The clinical hallmarks of asthma are recurrent, episodic bouts of coughing, shortness of breath, chest tightness, and wheezing. In mild asthma, symptoms occur only occasionally, eg, on exposure to allergens or certain pollutants, on exercise, or after a viral upper respiratory infection. More severe forms of asthma are associated with frequent attacks of wheezing dyspnea, especially at night, and even chronic limitation of activity. Asthma is the most common chronic disabling disease of childhood, but it affects all age groups.

Asthma is physiologically characterized by increased responsiveness of the trachea and bronchi to various stimuli and by widespread narrowing of the airways that changes in severity either spontaneously or as a result of therapy. Its pathologic features are contraction of airway smooth muscle, mucosal thickening from edema and cellular infiltration, and inspissation in the airway lumen of abnormally thick, viscid plugs of mucus. Of these causes of airway obstruction, contraction of smooth muscle is most easily reversed by current therapy; reversal of the edema and cellular infiltration requires sustained treatment with anti-inflammatory agents. Asthma therapies are thus sometimes divided into two categories: "short-term relievers" and "long-term controllers."

Short-term relief is most effectively achieved with bronchodilators, agents that increase airway caliber by relaxing airway smooth muscle, and of these the β-adrenoceptor stimulants (see Chapter 9: Adrenoceptor-Activating & Other Sympathomimetic Drugs) are the most widely used. Theophylline, a methylxanthine drug, and antimuscarinic agents (see Chapter 8: Cholinoceptor-Blocking Drugs) are also used for reversal of airway constriction. Long-term control is most often achieved with an anti-inflammatory agent such as an inhaled corticosteroid, with a leukotriene antagonist, or with an inhibitor of mast cell degranulation, eg, cromolyn or nedocromil. The distinction between "short-term relievers" and "long-term controllers" has become blurred by the finding that theophylline inhibits some lymphocyte functions and modestly reduces airway mucosal inflammation and that budesonide, an inhaled corticosteroid, produces modest immediate bronchodilation. Similarly, two recently released long-acting β-adrenoceptor stimulants, salmeterol and formoterol, appear to be effective in improving asthma control when taken regularly. Finally, clinical trials are demonstrating the efficacy of specifically targeting a mechanism thought to be fundamental to asthma's pathogenesis by repeated treatment with a humanized monoclonal anti-IgE antibody.

This chapter presents the basic pharmacology of the methylxanthines, cromolyn, leukotriene pathway inhibitors, and monoclonal anti-IgE antibody—agents whose medical use is almost exclusively for pulmonary disease. The other classes of drugs listed above are discussed in relation...
to the therapy of asthma.

Pathogenesis of Asthma

A rational approach to the pharmacotherapy of asthma depends on an understanding of the disease's pathogenesis. In the classic immunologic model, asthma is a disease mediated by reaginic (IgE) antibodies bound to mast cells in the airway mucosa (Figure 20–1). On reexposure to an antigen, antigen-antibody interaction on the surface of the mast cells triggers both the release of mediators stored in the cells' granules and the synthesis and release of other mediators. The agents responsible for the early reaction—immediate bronchoconstriction—include histamine, tryptase and other neutral proteases, leukotrienes C₄ and D₄, and prostaglandins. These agents diffuse throughout the airway wall and cause muscle contraction and vascular leakage. Other mediators are responsible for the more sustained bronchoconstriction, cellular infiltration of the airway mucosa, and mucus hypersecretion of the late asthmatic reaction that occurs 2–8 hours later. These mediators are thought to be cytokines characteristically produced by Th2 lymphocytes, especially GM-CSF and interleukins 4, 5, 9, and 13, which attract and activate eosinophils and stimulate IgE production by B lymphocytes. It is not clear whether lymphocytes or mast cells in the airway mucosa are the primary source of the cytokines and other mediators responsible for the late inflammatory response, but it is now thought that the benefits of corticosteroid therapy may result from their inhibition of cytokine production in the airways.

Figure 20–1.
Conceptual model for the immunopathogenesis of asthma. Exposure to allergen causes synthesis of IgE, which binds to mast cells in the airway mucosa. On reexposure to allergen, antigen-antibody interaction on mast cell surfaces triggers release of mediators of anaphylaxis: histamine, tryptase, prostaglandin D₂ (PGD₂), leukotriene C₄, and platelet-activating factor (PAF). These agents provoke contraction of airway smooth muscle, causing the immediate fall in FEV₁. Reexposure to allergen also causes the synthesis and release of a variety of cytokines: interleukins 4 and 5, granulocyte-macrophage colony stimulating factor (GM-CSF), tumor necrosis factor (TNF), and tissue growth factor (TGF) from T cells and mast cells. These cytokines in turn attract and activate eosinophils and neutrophils, whose products include eosinophil cationic protein (ECP), major basic protein (MBP), proteases, and platelet-activating factor. These mediators cause the edema, mucus hypersecretion, smooth muscle contraction, and increase in bronchial reactivity associated with the late asthmatic response, indicated by a fall in FEV₁ 2–8 hours after the exposure.
with asthma have no evidence of immediate hypersensitivity to antigens, most severe exacerbations of asthma appear to be provoked by viral respiratory infection, the severity of symptoms correlates poorly with the quantity of antigen in the atmosphere, and in many patients bronchospasm can be provoked by nonantigenic stimuli such as distilled water, exercise, cold air, sulfur dioxide, and rapid respiratory maneuvers.

This tendency to develop bronchospasm upon encountering stimuli that do not affect healthy nonasthmatic airways is characteristic of asthma and is sometimes called "nonspecific bronchial hyperreactivity" to distinguish it from bronchial responsiveness to specific antigens. Bronchial hyperreactivity is quantitated by measuring the fall in forced expiratory volume in 1 second (FEV₁) provoked by inhaling serially increasing concentrations of aerosolized histamine or methacholine. This exaggerated sensitivity of the airways appears to be fundamental to asthma's pathogenesis, for it is nearly ubiquitous in patients with asthma and its degree correlates with the symptomatic severity of the disease.

The mechanisms underlying bronchial hyperreactivity are somehow related to inflammation of the airway mucosa. The agents that increase bronchial reactivity, such as ozone exposure, allergen inhalation, and infection with respiratory viruses, also cause airway inflammation. In both dogs and humans, the increase in bronchial reactivity induced by ozone is associated with an increase in the number of polymorphonuclear leukocytes found in fluid obtained by bronchial lavage or from bronchial mucosal biopsies. The increase in reactivity due to allergen inhalation is associated with an increase in both eosinophils and polymorphonuclear leukocytes in bronchial lavage fluid. The increase in reactivity that is associated with the late asthmatic response to allergen inhalation (Figure 20–1) is sustained and, because it is prevented by treatment with inhaled corticosteroids immediately before antigen challenge, is thought to be caused by airway inflammation.

How the increase in airway reactivity is linked to inflammation is uncertain. Much evidence points to the eosinophil. The most consistent difference in bronchial mucosal biopsies obtained from asthmatic and healthy subjects is an increase in the number of eosinophils found beneath the airway epithelium. Immunohistochemical staining shows increased levels of eosinophil cationic protein, indicating activation of the cells. The number of eosinophils in expectorated sputum or in fluid lavaged from the lungs correlates roughly with the degree of bronchial hyperreactivity. Eosinophil products have in turn been shown to cause epithelial sloughing and an increase in contractile responsiveness of airway smooth muscle. The importance of the eosinophil has been challenged, however, by a study showing that treatment with an anti-IL-5 monoclonal antibody effectively blocks airway eosinophilia caused by allergen challenge but does not prevent bronchoconstriction or any further increase in bronchial hyperreactivity (Leckie, 2000).

The products of other cells in the airways, such as lymphocytes, macrophages, mast cells, sensory nerves, and epithelial cells, have also been shown to alter airway smooth muscle function, so a specific antagonist to a single mediator or class of mediators might not prove wholly effective as asthma therapy. Other evidence suggests a role for sensitization of sensory nerves in the airways as a mechanism for hyperreactivity (see Pharmacologic Significance of Lung Innervation).

Whatever the mechanisms responsible for bronchial hyperreactivity, bronchoconstriction itself seems to result not simply from the direct effect of the released mediators but also from their activation of neural or humoral pathways. Evidence for the importance of neural pathways stems largely from studies of laboratory animals. Thus, the bronchospasm provoked in dogs by histamine can be greatly reduced by pretreatment with an inhaled topical anesthetic agent, by transection of the vagus nerves, and by pretreatment with atropine. Studies of asthmatic humans, however, have shown that treatment with atropine causes only a reduction in—not abolition of—the
bronchospastic responses to antigens and to nonantigenic stimuli. While it is possible that activity in some other neural pathway (eg, the nonadrenergic, noncholinergic system; see Pharmacologic Significance of Lung Innervation) contributes to bronchomotor responses to nonspecific nonantigenic stimuli, their inhibition by cromolyn, a drug that appears to inhibit mast cell degranulation, suggests that both antigenic and nonantigenic stimuli may provoke the release from mast cells of mediators that stimulate smooth muscle contraction by direct and indirect mechanisms (Figure 20–2).

Figure 20–2.

Mechanisms of response to inhaled irritants. The airway is represented microscopically by a cross-section of the wall with branching vagal sensory endings lying adjacent to the lumen. Afferent pathways in the vagus nerves travel to the central nervous system; efferent pathways from the central nervous system travel to efferent ganglia. Postganglionic fibers release acetylcholine.
(ACh), which binds to muscarinic receptors on airway smooth muscle. Inhaled materials may provoke bronchoconstriction by several possible mechanisms. First, they may trigger the release of chemical mediators from mast cells. Second, they may stimulate afferent receptors to initiate reflex bronchoconstriction or to release tachykinins (eg, substance P) that directly stimulate smooth muscle contraction.

The hypothesis suggested by these studies—that asthmatic bronchospasm results from a combination of release of mediators and an exaggeration of responsiveness to their effects—predicts that asthma may be effectively treated by drugs with different modes of action. Asthmatic bronchospasm might be reversed or prevented, for example, by drugs that reduce the amount of IgE bound to mast cells (anti-IgE antibody), prevent mast cell degranulation (cromolyn or nedocromil, sympathomimetic agents, calcium channel blockers), block the action of the products released (antihistamines and leukotriene receptor antagonists), inhibit the effect of acetylcholine released from vagal motor nerves (muscarinic antagonists), or directly relax airway smooth muscle (sympathomimetic agents, theophylline).

The second approach to the treatment of asthma is aimed not just at preventing or reversing acute bronchospasm but at reducing the level of bronchial responsiveness. Because increased responsiveness appears to be linked to airway inflammation and because airway inflammation is a feature of late asthmatic responses, this strategy is implemented both by reducing exposure to the allergens that provoke inflammation and by prolonged therapy with anti-inflammatory agents, especially inhaled corticosteroids.

Pharmacologic Significance of Lung Innervation

As noted previously, the airways are richly supplied with afferent and efferent vagal nerves. The cholinergic motor fibers are clearly responsible in some patients for a portion of the bronchoconstriction characteristic of acute asthma. Such fibers innervate M3 receptors on the smooth muscle and contain modulatory M2 receptors on the nerve terminals. Selective inhibition of M2 receptors can increase bronchoconstrictor responses to a variety of stimuli, while M3 inhibitors can produce dilation of constricted airways.

In contrast, noradrenergic sympathetic innervation of the airways is sparse, and these fibers do not appear to play a major role in controlling airway diameter. Bronchodilation may be brought about by nonadrenergic, noncholinergic nerves releasing nitric oxide since nitric oxide synthase inhibitors have been shown to reduce bronchodilation produced by electrical field stimulation in vitro.

The role of peptidergic neurons is not so clear. Capsaicin, the hot chile pepper chemical that evokes release of peptide transmitters from several types of sensory nerves, has been shown to reproduce some of the signs of bronchial hyperreactivity in animal and human experiments. These findings led to the proposal that sensitization of afferent nerve endings played a major role in chronic airway hyperreactivity. However, peptide transmitter antagonists have not been able to prevent bronchoconstriction in several models. Clearly, much remains to be learned about airway pharmacology.
Basic Pharmacology of Agents Used in the Treatment of Asthma

The drugs most used for management of asthma are adrenoceptor agonists (used as "relievers" or bronchodilators) and inhaled corticosteroids (used as "controllers" or anti-inflammatory agents). Their basic pharmacology is presented elsewhere (see Chapter 9: Adrenoceptor-Activating & Other Sympathomimetic Drugs and Chapter 39: Adrenocorticosteroids & Adrenocortical Antagonists). In this chapter, we review their pharmacology relevant to asthma.

Sympathomimetic Agents

The adrenoceptor agonists have several pharmacologic actions important in the treatment of asthma. They relax airway smooth muscle and inhibit release of some bronchoconstricting substances from mast cells. They may also inhibit microvascular leakage and increase mucociliary transport by increasing ciliary activity or by affecting the composition of mucous secretions. As in other tissues, the β-adrenergic agonists stimulate adenylyl cyclase and increase the formation of cAMP in the airway tissues (Figure 20–3).

![Diagram](image)

Bronchodilation is promoted by cAMP. Intracellular levels of cAMP can be increased by β-adrenergic agonists, which increase the rate of its synthesis by adenylyl cyclase (AC); or by phosphodiesterase (PDE) inhibitors such as theophylline, which slow the rate of its degradation. Bronchoconstriction can be inhibited by muscarinic antagonists and possibly by adenosine antagonists.

The best-characterized action of the adrenoceptor agonists on airways is relaxation of airway smooth muscle that results in bronchodilation. Although there is no evidence for significant sympathetic innervation of human airway smooth muscle, there is ample evidence for the presence
smooth muscle, inhibits mediator release, and causes tachycardia and skeletal muscle tremor as toxic effects.

The sympathomimetic agents that have been widely used in the treatment of asthma include epinephrine, ephedrine, isoproterenol, and a number of $\beta_2$-selective agents (Figure 20–4). Because epinephrine and isoproterenol cause more cardiac stimulation (mediated mainly by $\beta_1$ receptors), they should probably be reserved for special situations (see below).

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**Figure 20–4.**

<table>
<thead>
<tr>
<th>Structures of isoproterenol and several $\beta_2$-selective analogs.</th>
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<tbody>
<tr>
<td><img src="image1" alt="Isoproterenol" /></td>
</tr>
<tr>
<td><img src="image3" alt="Isoetharine" /></td>
</tr>
<tr>
<td><img src="image5" alt="Metaproterenol" /></td>
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Epinephrine is an effective, rapidly acting bronchodilator when injected subcutaneously (0.4 mL of 1:1000 solution) or inhaled as a microaerosol from a pressurized canister (320 $\mu$g per puff). Maximal bronchodilation is achieved 15 minutes after inhalation and lasts 60–90 minutes. Because epinephrine stimulates $\beta_1$ as well as $\beta_2$ receptors, tachycardia, arrhythmias, and worsening of angina pectoris are troublesome adverse effects. Epinephrine is the active agent in many nonprescription inhalants (eg, Primatene Mist) but is now rarely prescribed.
Ephedrine was used in China for more than 2000 years before its introduction into Western medicine in 1924. Compared with epinephrine, ephedrine has a longer duration, oral activity, more pronounced central effects, and much lower potency. Because of the development of more efficacious and \( \beta_2 \)-selective agonists, ephedrine is now used infrequently in treating asthma.

Isoproterenol is a potent bronchodilator; when inhaled as a microaerosol from a pressurized canister, 80–120 \( \mu g \) causes maximal bronchodilation within 5 minutes. Isoproterenol has a 60- to 90-minute duration of action. An increase in the asthma mortality rate that occurred in the United Kingdom in the mid 1960s was attributed to cardiac arrhythmias resulting from the use of high doses of inhaled isoproterenol, though this attribution remains a subject of controversy.

Beta\(_2\) Selective Drugs

The \( \beta_2 \)-selective adrenoceptor agonist drugs are the most widely used sympathomimetics for the treatment of asthma at the present time (Figure 20–4). These agents differ structurally from epinephrine in having a larger substitution on the amino group and in the position of the hydroxyl groups on the aromatic ring. They are effective after inhaled or oral administration and have a long duration of action and significant \( \beta_2 \) selectivity.

Albuterol, terbutaline, metaproterenol, and pirbuterol are available as metered-dose inhalers. Given by inhalation, these agents cause bronchodilation equivalent to that produced by isoproterenol. Bronchodilation is maximal by 30 minutes and persists for 3–4 hours. Albuterol, levalbuterol, bitolterol, and metaproterenol can be diluted in saline for administration from a handheld nebulizer. Because the particles generated by a nebulizer are much larger than those from a metered-dose inhaler, much higher doses must be given (15 mg vs 2.5–5 mg) but are no more effective. Nebulized therapy should thus be reserved for patients unable to coordinate inhalation from a metered-dose inhaler.

Albuterol and terbutaline are also prepared in tablet form. One tablet two or three times daily is the usual regimen; the principal adverse effects of skeletal muscle tremor, nervousness, and occasional weakness may be reduced by starting the patient on half-strength tablets for the first 2 weeks of therapy.

Of these agents, only terbutaline is available for subcutaneous injection (0.25 mg). The indications for this route are similar to those for subcutaneous epinephrine—severe asthma requiring emergency treatment when aerosolized therapy is not available or has been ineffective—but it should be remembered that terbutaline's longer duration of action means that cumulative effects may be seen after repeated injections.

A new generation of long-acting \( \beta_2 \)-selective agonists includes salmeterol and formoterol. Both drugs are potent selective \( \beta_2 \) agonists that appear to achieve their long duration of action (12 hours or more) as a result of high lipid solubility, which permits them to dissolve in the smooth muscle cell membrane in high concentration or, possibly, attach to "mooring" molecules in the vicinity of the adrenoceptor. It is postulated that this local drug functions as a slow-release depot that provides drug to adjacent \( \beta \) receptors over a long period. These drugs appear to interact with inhaled corticosteroids to improve asthma control. They are not recommended as the sole therapy for asthma.

Although adrenoceptor agonists may be administered by inhalation or by the oral or parenteral routes, delivery by inhalation results in the greatest local effect on airway smooth muscle with the least systemic toxicity. Aerosol deposition depends on the particle size, the pattern of breathing
(tidal volume and rate of airflow), and the geometry of the airways. Even with particles in the optimal size range of 2–5 μm, 80–90% of the total dose of aerosol is deposited in the mouth or pharynx. Particles under 1–2 μm in size remain suspended and may be exhaled. Deposition can be increased by holding the breath in inspiration.

Toxicities

The use of sympathomimetic agents by inhalation at first raised fears about possible tachyphylaxis or tolerance to β agonists, cardiac arrhythmias, and hypoxemia. The concept that β-agonist drugs cause worsening of clinical asthma by inducing tachyphylaxis to their own action remains unestablished. Most studies have shown only a small change in the bronchodilator response to β stimulation after prolonged treatment with β-agonist drugs, but other studies have shown a loss in the ability of β-agonist treatment to inhibit the response to subsequent challenge with exercise, methacholine, or antigen challenge (referred to as a loss of bronchoprotective action).

Other experiments have demonstrated that arterial oxygen tension (PaO₂) may decrease after administration of β agonists if ventilation/perfusion ratios in the lung worsen. This effect is usually small, however, and may occur with any bronchodilator drug; the significance of such an effect will depend on the initial PaO₂ of the patient. Supplemental oxygen may be necessary if the initial PaO₂ is decreased markedly or if there is a large decrease in PaO₂ during treatment with bronchodilators. Finally, there is concern over myocardial toxicity from Freon propellants contained in all of the commercially available metered-dose canisters. While fluorocarbons may sensitize the heart to toxic effects of catecholamines, such an effect occurs only at very high myocardial concentrations, which are not achieved if inhalers are used as recommended. Under the terms of an international agreement, fluorocarbon-free inhalers will soon replace existing preparations.

Fears that heavy use of β-agonist inhalers could actually increase morbidity and mortality have not been borne out by careful epidemiologic investigations. Heavy use most often indicates that the patient should be receiving more effective prophylactic therapy with corticosteroids. In general, β₂-adrenoceptor agonists are safe and effective bronchodilators when given in doses that avoid systemic adverse effects.

Methylxanthine Drugs

The three important methylxanthines are theophylline, theobromine, and caffeine. Their major source is beverages (tea, cocoa, and coffee, respectively). The importance of theophylline as a therapeutic agent in the treatment of asthma has waned as the greater effectiveness of inhaled adrenoceptor agents for acute asthma and of inhaled anti-inflammatory agents for chronic asthma has been established, but theophylline's very low cost is an important advantage for economically disadvantaged patients in societies where health care resources are limited.

Chemistry

As shown below, theophylline is 1,3-dimethylxanthine; theobromine is 3,7-dimethylxanthine; and caffeine is 1,3,7-trimethylxanthine. A theophylline preparation commonly used for therapeutic purposes is aminophylline, a theophylline-ethylenediamine complex. A synthetic analog of theophylline (dyphylline) is both less potent and shorter-acting than theophylline. The pharmacokinetics of theophylline are discussed below (see Clinical Use of Methylxanthines). The metabolic products, partially demethylated xanthines (not uric acid), are excreted in the urine.
Mechanism of Action

Theophylline produces direct bronchodilation and has some anti-inflammatory actions in the airway as well. Several mechanisms have been proposed for these actions, but none have been firmly established. At high concentrations, the methylxanthines can be shown in vitro to inhibit several members of the phosphodiesterase (PDE) enzyme family (Figure 20–3). Since the phosphodiesterases hydrolyze cyclic nucleotides, this inhibition results in higher concentrations of intracellular cAMP and, in some tissues, cGMP. This effect could explain the cardiac stimulation and smooth muscle relaxation produced by these drugs as well as decreased release of inflammatory mediators from mast cells. PDE4 appears to be the isoform most directly involved in the airway actions of methylxanthines. More selective inhibitors of PDE4 have been developed in an effort to reduce toxicity while maintaining therapeutic efficacy. Thus far, such selective PDE4 inhibitors have proved more effective in chronic obstructive pulmonary disease (COPD) than in asthma. A major adverse effect of the PDE4-selective drugs is nausea and vomiting.

Another proposed mechanism is the inhibition of cell surface receptors for adenosine. These receptors modulate adenyl cyclase activity, and adenosine has been shown to cause contraction of isolated airway smooth muscle and to provoke histamine release from airway mast cells. These effects are antagonized by theophylline, which blocks cell surface adenosine receptors. It has also been shown, however, that xanthine derivatives devoid of adenosine-antagonistic properties (eg, enprofylline) may be more potent than theophylline in inhibiting bronchoconstriction in asthmatic subjects.

Pharmacodynamics of Methylxanthines

The methylxanthines have effects on the central nervous system, kidney, and cardiac and skeletal muscle as well as smooth muscle. Of the three agents, theophylline is most selective in its smooth muscle effects, while caffeine has the most marked central nervous system effects.

Central Nervous System Effects
In low and moderate doses, the methylxanthines—especially caffeine—cause mild cortical arousal with increased alertness and deferral of fatigue. The caffeine contained in beverages—e.g., 100 mg in a cup of coffee—is sufficient to cause nervousness and insomnia in unusually sensitive individuals and slight bronchodilation in patients with asthma. At very high doses, medullary stimulation and convulsions may occur and can lead to death; theophylline has been used successfully in suicide attempts. Nervousness and tremor are primary side effects in patients taking large doses of aminophylline for asthma.

Cardiovascular Effects

The methylxanthines have direct positive chronotropic and inotropic effects on the heart. At low concentrations, these effects appear to result from increased catecholamine release that is caused by inhibition of presynaptic adenosine receptors. At higher concentrations (> 10 μmol/L), calcium influx may be increased directly through the increase in cAMP that results from inhibition of phosphodiesterase. At very high concentrations (> 100 μmol/L), sequestration of calcium by the sarcoplasmic reticulum is impaired. In unusually sensitive individuals, consumption of a few cups of coffee may result in arrhythmias, but in most people even parenteral administration of higher doses of the methylxanthines produces only sinus tachycardia and increased cardiac output. In large doses, these agents also relax vascular smooth muscle except in cerebral blood vessels, where they cause contraction. Ordinary consumption of coffee and other methylxanthine-containing beverages, however, usually raises the peripheral vascular resistance and blood pressure slightly, probably through the release of catecholamines.

Methylxanthines decrease blood viscosity and may improve blood flow under certain conditions. The mechanism of this action is not well defined, but the effect is exploited in the treatment of intermittent claudication with pentoxifylline, a dimethylxanthine agent. However, no evidence suggests that this therapy is superior to other approaches.

Effects on Gastrointestinal Tract

The methylxanthines stimulate secretion of both gastric acid and digestive enzymes. However, even decaffeinated coffee has a potent stimulant effect on secretion, which means that the primary secretagogue in coffee is not caffeine.

Effects on Kidney

The methylxanthines—especially theophylline—are weak diuretics. This effect may involve both increased glomerular filtration and reduced tubular sodium reabsorption. The diuresis is not of sufficient magnitude to be therapeutically useful.

Effects on Smooth Muscle

The bronchodilation produced by the methylxanthines is the major therapeutic action in asthma. Tolerance does not develop, but adverse effects, especially in the central nervous system, may limit the dose (see below). In addition to this direct effect on the airway smooth muscle, these agents—in sufficient concentration—inhibit antigen-induced release of histamine from lung tissue; their effect on mucociliary transport is unknown.

Effects on Skeletal Muscle

The therapeutic actions of the methylxanthines may not be confined to the airways, for they also
strengthen the contractions of isolated skeletal muscle in vitro and have potent effects in improving contractility and in reversing fatigue of the diaphragm in patients with chronic obstructive lung diseases. This effect on diaphragmatic performance—rather than an effect on the respiratory center—may account for theophylline's ability to improve the ventilatory response to hypoxia and to diminish dyspnea even in patients with irreversible airflow obstruction.

Clinical Use of Methylxanthines

Of the xanthines, theophylline is the most effective bronchodilator, and it has been shown repeatedly both to relieve airflow obstruction in acute asthma and to reduce the severity of symptoms and time lost from work or school in patients with chronic asthma. Theophylline base is only slightly soluble in water, so it has been administered as several salts containing varying amounts of theophylline base. Most preparations are well absorbed from the gastrointestinal tract, but absorption of rectal suppositories is unreliable.

Improvements in theophylline preparations have come from alterations in the physical state of the drugs rather than from new chemical formulations. For example, several companies now provide anhydrous theophylline in a microcrystalline form in which the increased surface area facilitates solubilization for complete and rapid absorption after oral administration. In addition, several sustained-release preparations (eg, Slo-Phyllin, Theo-Dur) are available and can produce therapeutic blood levels of the theophylline for 12 hours or more. These preparations offer the advantages of less frequent drug administration, less fluctuation of theophylline blood levels, and, in many cases, more effective treatment of nocturnal bronchospasm.

Theophylline should only be used where methods to measure theophylline blood levels are available because it has a narrow therapeutic window and its therapeutic and toxic effects are related to its plasma concentrations. Improvement in pulmonary function is correlated with plasma concentration in the range of 5–20 mg/L. Anorexia, nausea, vomiting, abdominal discomfort, headache, and anxiety occur at concentrations of 15 mg/L in some patients and become common at concentrations greater than 20 mg/L. Higher levels (> 40 mg/L) may cause seizures or arrhythmias; these may not be preceded by gastrointestinal or neurologic warning symptoms.

The plasma clearance of theophylline varies widely. Theophylline is metabolized by the liver, so usual doses may lead to toxic concentrations of the drug in patients with liver disease. Conversely, clearance may be increased through the induction of hepatic enzymes by cigarette smoking or by changes in diet. In normal adults, the mean plasma clearance is 0.69 mL/kg/min. Children clear theophylline faster than adults (1–1.5 mL/kg/min). Neonates and young infants have the slowest clearance (see Chapter 60: Special Aspects of Perinatal & Pediatric Pharmacology). Even when maintenance doses are altered to correct for the above factors, plasma concentrations vary widely.

Theophylline improves long-term control of asthma when taken as the sole maintenance treatment or when added to inhaled corticosteroids. It is inexpensive, and it can be taken orally. Its use, however, also requires occasional measurement of plasma levels; it often causes unpleasant minor side effects (especially insomnia); and accidental or intentional overdose can result in severe toxicity or death. For oral therapy with the prompt-release formulation, the usual dose is 3–4 mg/kg of theophylline every 6 hours. Changes in dosage will result in a new steady state concentration of theophylline in 1–2 days, so the dose may be increased at intervals of 2–3 days until therapeutic plasma concentrations are achieved (10–20 mg/L) or until adverse effects develop.

Antimuscarinic Agents
Leaves from *Datura stramonium* have been used in treating asthma for hundreds of years. Interest in the potential value of antimuscarinic agents increased with demonstration of the importance of the vagus in bronchospastic responses of laboratory animals and by the development of a potent antimuscarinic agent that is poorly absorbed after aerosol administration to the airways and is therefore not associated with systemic atropine effects.

**Mechanism of Action**

Muscarinic antagonists competitively inhibit the effect of acetylcholine at muscarinic receptors (see Chapter 8: Cholinoceptor-Blocking Drugs). In the airways, acetylcholine is released from efferent endings of the vagus nerves, and muscarinic antagonists can effectively block the contraction of airway smooth muscle and the increase in secretion of mucus that occurs in response to vagal activity (Figure 20–2). Very high concentrations—well above those achieved even with maximal therapy—are required to inhibit the response of airway smooth muscle to nonmuscarinic stimulation. This selectivity of muscarinic antagonists accounts for their usefulness as investigative tools in examining the role of parasympathetic pathways in bronchomotor responses but limits their usefulness in preventing bronchospasm. In the doses given, antimuscarinic agents inhibit only that portion of the response mediated by muscarinic receptors, and the involvement of parasympathetic pathways in bronchospastic responses appears to vary among individuals.

**Clinical Use of Muscarinic Antagonists**

Antimuscarinic agents are effective bronchodilators. When given intravenously, atropine, the prototypical muscarinic antagonist, causes bronchodilation at a lower dose than that needed to cause an increase in heart rate. The selectivity of atropine's effect can be increased further by administering the drug by inhalation or by use of a more selective quaternary ammonium derivative of atropine, *ipratropium bromide*. Ipratropium can be delivered in high doses to muscarinic receptors in the airways because this compound is poorly absorbed and does not readily enter the central nervous system. Studies with this agent have shown that the degree of involvement of parasympathetic pathways in bronchomotor responses varies among subjects. In some, bronchoconstriction is inhibited effectively; in others, only modestly. The failure of higher doses of the muscarinic antagonist to further inhibit the response in these individuals indicates that mechanisms other than parasympathetic reflex pathways must be involved.

Even in the subjects least protected by this antimuscarinic agent, however, the bronchodilation and partial inhibition of provoked bronchoconstriction are of potential clinical value, and antimuscarinic agents are valuable for patients intolerant of inhaled β-agonist agents. While antimuscarinic drugs appear to be slightly less effective than β-agonist agents in reversing asthmatic bronchospasm, the addition of ipratropium enhances the bronchodilation produced by nebulized albuterol in acute severe asthma.

Ipratropium appears to be at least as effective in patients with chronic obstructive pulmonary disease that includes a partially reversible component. A longer-acting, selective antimuscarinic agent, *tiotropium*, is in clinical trials as treatment for COPD. This drug's 24-hour duration of action is a potentially important advantage.

**Corticosteroids**

**Mechanism of Action**

Corticosteroids have been used to treat asthma since 1950 and are presumed to act by their broad
anti-inflammatory efficacy, mediated in part by inhibition of production of inflammatory cytokines (see Chapter 39: Adrenocorticosteroids & Adrenocortical Antagonists). They do not relax airway smooth muscle directly but reduce bronchial reactivity and reduce the frequency of asthma exacerbations if taken regularly. Their effect on airway obstruction may be due in part to their potentiation of the effects of β-receptor agonists, but their most important action is their inhibition of the lymphocytic, eosinophilic airway mucosal inflammation of asthmatic airways.

Clinical Use of Corticosteroids

Clinical studies of corticosteroids consistently show them to be effective in improving all indices of asthma control—severity of symptoms, tests of airway caliber and bronchial reactivity, frequency of exacerbations, and quality of life. Because of severe adverse effects when given chronically, oral and parenteral corticosteroids are reserved for patients who require urgent treatment, ie, those who have not improved adequately with bronchodilators or who experience worsening symptoms despite maintenance therapy. Regular or "controller" therapy is maintained with aerosol corticosteroids.

Urgent treatment is often begun with an oral dose of 30–60 mg of prednisone per day or an intravenous dose of 1 mg/kg of methylprednisolone every 6 hours; the daily dose is decreased gradually after airway obstruction has improved. In most patients, systemic corticosteroid therapy can be discontinued in a week or 10 days, but in other patients symptoms may worsen as the dose is decreased to lower levels. Because adrenal suppression by corticosteroids is related to dose and because secretion of corticosteroids has a diurnal variation, it has become customary to administer corticosteroids early in the morning, after endogenous ACTH secretion has peaked. For prevention of nocturnal asthma, however, oral or inhaled corticosteroids are most effective when given in the late afternoon.

Aerosol treatment is the most effective way to decrease the systemic adverse effects of corticosteroid therapy. The introduction of lipid-soluble corticosteroids such as beclomethasone, budesonide, flunisolide, fluticasone, and triamcinolone makes it possible to deliver corticosteroids to the airways with minimal systemic absorption. An average daily dose of four puffs twice daily of beclomethasone (400 μg/d) is equivalent to about 10–15 mg/d of oral prednisone for the control of asthma, with far fewer systemic effects. Indeed, one of the cautions in switching patients from oral to inhaled corticosteroid therapy is to taper oral therapy slowly to avoid precipitation of adrenal insufficiency. In patients requiring continued prednisone treatment despite inhalation of standard doses of an aerosol corticosteroid, higher doses appear to be more effective; inhaled dosages up to 2000 μg/d of fluticasone are effective in weaning patients from chronic prednisone therapy. While these high doses of inhaled steroids may cause adrenal suppression, the risks of systemic toxicity from chronic use appear negligible compared with those of the oral corticosteroid therapy they replace. A special problem caused by inhaled topical corticosteroids is the occurrence of oropharyngeal candidiasis. The risk of this complication can be reduced by having patients gargle water and spit after each inhaled treatment. Hoarseness can also result from a direct local effect of inhaled corticosteroids on the vocal cords. These agents are remarkably free of other short-term complications in adults but may increase the risks of osteoporosis and cataracts over the long term. In children, inhaled corticosterone therapy has been shown to slow the rate of growth, but asthma itself delays puberty, and there is no evidence that inhaled corticosteroid therapy influences adult height.

Chronic use of inhaled corticosteroids effectively reduces symptoms and improves pulmonary function in patients with mild asthma. Such use also reduces or eliminates the need for oral corticosteroids in patients with more severe disease. In contrast to β-stimulant agents and theophylline, chronic use of inhaled corticosteroids reduces bronchial reactivity. Because of the
efficacy and safety of inhaled corticosteroids, they are now routinely prescribed for patients who require more than occasional inhalations of a β₂ agonist for relief of symptoms. This therapy is continued for 10–12 weeks and then withdrawn to determine if more prolonged therapy is needed.

Inhaled corticosteroids are not curative. In most patients, the manifestations of asthma return within a few weeks after stopping therapy even if they have been taken in high doses for 2 years or longer.

Cromolyn & Nedocromil

Cromolyn sodium (disodium cromoglycate) and nedocromil sodium are stable but extremely insoluble salts (see structures below). When used as aerosols (metered-dose inhalers), they effectively inhibit both antigen- and exercise-induced asthma, and chronic use (four times daily) slightly reduces the overall level of bronchial reactivity. However, these drugs have no effect on airway smooth muscle tone and are ineffective in reversing asthmatic bronchospasm; they are only of value when taken prophylactically.

![Cromolyn sodium](image)

![Nedocromil sodium](image)

Cromolyn is poorly absorbed from the gastrointestinal tract and must be inhaled as a microfine powder or aerosolized solution. Nedocromil also has a very low bioavailability and is available only in metered-dose aerosol form.

Mechanism of Action

Cromolyn and nedocromil differ structurally but are thought to share a common mechanism of action, an alteration in the function of delayed chloride channels in the cell membrane, inhibiting cellular activation. This action on airway nerves is thought to be responsible for nedocromil's inhibition of cough; on mast cells, for inhibition of the early response to antigen challenge; and on eosinophils, for inhibition of the inflammatory response to inhalation of allergens. The inhibitory effect on mast cells appears to be specific for cell type, since cromolyn has little inhibitory effect on mediator release from human basophils. It may also be specific for different organs, since cromolyn inhibits mast cell degranulation in human and primate lung but not in skin. This in turn may reflect known differences in mast cells found in different sites, as in their neutral protease content.
Until recently, the idea that cromolyn inhibits mast cell degranulation was so well accepted that the inhibition of a response by cromolyn was thought to indicate the involvement of mast cells in the response. This simplistic idea has been overturned in part by the finding that cromolyn and nedocromil inhibit the function of cells other than mast cells and in part by the finding that nedocromil inhibits appearance of the late response even when given after the early response to antigen challenge, ie, after mast cell degranulation has occurred.

Clinical Use of Cromolyn & Nedocromil

In short-term clinical trials, pretreatment with cromolyn or nedocromil blocks the bronchoconstriction caused by antigen inhalation, by exercise, by aspirin, and by a variety of causes of occupational asthma. This acute protective effect of a single treatment makes cromolyn useful for administration shortly before exercise or before unavoidable exposure to an allergen.

When taken regularly (two to four puffs two to four times daily) by patients with perennial asthma, both agents reduce symptomatic severity and the need for bronchodilator medications. These drugs are neither as potent nor as predictably effective as inhaled corticosteroids. In general, young patients with extrinsic asthma are most likely to respond favorably. At present, the only way of determining whether a patient will respond is by a therapeutic trial for 4 weeks. The addition of nedocromil to a standard dose of an inhaled corticosteroid appears to improve asthma control.

Cromolyn solution is also useful in reducing symptoms of allergic rhinoconjunctivitis. Applying the solution by nasal spray or eye drops several times a day is effective in about 75% of patients, even during the peak pollen season.

Because the drugs are so poorly absorbed, adverse effects of cromolyn and nedocromil are minor and are localized to the sites of deposition. These include such symptoms as throat irritation, cough, mouth dryness, chest tightness, and wheezing. Some of these symptoms can be prevented by inhaling a $\beta_2$-adrenoceptor agonist before cromolyn or nedocromil treatment. Serious adverse effects are rare. Reversible dermatitis, myositis, or gastroenteritis occurs in fewer than 2% of patients, and a very few cases of pulmonary infiltration with eosinophilia and anaphylaxis have been reported. This lack of toxicity accounts for cromolyn's widespread use in children, especially those at ages of rapid growth. For children who have difficulty coordinating the use of the inhaler device, cromolyn may be given by aerosol of a 1% solution.

Leukotriene Pathway Inhibitors

Because of the evidence of leukotriene involvement in many inflammatory diseases (see Chapter 18: The Eicosanoids: Prostaglandins, Thromboxanes, Leukotrienes, & Related Compounds) and in anaphylaxis, considerable effort has been expended on the development of drugs that block the synthesis of these arachidonic acid derivatives or their receptors. Leukotrienes result from the action of 5-lipoxygenase on arachidonic acid and are synthesized by a variety of inflammatory cells in the airways, including eosinophils, mast cells, macrophages, and basophils. Leukotriene B4 is a potent neutrophil chemoattractant, and LTC4 and LTD4 exert many effects known to occur in asthma, including bronchoconstriction, increased bronchial reactivity, mucosal edema, and mucus hypersecretion. Early studies established that antigen challenge of sensitized human lung tissue results in the generation of leukotrienes, while other studies of human subjects have shown that inhalation of leukotrienes causes not only bronchoconstriction but also an increase in bronchial reactivity to histamine that persists for several days.

Two approaches to interrupting the leukotriene pathway have been pursued: inhibition of 5-
lipoxygenase, thereby preventing leukotriene synthesis; and inhibition of the binding of leukotriene D4 to its receptor on target tissues, thereby preventing its action. Efficacy in blocking airway responses to exercise and to antigen challenge has been shown for drugs in both categories: zileuton, a 5-lipoxygenase inhibitor, and zafirlukast and montelukast, LTD4-receptor antagonists. All have been shown to be effective when taken regularly in outpatient clinical trials. Their effects on symptoms, airway caliber, bronchial reactivity, and airway inflammation are less marked than the effects of inhaled corticosteroids, but they are almost equally effective in reducing the frequency of exacerbations. Their principal advantage is that they are taken orally; some patients—especially children—comply poorly with inhaled therapies. Montelukast is approved for children as young as 6 years of age.

![Zafirlukast](image)

Some patients appear to have particularly favorable responses, but no clinical features allow identification of "responders" before a trial of therapy. In the USA, zileuton is approved for use in an oral dosage of 600 mg given four times daily; zafirlukast, 20 mg twice daily; and montelukast, 10 mg once daily.

Trials with leukotriene inhibitors have demonstrated an important role for leukotrienes in aspirin-induced asthma. It has long been known that 5–10% of asthmatics are exquisitely sensitive to aspirin, so that ingestion of even a very small dose causes profound bronchoconstriction and symptoms of systemic release of histamine, such as flushing and abdominal cramping. Because this reaction to aspirin is not associated with any evidence of allergic sensitization to aspirin or its metabolites, and because it is produced by any of the nonsteroidal anti-inflammatory agents, it is thought to result from inhibition of prostaglandin synthetase, shifting arachidonic acid metabolism from the prostaglandin to the leukotriene pathway. Support for this idea was provided by the
demonstration that leukotriene pathway inhibitors impressively reduce the response to aspirin challenge and improve overall control of asthma on a day-to-day basis.

Of these agents, zileuton is the least prescribed because of the requirement of four times daily dosing and because of occasional liver toxicity. The receptor antagonists appear to be safe to use. Reports of Churg-Strauss syndrome (a systemic vasculitis characterized by worsening asthma, pulmonary infiltrates, and eosinophilia) appear to have been coincidental, with the syndrome unmasked by the reduction in prednisone dosage made possible by the addition of zafirlukast or montelukast.

Other Drugs in the Treatment of Asthma

Anti-IgE Monoclonal Antibodies

An entirely new approach to the treatment of asthma exploits advances in molecular biology to target IgE antibody. From a collection of monoclonal antibodies raised in mice against IgE antibody itself, a monoclonal antibody was selected that appeared to be targeted against the portion of IgE that binds to its receptors (Fce-R1 and -R2 receptors) on mast cells and other inflammatory cells. **Omalizumab** (anti-IgE Mab) inhibits the binding of IgE to mast cells but does not activate IgE already bound to these cells and thus does not provoke mast cell degranulation. In mice, it also appears to inhibit IgE synthesis by B lymphocytes. The murine antibody has been genetically "humanized" by replacing all but a small fraction of its amino acids with those found in human proteins, and it does not appear to cause sensitization when given to human subjects.

Studies of omalizumab in asthmatic volunteers showed that its administration over 10 weeks lowered plasma IgE to undetectable levels and significantly reduced the magnitude of both the early and the late bronchospastic responses to antigen challenge. Clinical trials have shown repeated intravenous or subcutaneous injection of anti-IgE MAb to lessen asthma severity and reduce the corticosteroid requirement in patients with moderate to severe disease, especially those with a clear environmental antigen precipitating factor, and to improve nasal and conjunctival symptoms in patients with perennial or seasonal allergic rhinitis.

Calcium Channel Blockers

Each of the cell functions that may become abnormal in patients with asthma depends to some degree on the movement of calcium into cells. The calcium channel blockers have no effect on baseline airway diameter but do significantly inhibit the airway narrowing that is induced by various stimuli. In patients, both **nifedipine** and **verapamil** given by inhalation significantly inhibited the bronchoconstriction induced by a variety of stimuli. However, both drugs were much less effective than inhaled albuterol.

Nitric Oxide Donors

Preliminary studies in animals suggest that airway smooth muscle, like that in the vasculature, is effectively relaxed by nitric oxide. This very lipophilic drug can be inhaled as a gas in acute asthma and dilates the pulmonary blood vessels as well as the airway smooth muscle. Although nitric oxide itself—or nitric oxide donors—may prove of value in acute severe asthma, it appears likely that they will be more useful in pulmonary hypertension (for which nitric oxide is already approved).

Possible Future Therapies
The rapid advance in the scientific description of the immunopathogenesis of asthma has spurred the development of many new therapies targeting different sites in the immune cascade. These include monoclonal antibodies directed against cytokines (IL-4, IL-5, IL-8), antagonists of cell adhesion molecules, protease inhibitors, and immunomodulators aimed at shifting CD4 lymphocytes from the Th2 to the Th1 phenotype. There is evidence that asthma may be aggravated—or even caused—by chronic airway infection with *Chlamydia pneumoniae* or *Mycoplasma pneumoniae*. This may explain the reports of benefit from treatment with macrolide antibiotics and, if confirmed, would stimulate the development of new diagnostic methods and antimicrobial therapies.

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Clinical Pharmacology of Drugs Used in the Treatment of Asthma

**Bronchodilators**

Patients with mild asthma and only occasional symptoms require no more than an inhaled β-receptor agonist (eg, albuterol) on an "as-needed" basis. If symptoms require frequent inhalations (more often than twice a week), or if nocturnal symptoms occur, additional treatment is needed, preferably with an inhaled anti-inflammatory agent such as a corticosteroid or cromolyn, or with oral therapy with a leukotriene receptor antagonist. Theophylline is now largely reserved for patients in whom symptoms remain poorly controlled despite the combination of regular treatment with an inhaled anti-inflammatory agent and as-needed use of a β2 agonist. If the addition of theophylline fails to improve symptoms or if adverse effects become bothersome, it is important to check the plasma level of theophylline to be sure it is in the therapeutic range (10–20 mg/L).

**Corticosteroids**

If asthmatic symptoms occur frequently or if significant airflow obstruction persists despite bronchodilator therapy, inhaled corticosteroids should be started. For patients with severe symptoms or severe airflow obstruction (eg, FEV1 < 1.5 L), initial treatment with oral corticosteroid (eg, 30 mg/d of prednisone for 3 weeks) is appropriate. Once clinical improvement is noted, inhaled corticosteroid treatment should be started and the oral dose reduced to the minimum necessary to control symptoms. For patients with milder symptoms but still inadequately controlled by as-needed use of an inhaled bronchodilator, corticosteroids may be initiated by the inhaled route.

In patients whose symptoms are inadequately controlled by a standard dose of an inhaled corticosteroid, the addition of a long-acting inhaled β-receptor agonist (salmeterol, formoterol) is more effective than is doubling the dose of the inhaled corticosteroid. The improvement in clinical symptoms and peak flow is usually prompt and sustained. In patients on such a combined treatment regimen, it is important to provide explicit instructions that a standard, short-acting inhaled β agonist, like albuterol, be used for relief of acute symptoms. It is also important that the patient not stop the inhaled corticosteroid, continuing only the long-acting βagonist, because exacerbations are not prevented by this monotherapy. For this reason—and because long-acting βagonists appear to enhance the local but not the systemic actions of inhaled corticosteroids—inhalers containing both agents have been developed (see Preparations Available).
Cromolyn & Nedocromil

Cromolyn or nedocromil may be considered as an alternative to inhaled corticosteroids in patients with symptoms occurring more than twice a week or who are wakened from sleep by asthma. They may also be useful in patients whose symptoms occur seasonally or after clear-cut inciting stimuli such as exercise or exposure to animal danders or irritants. In patients whose symptoms are continuous or occur without an obvious inciting stimulus, the value of these drugs can only be established with a therapeutic trial of inhaled drug four times a day for 4 weeks. If the patient responds to this therapy, the dose can be reduced. Maintenance therapy with cromolyn appears to be as effective as maintenance therapy with theophylline and, because of concerns over the possible long-term toxicity of systemic absorption of inhaled corticosteroids, has become widely used for treating children in the USA.

Muscarinic Antagonists

Inhaled muscarinic antagonists have so far earned a limited place in the treatment of asthma. When adequate doses are given, their effect on baseline airway resistance is nearly as great as that of the sympathomimetic drugs. The airway effects of antimuscarinic and sympathomimetic drugs given in full doses have been shown to have significant additive effects only in patients with severe airflow obstruction who present for emergency care. Antimuscarinic agents appear to be of significant value in chronic obstructive pulmonary disease—perhaps more so than in asthma. They are useful as alternative therapies for patients intolerant of β-adrenoceptor agonists.

When muscarinic antagonists are used for long-term treatment, they appear to be effective bronchodilators. Although it was predicted that muscarinic antagonists might dry airway secretions, direct measurements of fluid volume secretion from single airway submucosal glands in animals show that atropine decreases secretory rates only slightly; however, the drug does prevent excessive secretion caused by vagal reflex stimulation. No cases of inspissation of mucus have been reported following administration of these drugs.

Other Anti-Inflammatory Therapies

Some recent reports suggest that agents commonly used to treat rheumatoid arthritis might also be used to treat patients with chronic steroid-dependent asthma. The development of an alternative treatment is important, since chronic treatment with oral corticosteroids may cause osteoporosis, cataracts, glucose intolerance, worsening of hypertension, and cushingoid changes in appearance. Initial studies suggested that oral methotrexate or gold salt injections were beneficial in prednisone-dependent asthmatics, but subsequent studies did not confirm this promise. The benefit from treatment with cyclosporine seems real. However, this drug's great toxicity makes this finding only a source of hope that other immunomodulatory therapies will ultimately be developed for the small proportion of patients whose asthma can be managed only with high oral doses of prednisone.

Management of Acute Asthma

The treatment of acute attacks of asthma in patients reporting to the hospital requires more continuous assessment and repeated objective measurement of lung function. For patients with mild attacks, inhalation of a β-receptor agonist is as effective as subcutaneous injection of epinephrine. Both of these treatments are more effective than intravenous administration of aminophylline. Severe attacks require treatment with oxygen, frequent or continuous administration of aerosolized albuterol, and systemic treatment with prednisone or methylprednisolone (0.5 mg/kg every 6 hours). Even this aggressive treatment is not invariably effective, and patients must be watched closely for
signs of deterioration. Intubation and mechanical ventilation of asthmatic patients cannot be undertaken lightly but may be lifesaving if respiratory failure supervenes.

Preparations Available

Sympathomimetics Used in Asthma

**Albuterol** (generic, Proventil, Ventolin, others)

Inhalant: 90 µg/puff aerosol; 0.083, 0.5% solution for nebulization

Oral: 2, 4 mg tablets; 2 mg/5 mL syrup

Oral sustained-release: 4, 8 mg tablets

**Albuterol/Ipratropium** (Combivent, DuoNeb)

Inhalant: 103 µg albuterol + 18 µg ipratropium/ puff; 3 mg albuterol + 0.5 mg ipratropium/3 mL solution for nebulization

**Bitolterol** (Tornalate)

Inhalant: 0.2% solution for nebulization

**Ephedrine** (generic)

Oral: 25 mg capsules

Parenteral: 50 mg/mL for injection

**Epinephrine** (generic, Adrenalin, others)

Inhalant: 1, 10 mg/mL for nebulization; 0.22 mg epinephrine base aerosol

Parenteral: 1:10,000 (0.1 mg/mL), 1:1000 (1 mg/mL)

**Formoterol** (Foradil)

Inhalant: 12 µg/puff aerosol; 12 µg/unit inhalant powder

**Isoetharine** (generic)

Inhalant: 1% solution for nebulization

**Isoproterenol** (generic, Isuprel, others)

Inhalant: 0.5, 1% for nebulization; 80, 131 µg/puff aerosols
Parenteral: 0.02, 0.2 mg/mL for injection

**Levalbuterol** (Xenopex)

Inhalant: 0.31, 0.63, 1.25 mg/3 mL solution

**Metaproterenol** (Alupent, generic)

Inhalant: 0.65 mg/puff aerosol in 7, 14 g containers; 0.4, 0.6, 5% for nebulization

**Pirbuterol** (Maxair)

Inhalant: 0.2 mg/puff aerosol in 80 and 300 dose containers

**Salmeterol** (Serevent)

Inhalant aerosol: 25 \(\mu\)g salmeterol base/puff in 60 and 120 dose containers

Inhalant powder: 50 \(\mu\)g/unit

**Salmeterol/Fluticasone** (Advair Diskus)

Inhalant: 100, 250, 500 \(\mu\)g fluticasone + 50 \(\mu\)g salmeterol/unit

**Terbutaline** (Brethine, Bricanyl)

Inhalant: 0.2 mg/puff aerosol

Oral: 2.5, 5 mg tablets

Parenteral: 1 mg/mL for injection

Aerosol Corticosteroids (See Also Chapter 39: Adrenocorticosteroids & Adrenocortical Antagonists.)

**Beclomethasone** (QVAR, Vanceril)

Aerosol: 40, 80 \(\mu\)g/puff in 200 dose containers

**Budesonide** (Pulmicort)

Aerosol powder: 160 \(\mu\)g/activation

**Flunisolide** (AeroBid)

Aerosol: 250 \(\mu\)g/puff in 100 dose container

**Fluticasone** (Flovent)

Aerosol: 44, 110, and 220 \(\mu\)g/puff in 120 dose container; powder, 50, 100, 250 \(\mu\)g/activation
**Fluticasone/Salmeterol** (Advair Diskus)
Inhalant: 100, 250, 500 μg fluticasone + 50 μg salmeterol/unit

**Triamcinolone** (Azmacort)
Aerosol: 100 μg/puff in 240 dose container

**Leukotriene Inhibitors**
**Montelukast** (Singulair)
Oral: 10 mg tablets; 4, 5 mg chewable tablets; 4 mg/packet granules

**Zafirlukast** (Accolate)
Oral: 10, 20 mg tablets

**Zileuton** (Zyflo)
Oral: 600 mg tablets

**Cromolyn Sodium & Nedocromil Sodium**

**Cromolyn sodium**
Pulmonary aerosol (generic, Intal): 800 μg/puff in 200 dose container; 20 mg/2 mL for nebulization (for asthma)
Nasal aerosol (Nasalcrom):* 5.2 mg/puff (for hay fever)
Oral (Gastrocrom): 100 mg/5 mL concentrate (for gastrointestinal allergy)

**Nedocromil sodium** (Tilade)
Pulmonary aerosol: 1.75 mg/puff in 112 metered-dose container
*OTC preparation.

**Methylxanthines: Theophylline & Derivatives**

**Aminophylline** (theophylline ethylenediamine, 79% theophylline) (generic, others)
Oral: 105 mg/5 mL liquid; 100, 200 mg tablets
Oral sustained-release: 225 mg tablets
Rectal: 250, 500 mg suppositories
Parenteral: 250 mg/10 mL for injection
**Theophylline** (generic, Elixophyllin, Slo-Phyllin, Uniphyl, Theo-Dur, Theo-24, others)

Oral: 100, 125, 200, 250, 300 mg tablets; 100, 200 mg capsules; 26.7, 50 mg/5 mL elixirs, syrups, and solutions

Oral sustained-release, 8–12 hours: 50, 60, 75, 100, 125, 130, 200, 250, 260, 300 mg capsules

Oral sustained-release, 8–24 hours: 100, 200, 300, 450 mg tablets

Oral sustained-release, 12 hours: 100, 125, 130, 200, 250, 260, 300 mg capsules

Oral sustained-release, 12–24 hours: 100, 200, 300 tablets

Oral sustained-release, 24 hours: 100, 200, 300 tablets and capsules; 400, 600 mg tablets

Parenteral: 200, 400, 800 mg/container, theophylline and 5% dextrose for injection

Other Methylxanthines

**Dyphylline** (generic, other)

Oral: 200, 400 mg tablets; 33.3, 53.3 mg/5 mL elixir

Parenteral: 250 mg/mL for injection

**Oxtriphylline** (generic, Choledyl)

Oral: equivalent to 64, 127, 254, 382 mg theophylline tablets; 32, 64 mg/5 mL syrup

**Pentoxifylline** (generic, Trental)

Oral: 400 mg tablets and controlled-release tablets

*Note:* Pentoxifylline is labeled for use in intermittent claudication only.

**Antimuscarinic Drugs Used in Asthma**

**Ipratropium** (generic, Atrovent)

Aerosol: 18 mcg/puff in 200 metered-dose inhaler; 0.02% (500 mcg/vial) for nebulization

Nasal spray: 21, 42 mcg/spray

**Antibody**

**Omalizumab** (Xolair)

Powder for SC injection, 202.5 mg