Effective treatments for asthma exist, but morbidity and mortality have continued to climb. Many attempts have been made to refine rather than change therapy over the past 20 years. Drugs currently used to treat asthma include β2-agonists, glucocorticoids, theophylline, cromones, and anticholinergic agents. For acute, severe asthma, the inhaled β2-agonists are the most effective bronchodilators. Short-acting forms give rapid relief; long-acting agents provide sustained relief and help nocturnal asthma; and serious adverse effects are rare when these drugs are used properly. First-line therapy for chronic asthma is inhaled glucocorticoids, the only currently available agents that reduce airway inflammation. Their side effects can be reduced by rinsing the mouth or by using large-volume spacers. Theophylline is a bronchodilator that is useful for severe and nocturnal asthma, but recent studies suggest that it may also have an immunomodulatory effect. Although theophylline is inexpensive, monitoring its plasma concentrations is both expensive and inconvenient. Cromones work best for patients who have mild asthma: they have few adverse effects, but their activity is brief, so they must be given four times daily. The anticholinergic bronchodilators are more useful for treating COPD than for chronic asthma. These drugs have virtually no side effects, and their onset is slower and their action longer than inhaled β2-agonists. The new direction in treating asthma will be orally administered medication that has few side effects and is targeted specifically to the pathogenesis of asthma.

Key words: anticholinergic agent; asthma; β2-agonist; cromone; efficacy; glucocorticoid; inhalation therapy; leukotriene; theophylline

Effectiveness treatments for asthma exist, but morbidity and mortality have continued to climb. Many attempts have been made to refine rather than change therapy. For example, new, long-acting inhaled β2-agonists are more effective than oral β2-agonists, and inhaled glucocorticoids have fewer systemic effects than oral glucocorticoids. Current asthma therapy is delivered predominantly by aerosol therapy, and inhalant drug-delivery devices have been improved. The primary goal of inhalational delivery is the reduction of systemic side effects by delivery of a smaller dose to the presumed site of the disease. When comparing different types of asthma therapy, both the drugs and the inhalant devices must be assessed.

The pathophysiology and clinical manifestations of asthma are similar throughout the world, yet asthma treatment differs markedly from country to country. These differences may be related to the way medicine is practiced, to economic factors, to cultural differences, or to the influence of pharmaceutical companies. In the United Kingdom, Australia, Scandinavia, and the Netherlands, inhaled glucocorticoids are widely used; conversely in the United States, their use is low, albeit increasing rapidly. In Japan and other Asian countries, oral agents are preferred, and there appears to be a prejudice against the use of inhalers. International guidelines for asthma management may lead to a more uniform therapeutic approach; however, many of the recommended guidelines have not yet been validated by carefully controlled studies.

Despite worldwide differences in asthma therapy, it is nevertheless valuable to describe how asthma is typically managed and to point out the advantages and limitations of each class of drugs used (Table 1). This review assesses the β2-agonists, the glucocorticoids, theophylline, the cromones (cromolyn sodium), and the anticholinergic bronchodilators. It also briefly describes future directions asthma therapy research may take.

β2-Agonists

The target for inhaled β2-agonists is presumed to be airway smooth muscle cells, which in humans...
express β₂-receptors from the trachea to the terminal bronchioles. As functional antagonists, β₂-agonists can prevent and reverse the effects of all bronchoconstrictor substances, including leukotriene (LT) D₄, acetylcholine, bradykinin, prostaglandins, histamine, and endothelins. Because β₂-receptors are so widely distributed in the airway, β₂-agonists may also affect other types of cells that play a role in asthma. For example, it has been reported that β₂-agonists may stabilize mast cells, possibly explaining why β₂-agonists protect better against an adenosine monophosphate challenge, which releases bronchoconstrictor mediators from airway mast cells, than against bronchoconstriction induced by a cholinergic agonist. Inhibiting mast-cell bronchoconstrictor substances may be how β₂-agonists block the bronchoconstriction induced by allergens, exercise, and fog.

Furthermore, β₂-agonists inhibit cholinergic neurotransmission in the human airway, which can result in reduced cholinergic-reflex bronchoconstriction. Although the highest density of β₂-receptors in the human airway is found in its epithelial cells, the effect of β₂-agonists on the functions of these cells is not clear. These agents do increase ciliary beat frequency, but whether they influence the release of mediators such as cytokines and lipid mediators is uncertain.

**Long-Acting Inhaled β₂-Agonists**

The bronchodilator action of salmeterol and formoterol have a similar duration of action in patients

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**Table 1—Summary of the Classes of Drugs Currently Available for the Treatment of Asthma**

<table>
<thead>
<tr>
<th>Class</th>
<th>Mechanism of Action</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>β₂-Agonists</td>
<td>Stimulate intracellular adenyly cyclase, inhibit mast-cell mediators</td>
<td>Rapid relief of symptoms</td>
<td>Tolerance to protective effects</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Effective on large and small airways</td>
<td>No effect on or possible increase in inflammation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Side effects rarely problematic</td>
<td>May worsen asthma control</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>May increase mortality</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>May induce steroid resistance</td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td>Inhibit activity of many cells involved in airway inflammation</td>
<td>Most effective control of asthma</td>
<td>Local side effects</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reduce airway inflammation</td>
<td>Absorption from lung causes systemic side effects</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prevent asthma exacerbations</td>
<td>Steroid or “corticophobia”</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Side effects rarely problematic</td>
<td>Poor compliance</td>
</tr>
<tr>
<td>Theophylline</td>
<td>Uncertain, but blocks late response to allergen; may affect trafficking of activated lymphocytes in asthmatic airways</td>
<td>Bronchodilator, relatively weak</td>
<td>Side effects common</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Oral administration</td>
<td>Monitoring blood levels is inconvenient, expensive</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Many drug interactions</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Less effective than inhaled glucocorticoids</td>
</tr>
<tr>
<td>Cromones</td>
<td>Uncertain, but may block swelling-dependent chloride channels that may be important in mast cells, sensory nerves, and epithelial cells</td>
<td>Control symptoms</td>
<td></td>
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<tr>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prevent induced bronchoconstriction</td>
<td>Only effective for some cases of mild asthma</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Do not reduce airway inflammation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Four-times-daily administration</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Relatively expensive</td>
</tr>
<tr>
<td>Anticholinerges</td>
<td>Block vagal cholinergic tone of airway smooth muscle; may inhibit airway mucus hypersecretion</td>
<td>Useful in COPD</td>
<td>Less effective than β₂-agonists because they block only cholinergic bronchoconstriction</td>
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<tr>
<td></td>
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<td></td>
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<tr>
<td></td>
<td></td>
<td>Bronchodilator</td>
<td>Slow onset of action</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No side effects</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Especially useful for neonates and elderly</td>
<td></td>
</tr>
</tbody>
</table>

### Notes
- β₂-Agonists:
  - Rapid relief of symptoms
  - Effective on large and small airways
  - Side effects rarely problematic

- Glucocorticoids:
  - Most effective control of asthma
  - Reduce airway inflammation
  - Prevent asthma exacerbations

- Theophylline:
  - Bronchodilator, relatively weak

- Cromones:
  - Control symptoms

- Anticholinerges:
  - Prevent induced bronchoconstriction

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Asthma Management: Perspectives and Paradigms in a Changing Environment
who have asthma. Salmeterol, which appears to act longer in vitro,\textsuperscript{29} is a partial agonist, whereas formoterol is a nearly full agonist. Whether these pharmacologic differences have clinical significance is not yet clear. Theoretically, a full agonist more readily downregulates β\(_2\)-receptors, and a partial agonist may control more severe bronchoconstriction less effectively. A single case report has suggested that formoterol may be useful for patients who do not respond to salmeterol therapy.\textsuperscript{29} Controlled comparative studies are now needed.

Long-acting inhaled preparations of salmeterol and formoterol have been introduced in several countries.\textsuperscript{30} Both provide effective bronchodilation over a 12-h period, making them particularly useful for patients who have nocturnal asthma. Because these drugs have no anti-inflammatory effects, they should always be used with an inhaled glucocorticoid. When asthma is not adequately controlled in patients by low-dose inhaled steroids, inhaled salmeterol may provide better control than an increased dose of inhaled steroids.\textsuperscript{31,32} Patients exhibit markedly heterogeneous responses to inhaled salmeterol: some show dramatically improved conditions, and others, particularly those who have more severe asthma, obtain no benefit.

A fixed-combination inhaler containing a long-acting β\(_2\)-agonist and a steroid could be useful. It could improve compliance and ensure that the patient receives an inhaled steroid with a long-acting β\(_2\)-agonist. A recent study in which patients were treated with terbutaline and budesonide (using a Turbuhaler; Astra; Lund, Sweden) demonstrated the benefits of using a fixed combination.\textsuperscript{33} Fixed-combination inhalers will likely become more popular in the future.

\textbf{Advantages of β\(_2\)-Agonists}

The β\(_2\)-agonists are by far the most useful bronchodilators used for treating asthma, and they are most effective when inhaled.\textsuperscript{34} Inhaled short-acting β\(_2\)-agonists such as albuterol and terbutaline provide rapid symptomatic relief.

When inhaled at recommended dosages, these agents have very few side effects. However, when they are taken orally, muscle tremor, tachycardia, palpitations, and restlessness are common; these side effects are particularly problematic for elderly patients. Because of these adverse effects and their slow onset of action, there is little use for oral β\(_2\)-agonists. The one advantage of slow-release oral agents—a longer duration of action—was eliminated with the introduction of long-acting inhaled β\(_2\)-agonists, which more effectively prevent induced bronchoconstriction than equivalent doses of oral β\(_2\)-agonists.\textsuperscript{35} Inhaled drugs may reach superficial airway cells, such as mast cells and epithelial cells, that are less easily reached by oral drugs. Thus, nebulized β\(_2\)-agonist therapy is the first choice for acute severe asthma and may be life saving.\textsuperscript{36}

\textbf{Disadvantages of β\(_2\)-Agonists}

Adverse effects of the β\(_2\)-agonists include muscle tremor, tachycardia, palpitations, and restlessness. Although these are not usually a problem for patients using recommended doses of inhaled β\(_2\)-agonists, they may be clinically significant for patients who take high doses of inhaled or oral β\(_2\)-agonists. Metabolic side effects, including hypokalemia, rarely pose a problem unless IV β\(_2\)-agonists are used.

\textit{Tolerance}: Tolerance may develop to the antiasthmatic effects of inhaled β\(_2\)-agonists,\textsuperscript{24,37} but there is little evidence for loss of bronchodilator effects with the short-acting forms. Some loss of bronchodilator effect with formoterol has been reported in studies that had a washout period for β\(_2\)-agonist therapy.\textsuperscript{38,39} A reduced bronchodilator response to albuterol after salmeterol administration also has been reported.\textsuperscript{40}

Increasing evidence suggests that tolerance to the bronchoprotective effects of both short- and long-acting β\(_2\)-agonists does develop.\textsuperscript{39,41-44} Tolerance is seen most commonly with triggers that operate via mast-cell activation, such as adenosine, allergens, and exercise, although studies have shown reduced protection rather than loss of protection.\textsuperscript{41,43,44} The clinical relevance of this effect is not yet known. Whether inhaled steroids protect against developing tolerance is also unknown. In experimental animal studies, pretreatment with a glucocorticoid protected against the downregulation of β\(_2\)-receptors in the lung induced by long-term exposure to a β\(_2\)-agonist.\textsuperscript{45} A preliminary study suggests, however, that inhaled steroids may not completely prevent developing tolerance to β\(_2\)-agonists.\textsuperscript{46} Patients may avoid developing tolerance by taking the long-acting β\(_2\)-agonist only at night.

Recent studies of the polymorphism of human β\(_3\)-receptors suggest that some forms of the receptor may be more likely to be downregulated.\textsuperscript{47} Patients who have the Arg16>Gly form of the receptor, which is more readily downregulated \textit{in vitro}, have more frequent nocturnal asthma.\textsuperscript{48} In contrast, the Gln27>Glu form of the receptor resists downregulation \textit{in vitro} and is associated with less airway hyperreactivity.\textsuperscript{49}

\textbf{Concerns About Increased Asthma Morbidity and Mortality:} Concern exists about the use of excessive doses of short-acting inhaled β\(_2\)-agonists;\textsuperscript{30} high doses are associated with increased risks of death and morbidity from asthma.\textsuperscript{51-53} These findings are con-
troversial, however, because it is still not clear whether inhaled β₂-agonists have long-term adverse effects or whether the high usage of these drugs reflects severe unstable asthma. Possibly, short-acting inhaled β₂-agonists are problematic only when taken in high doses, and the risk of death increases significantly only when more than one canister is used per month. Some evidence also suggests that high concentrations of β₂-agonists inhibit the effects of glucocorticoids in human and animal lungs in vitro and in target cells such as airway epithelial cells and T lymphocytes. Further, high doses of inhaled β₂-agonists may block the protective effects of steroids in an allergen challenge.

Clearly, both short-acting and long-acting β₂-agonists fail to reduce the inflammation in asthmatic airways, and some evidence suggests that inflammation actually may be increased. Accordingly, these agents should be used in conjunction with anti-inflammatory drugs.

**Glucocorticoids**

Although the molecular mechanisms of the anti-inflammatory action of steroids are better understood, the key cellular targets in asthma have not yet been established. It appears that airway epithelial cells are important target cells and that steroids inhibit the expression of cytokines (such as interleukin [IL]-1, IL-8, regulated on activation normal T-expressed and secreted [RANTES], and granulocyte-macrophage colony-stimulating factor), lipid mediators, nitric oxide, and adhesion molecules. Glucocorticoids may inhibit the expression of inducible genes in airway epithelial cells by blocking key transcription factors such as nuclear factor-kappa B and activator protein-1. A good example of this inhibition is the ability of inhaled steroids to reduce the elevated concentration of nitric oxide in the air exhaled by patients who have asthma. This reduction suggests that steroids inhibit the inducible enzyme nitric oxide synthetase in the airway epithelial cells of these patients, which may in turn reduce inflammation in the airway wall.

Inhaled steroids have many other possible inflammatory-cell targets, including macrophages, T lymphocytes, dendritic cells, and eosinophils. Inhaled glucocorticoids are highly lipophilic, and it is unlikely that they can penetrate far into the airways, so it appears that their effects are exerted largely at the surface of the airway.

An important unresolved question is whether inhaled steroids exert a therapeutic effect on the airways through a systemic action. That they reduce the number of circulating low-density eosinophils suggests an effect in the circulation or in the bone marrow. However, this phenomenon could also be explained by a local airway effect through inhibition of synthesis of the eosinophil-stimulating cytokines IL-5 and RANTES. Studies in dogs have suggested that inhaled steroids affect the production of leukocyte progenitors in the bone marrow, but it is unclear whether this results from affecting the synthesis of some stimulatory factor in the airways or from the action of the systemically absorbed fraction of the inhaled steroids on the bone marrow.

It is also uncertain whether steroids deposited in the proximal airway can be distributed via the airway circulation to the more distal airway. This issue must be resolved, because if a systemic effect is desirable, then developing steroids that have even greater topical-to-systemic ratios may not improve their clinical efficacy.

Evidence is increasing that introducing inhaled steroids early may improve lung function more than bronchodilator treatment. Thus, administering an inhaled steroid may prevent the decline in lung function that occurs in patients who have chronic asthma. The logical corollary is that inhaled steroids should be given to all patients when asthma is first detected. Additional controlled long-term studies are needed to justify universal adoption of this policy.

**Advantages of the Glucocorticoids**

Inhaled glucocorticoids have revolutionized the treatment of asthma and are highly effective in controlling asthma in all patients. The use of inhaled steroids increased enormously after long-term studies offered reassuring data about their safety. Moreover, it is widely recognized that airway inflammation occurs even in patients with mild asthma, and glucocorticoids are the only approved therapy that reduces inflammation in the airways of patients who have asthma.

The introduction of guidelines for asthma therapy has led to much earlier use of inhaled steroids for both adult and childhood asthma, and inhaled steroids have now become first-line therapy for chronic asthma. This strategy has led to improved asthma control, reduced hospital admissions, and improved lung function. Inhaled glucocorticoids are usually effective when given twice daily, and in patients receiving low doses, they are also effective when given once daily. This convenient regimen leads to compliance.
Disadvantages of the Glucocorticoids

Many studies have been undertaken in response to concerns about local and systemic side effects of inhaled glucocorticoids.71

Local Side Effects: These are caused by deposition of glucocorticoids in the upper airway. They may be reduced by the use of a large-volume spacer, which removes most of the fraction of drug that would otherwise be deposited in the oropharynx.72,73 Rinsing the mouth may reduce the local deposition associated with dry-powder inhalers. Dysphonia, the most common local side effect of inhaled glucocorticoids, can occur in more than 50% of patients given high-dose therapy.74 The multiple-dose, dry-powder delivery system (Turbuhaler) reduces laryngeal symptoms, probably because inspiration against the device’s resistance deposits drug on the false vocal cords, protecting the vocal cords.

Systemic Side Effects: These side effects arise from GI absorption of the swallowed fraction of the drug as well as from the fraction deposited in the lung.70,75 As already mentioned, the latter can be reduced markedly by rinsing or using a large-volume spacer. Side effects can also be reduced by choosing a steroid such as budesonide or fluticasone propionate that undergoes extensive first-pass hepatic metabolism, allowing little of the drug to enter the systemic circulation. With the use of such agents, the fraction absorbed from the lungs becomes the major, unavoidable source of systemic availability.

Fortunately, the systemic effects of inhaled steroids at the doses that are needed to control asthma have little clinical significance for most patients.70,71 Little convincing evidence substantiates the concerns raised about the long-term systemic side effects of inhaled glucocorticoids, including growth stunting in children and the development of osteoporosis in adults; nevertheless, careful long-term follow-up studies are needed.70 Systemic effects may occur in patients who have severe asthma and who must use high doses of inhaled steroids; the only effective therapeutic alternative for these patients is the oral glucocorticoids, which have a far greater risk of adverse effects.

Compliance with inhaled glucocorticoids is poor76 because patients do not perceive immediate benefit from the treatment, and they may also have concerns about the side effects of steroids. Both of these problems have yet to be overcome by education.

Theophylline

Theophylline has been used for more than 50 years, but its mode of action is still uncertain. In many countries, it is third-line therapy, used as an additional bronchodilator after high-dose inhaled steroids. Because theophylline is a relatively weak relaxant of airway smooth muscle, high doses are needed for useful bronchodilation. Recent evidence indicates that it may have anti-inflammatory or immunomodulatory effects at lower doses than those needed for bronchodilation, and this has led to a reevaluation of its use for patients who have asthma.77

Theophylline blocks the late response to allergen at doses that have little effect on the early response;14,15 an effect that is associated with a reduced number of eosinophils in the airway.16 A controlled withdrawal of theophylline therapy would subsequently worsen asthma.77,78 In addition, it decreases the number of activated T lymphocytes in the circulation and increases their number in the airway,79 which suggests that theophylline affects the trafficking of activated lymphocytes in the airway.

Advantages of Theophylline

An important advantage of theophylline is that it can be taken orally as a once- or twice-daily slow-release preparation. Compared with the use of inhaled medication, the use of this oral regimen may improve patient compliance.80 Theophylline is particularly useful for treating patients who have more severe asthma, and it is also beneficial for nocturnal asthma.81-83

Although theophylline is generally less effective than inhaled glucocorticoids, one study that compared inhaled glucocorticoids and theophylline in children who had mild asthma found similar efficacy in asthma control.84

Disadvantages of Theophylline

A major reason for the decline in popularity of theophylline is the frequency of the side effects, including nausea and headaches, which occur frequently. More serious but less common effects are cardiac arrhythmias and seizures. The side effects are usually correlated with the plasma concentration of the drug, and several drug interactions may raise the plasma concentrations of theophylline to toxic levels. Clinically significant increases in the plasma concentrations of theophylline may also depend on hepatic metabolism and on diseases that result in a reduced plasma clearance. Although theophylline itself is inexpensive, its plasma-level monitoring can be both expensive and inconvenient. Because useful immunomodulatory effects may be achieved with lower concentrations than those needed for bronchodilation, however, these problematic side effects will likely occur less frequently, and most patients will not require plasma monitoring.
CROMONES

A recent biopsy study cast doubt on whether cromones are truly anti-inflammatory agents when it found no evidence of a decrease of inflammatory cells in airways after treatment with nedocromil sodium.17

Other recent evidence suggests that cromones may block swelling-dependent chloride channels.18 Additional chloride channels in mast cells, sensory nerves, and epithelial cells may also be important, and this evidence could lead to the development of new, more potent drugs.

Advantages of Cromones

The cromones include cromolyn sodium and nedocromil sodium, both of which control symptoms of asthma and effectively block bronchospasm induced by allergens, exercise, adenosine, Bradykinin, propranolol, and sulfur dioxide. Both drugs are safe and have no significant side effects.19 One study found that nedocromil sodium may have steroid-sparing effects,20 but this has not been confirmed in other studies.85

Disadvantages of Cromones

Inhaled cromones are less effective than inhaled glucocorticoid drugs, and they are also more expensive than the inhaled glucocorticoids. The cromones appear to work best for patients who have mild asthma, although they are not effective for all such patients, and it is difficult to predict which patients will respond. Recent evidence suggests that cromones may be most beneficial for patients whose predominant symptom is coughing.

Because their action is short, inhaled cromones must be used four times daily, an inconvenient regimen for long-term prophylaxis of asthma. Since the molecular basis of the action of the cromones is not yet established, it has been difficult to develop longer-acting forms of these drugs.

Anticholinergic Bronchodilators

In several studies, anticholinergic bronchodilators were found to be more effective than β2-agonists in patients with COPD, which suggests that in addition to blocking the vagal cholinergic tone of airway smooth muscle, they have another effect on the airway. Possibly, this effect is inhibition of hypersecretion of mucus in the airway, which has been demonstrated recently with oxitropium bromide.21

Advantages of Anticholinergic Bronchodilators

Currently available anticholinergic bronchodilators are given by inhalation to avoid systemic antimuscarinic effects. Ipratropium bromide and oxitropium bromide are quaternary compounds that are absorbed negligibly; because systemic absorption is minimal, these drugs have virtually no side effects.

Both of these drugs are useful bronchodilators in patients who have COPD but are less effective in those who have chronic asthma.22 Nebulized ipratropium bromide is almost as effective as nebulized β2-agonists in treating acute severe asthma.23,86,87

Disadvantages of Anticholinergic Bronchodilators

Anticholinergic bronchodilators are less effective than inhaled β2-agonists because they counteract only cholinergic neural bronchoconstriction, which may be a relatively minor part of the bronchoconstrictor mechanism in asthma. In contrast with the short-acting inhaled β2-agonists, their onset of action is slow, although their duration is longer.

The recent recognition that at least four subtypes of muscarinic receptors are expressed in the airways87 has led to a search for receptor-subtype-selective antagonists. The M3 receptors play the major role in causing bronchoconstriction, whereas the M2 receptors mediate the feedback inhibition of acetylcholine release from airway sensory nerves.88 Nonselective antagonists such as ipratropium bromide and oxitropium bromide produce beneficial effects by blocking M3 receptors, but they may have relatively deleterious effects by increasing the release of acetylcholine through blockade of prejunctional M2 receptors. This has prompted a search for M3-selective receptor antagonists.

The Direction of Future Asthma Treatment

Despite a much fuller understanding of the pathogenetic mechanisms of asthma, it has proved very difficult to develop new antiasthma treatments. Many of the available treatments combine good control of asthma with an acceptable side-effect profile, although all of these therapies have certain disadvantages that limit their usefulness (Table 2). When selecting the most appropriate medication or combination of medications for a specific patient, the

<table>
<thead>
<tr>
<th>Table 2—Limitations of Current Antiasthma Therapies</th>
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</thead>
<tbody>
<tr>
<td>Limitations</td>
</tr>
<tr>
<td>No treatment is curative</td>
</tr>
<tr>
<td>The most effective therapies are administered by inhalation</td>
</tr>
<tr>
<td>Patients tend to comply poorly with complex dosing regimens</td>
</tr>
<tr>
<td>Patients who have severe asthma are poorly responsive, perhaps as a result of steroid resistance</td>
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</table>
clinician must consider the patient’s needs and preferences, the risk-to-benefit ratio (including long-term effects) of the proposed treatment, and its costs (Table 3). The new direction in the treatment of asthma will be a medication that is orally administered, has few side effects, and is targeted specifically at the pathogenesis of asthma.

**Characteristics of Improved Drug Therapies**

**Oral Administration:** Although most effective asthma drugs are now administered by inhalation, it would be desirable to develop oral medications. Compliance with long-term medication regimens is a known problem, particularly when symptoms are controlled, but studies have shown that better compliance is achieved with oral than with inhaled therapy.  

Once- or twice-daily formulations of oral medication, dispensed from convenient packaging that encourages compliance, may be the optimal way to treat chronic asthma. Another advantage of oral medication is that it may also control concomitant allergic conditions such as rhinitis and atopic dermatitis. Inhaled therapy may be difficult to deliver to the peripheral airway that is inflamed in asthma. Possibly, for example, currently available inhaled steroids are absorbed into the airway circulation and distributed peripherally via the bloodstream. An oral medication, however, would be delivered by the bronchial circulation to all the airways.

**Fewer Adverse Effects:** Although adverse effects are not a major problem with existing inhaled therapies, some patients who have severe disease and who are taking high-dose β₂-agonists and glucocorticoids may be troubled by systemic side effects. Because both of these classes of drugs have effects on many types of cells, achieving significant concentrations outside the airway almost inevitably leads to adverse effects. In the future, drugs that more specifically affect the pathophysiologic condition of asthma may result in fewer untoward effects; for example, although the currently available cromones have relatively limited efficacy, their specific mechanism of action on allergic inflammation means few significant side effects. Similarly, the highly specific LT antagonists and LT synthesis inhibitors that are currently under investigation are free from obvious side effects, a finding that suggests that LTs are not involved in normal physiologic processes.

**Targeting Therapy to the Disease**

*Treating a Heterogeneous Disease:* Clearly, asthma is a heterogeneous disease. Patients who have mild episodic asthma may have a different disease than patients who have persistent asthma, and those who have severe disease may be experiencing a different underlying molecular process than those who have a milder form of the disorder. Aspirin-sensitive asthma is an obvious example of a specific type of asthma. As more specific treatments are developed, it may be possible to discriminate several types of asthma, each of which would benefit from a different type of therapy. Thus, the condition of patients who have aspirin-sensitive asthma might improve in response to an LT antagonist or synthesis inhibitor, perhaps without a need for other therapies.

*Treating Severe Asthma:* Approximately 10% of patients with asthma have severe disease and require high doses of inhaled or oral glucocorticoids. Some of these patients may have more severe disease because of relative resistance to the effects of glucocorticoids. Although these persons represent a small minority of patients who have asthma, they consume more than 50% of the resources devoted to this disorder. They require more frequent medical attention, need more expensive therapies, are more often treated as hospital inpatients, and miss more time from work and school than patients who have milder forms of the disease.

To deal effectively with this human and economic challenge, we must understand more about the underlying mechanisms in severe asthma. That will be a first step in developing new treatment alternatives to glucocorticoids. Methotrexate and cyclosporine have some steroid-sparing effects, but they also have severe side effects and limited efficacy; treatment with IL-5 antagonists and tumor necrosis factor antagonists eventually may be found to be suitable.

**Table 3—Considerations in Selecting a Drug for a Patient Who Has Asthma**

<table>
<thead>
<tr>
<th>Considerations</th>
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<tbody>
<tr>
<td>Efficacy</td>
</tr>
<tr>
<td>Oral administration</td>
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<tr>
<td>Convenience for patient (compliance)</td>
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<tr>
<td>Side effects (risk/benefit ratio)</td>
</tr>
<tr>
<td>Long-term outcome</td>
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<tr>
<td>Costs (direct and indirect)</td>
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</table>

None of the existing treatments for asthma is curative, and symptoms return soon after treatment is stopped. Even patients who are started on a regimen of an effective dose of an inhaled glucocorticoid at the onset of asthma and who are successfully maintained on that regimen for 2 years demonstrate a return in symptoms after withdrawal of treatment. Although glucocorticoids are highly effective
in controlling the inflammatory process in asthma, they appear to have little effect on the release of LTs, another process that plays a major role in the pathophysiologic condition of asthma.94,95 This observation suggests that LT antagonists and LT synthesis inhibitors may be a useful treatment option in patients who have asthma.

It is unlikely that current approaches to asthma will lead to a cure, because we still do not understand the underlying causes of asthma. Furthermore, the mechanisms involved in the persistence of inflammation are poorly understood. Ideally, we eventually will be in a position to identify and manipulate the molecular “switches” that result in asthmatic inflammation. It may then be possible to treat infants and thus prevent the disease from ever becoming established.

REFERENCES
1 Barnes PJ. New drugs for asthma. Eur Respir J 1992; 5:1126-36
13 Schleimer RP. Effects of glucocorticoids on inflammatory cells relevant to their therapeutic application in asthma. Am Rev Respir Dis 1990; 141(2 pt 2):555-69
20 Svedenbg UF, Jorgensen H. Inhaled nedocromil sodium as additional treatment to high dose inhaled corticosteroids in the management of bronchial asthma. Eur Respir J 1991; 4:992-90
33 Barnes PJ, O’Connor BJ. Use of a fixed combination of beta2-agonist and steroid dry powder inhaler in asthma. Am J Respir Crit Care Med 1995; 151:1053-57

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Brenner, M., Berkowitz, R., Marshall, N., et al. (1995) Need for...
80 Kelloway JS, Wyatt RA, Adlis SA. Comparison of patients' compliance with prescribed oral and inhaled asthma medications. Arch Intern Med 1994; 154:1349-52
81 Barnes PJ, Greening AP, Neville L, et al. Single dose slow-release aminophylline at night prevents nocturnal asthma. Lancet 1982; 1:299-301
87 Barnes PJ. Muscarinic receptor subtypes in airways. Life Sci 1993; 52:251-27
91 Alexander AG, Barnes NC, Kay AB. Trial of cyclosporin in corticosteroid-dependent chronic severe asthma. Lancet 1992; 339:324-28