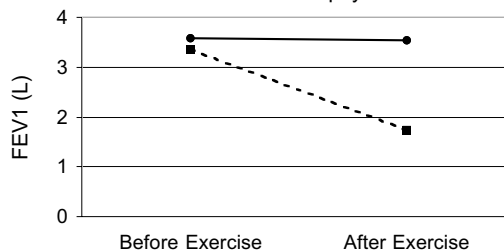


■=Symptom-free; □=Excessive Inhaled Bronchodilator

tential for acute overdose. Nonetheless, theophylline continued to be useful as an additive agent to both alternate-morning prednisolone and inhaled corticosteroids (Figure 2).<sup>29,30</sup> Demonstration that theophylline had anti-inflammatory effects added to the continuing interest in using this medication.<sup>31</sup> Likewise, the long-acting β<sub>2</sub>-agonist (e.g., salmeterol) has a similar additive effect to that noted with inhaled corticosteroids.<sup>32,33</sup> Salmeterol is not only easy to use, but it is marketed as a combination inhaler with an inhaled corticosteroid. Unfortunately, these long-acting agents may down-regulation of the β<sub>2</sub>-receptor in a subset of patients. A consequence of down-regulation is the loss of bronchoprotective effect of shorter-acting β<sub>2</sub>-agonists when used as rescue medications or to prevent exercise-induced bronchospasm (Figure 3).<sup>34</sup>

Other moieties with unique mechanisms of action have been introduced. Cromolyn sodium (disodium cromoglycate) and nedocromil pharmacologically act to inhibit the release of mediators from mast cells and basophils. However, their very modest degree of effect and 4-times-daily administration have made them of little clinical interest when compared to alternative therapies. More recently, leukotriene modifiers have been introduced. These medications selectively bind to the cysteinyl leukotriene receptor

**Figure 3.** FEV<sub>1</sub> before and after 6 minutes of treadmill exercise at a speed and incline sufficient to maintain the heart rate at 85% of aerobic capacity in a 15-year-old male with severe chronic asthma and exercise intolerance.<sup>34</sup> The results are the mean of two tests performed on different days while the patient was being treated with salmeterol and high dose inhaled corticosteroids and two tests subsequent to stopping the salmeterol and adding theophylline to the same dose of inhaled corticosteroids. Each exercise test was preceded by 4 inhalations of pirbuterol (a therapeutic equivalent of albuterol) from a Maxair Autohaler. Despite the pre-exercise administration of the pirbuterol, the FEV<sub>1</sub> decreased by 40 and 60% on the two days while receiving salmeterol. Exercise-induced bronchospasm was completely blocked when salmeterol was discontinued and theophylline was substituted.



ICS= inhaled corticosteroid

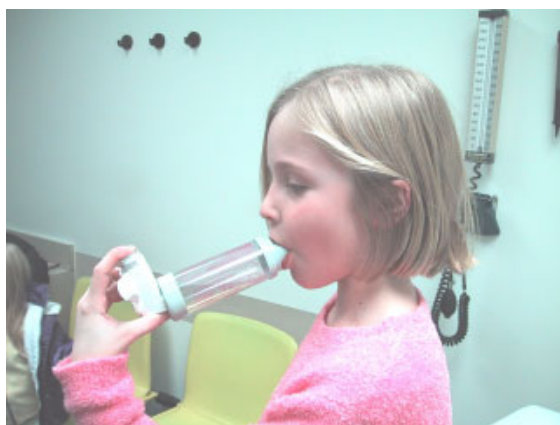
■=ICS + Salmeterol; ●= ICS + Theophylline

to inhibit the action of leukotrienes released from mast cells. Montelukast has been the leading medication in this class. Controlled clinical trials have shown measurable benefit; however, the effect is generally small.

### CURRENT STATE OF THE ART FOR PHARMACOTHERAPY FOR ASTHMA

Currently available therapeutic options have the potential to minimize morbidity and provide normal functioning for most patients. Acute symptoms can generally be relieved by an inhaled  $\beta_2$  agonist administered via a metered dose inhaler (MDI) (Figure 4). The progression of an acute exacerbation, most of which are triggered by vi-

Figure 4. Demonstration of inhaled medication from a metered dose inhaler (MDI) with a valved holding chamber in a pre-school age child (upper photo) and with a face mask in a toddler (lower photo). The MDI injects aerosol into the chamber with one way valves that permits inhalation of the medication from the chamber while exhalation is into the ambient air. Three to six actuations of albuterol (90 mg/actuation) in this manner with at least 3-4 breaths after each actuation to evacuate the chamber provides bronchodilator effectiveness equivalent to 2.5 mg of albuterol by open nebulizer.<sup>61</sup>



ral respiratory infections, can usually be stopped by the use of a short course of oral corticosteroid.<sup>35,36</sup>

A small dose of inhaled corticosteroid is the most effective and safe monotherapeutic regimen for chronic asthma. The use of a combination of low dose inhaled corticosteroid with salmeterol is generally more effective than a larger dose of an inhaled steroid. For this reason, the combination of the two medications is the primary regimen of choice when low doses of inhaled corticosteroid have failed to control the disease. Alternatively, theophylline can be used as an additive agent in the sub-group of individuals who develop salmeterol-induced loss of response to the rescue or bronchoprotective effects of albuterol or pirbuterol.<sup>34</sup> Montelukast may be useful for very mild daily symptoms in young children where delivery of an inhaled medication is problematic.

The most common form of asthma in young children is an intermittent pattern characterized by exacerbations from viral respiratory infections.<sup>37</sup> Highly successful outcomes for this pattern of asthma are attained with intervention measures that include a systemic corticosteroid.<sup>38,39</sup> Parents are given a limited supply of oral corticosteroid and instructions for its use. Because it can be given as soon as the response to bronchodilator therapy is incomplete, this type of self-management permits initiation of more prompt and effective treatment than is likely to occur when a patient must first go to a physician's office or emergency department. The addition of maintenance medication, including inhaled corticosteroids, does not prevent viral-induced exacerbations and is therefore not indicated for this pattern of asthma.<sup>40-42</sup>

Although all healthcare providers have access to the same medications, outcome varies greatly among different practitioners. Asthma-associated hospitalization is a major component of morbidity. Unfortunately, there have been no signs of decreased hospitalization over the past 20 years despite the widespread distribution of the 1991 national guidelines for the management of asthma (Figure 5).<sup>43</sup> This continuing high hospitalization rate reflects the practice in the general medical community. Conversely, specialty programs have consistently had fewer emergency care visits and lower rates of hospitalization.<sup>39,44-46</sup> This reflects more skilled decision

making, closer follow-up with regularly scheduled visits, use of physiological measurements of lung function, and more time and effort spent on patient education.<sup>47</sup>

**WHAT'S NEXT?**

The newest therapeutic modality with a unique mechanism of action is a monoclonal antibody that is directed against immunoglobulin E (IgE). This agent (omalizumab; Xolair) profoundly decreases the amount of the immunoglobulin class that contains specific antibody to inhalant allergens. It does this by adhering to the high affinity binding sites on the IgE molecule. Allergic respiratory symptoms occur when an IgE antibody, which is bound to the high-affinity receptor [Fc(epsilon)RI] on mast cells, interacts or cross-links with an allergen to cause the release of mediators. It is this IgE antibody high-affinity receptor cross-linking that interacts with an allergen to cause release of mediators that result in allergic respiratory symptoms.

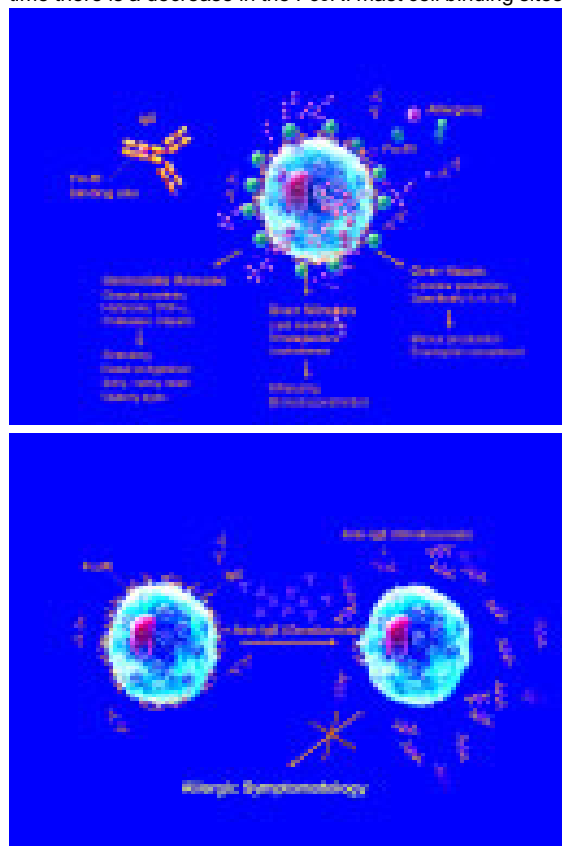
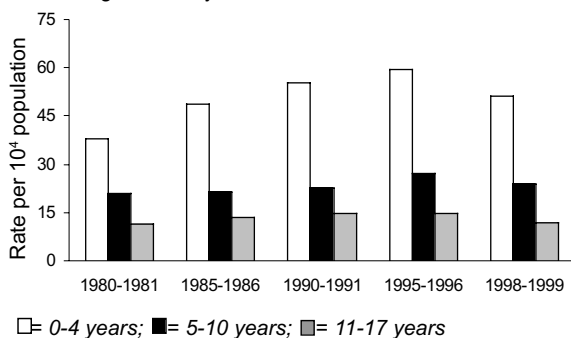
The anti-IgE minimizes the potential for an allergen to cause mediator release by tying up the binding sites on the IgE molecule. Over time, this is associated with down regulation of the high-affinity receptors (Figure 6).<sup>48</sup> The use of this new agent is hampered by the availability of alternative medications, the very high cost of this medication, and its limitation to affect the allergic component of asthma. For these reasons, omalizumab is currently used in highly selective patients who have an identified major allergic

component to their disease and whose asthma is poorly controlled with conventional therapy.

Since multiple mediators are involved in the inflammatory component of asthma, the development of new therapeutic modalities has focused on antagonists to those mediators. Interleukin 4 (IL-4) appears to play an important role in the inflammatory component of asthma. Soluble recombinant human IL-4 receptor (IL-4R) inactivates human IL-4 without mediating cellular activation. An inhaled dose of this agent is reported to have pharmacodynamic or pharmacokinetic activity that is characterized by a serum half-life of about one week. Measurable anti-asthmatic effect has been reported with the use of this agent.<sup>49,50</sup> A humanized monoclonal antibody directed against IL-4 has also been developed, and studies are planned.<sup>51</sup> Interleukin 5 (IL-5) appears to be essential for the formation

**Figure 6.** Effect of IgE on release of mediators of asthma from mast cells. The binding site on the IgE molecule binds to the high affinity receptor on the mast cell (Fc<sub>ε</sub>RI). Bridging of the mast cell bound IgE by allergen results in release of the mediators (upper figure). Omalizumab binds to the Fc<sub>ε</sub>RI binding site on the IgE molecule, thereby preventing it from binding to the high affinity receptor on the mast cell. Over time there is a decrease in the Fc<sub>ε</sub>RI mast cell binding sites.

**Figure 5.** Hospitalization rate from the National Hospital Discharge Survey, National Center for Health Statistics, Center for Disease Control.<sup>43</sup> Pre-school age children with an annual rate of about one hospitalization per 200 children in that age group have twice the hospitalization rate for asthma of children 5–10 years of age and about 5 times the rate for children ages 11–17 years.



of eosinophils, which are thought to have a major role in the pathogenesis of asthma. A single dose of a monoclonal antibody to IL-5 decreases blood and sputum eosinophils for weeks. However, clinical efficacy has yet to be demonstrated.<sup>52,53</sup>

Recognition of the anti-inflammatory effects of theophylline, which is mediated through its effect on phosphodiesterase enzymes, has led to interest in more specific phosphodiesterase inhibitors that are associated with less potential for adverse effects than theophylline.<sup>54-58</sup> While further developments in this class continue, none have yet shown clinical advantage over theophylline.

Viral respiratory infections are a major cause for acute exacerbation of asthma. For this reason, the greatest need for future developments must focus on therapies that effectively deal with viral-associated exacerbations. An effective vaccine for respiratory syncytial virus (RSV) would potentially prevent the most common cause of hospitalization in infants beyond the neonatal period and the most common cause of recurrent asthmatic episodes in pre-school age children.<sup>37</sup> Since the rhinoviruses predominate as a major trigger for acute asthma, among school age children and adults, prevention or effective anti-viral treatment of the common cold could be invaluable in improving asthma control. Since the intercellular adhesion molecule-1 (ICAM-1) is the cell surface receptor for human rhinoviruses, use of recombinant soluble ICAM-1 as a preventative has been under study.<sup>59,60</sup>

## CONCLUSIONS

Managing asthma has progressed from the earliest days when treatment was focused on measures that provided short-term relief of symptoms. The introduction of corticosteroids enabled the inflammatory component of asthma to be modified. Pharmacological development of corticosteroids with high topical potency that could be given by inhalation overcame the toxic potential associated with prolonged oral use and largely replaced the role of theophylline as the major maintenance medication for chronic asthma. The addition of salmeterol or theophylline provides greater efficacy than larger doses of inhaled corticosteroids. A monoclonal antibody against IgE provides a new potential treat-

ment for selected patients. For the future, we may see successful application of agents that target specific mediators, but the data will have to be more impressive than has been seen with leukotriene modifiers. Investigations continue to identify more specific phosphodiesterase inhibitors in the hope of obtaining the efficacy and anti-inflammatory effect of theophylline without its narrow therapeutic range and potential for adverse effects. Perhaps the future will eventually provide an effective RSV vaccine and measures that can prevent the other viral respiratory infections that are the major triggers of acute exacerbations of asthma. While we await further advancements, including a cure for the common cold, the morbidity from asthma is already effectively minimized in specialized care programs utilizing the effective and safe medications currently available accompanied by patient education in the appropriate use of those agents.

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