those due to *Staphylococcus aureus* and *Pseudomonas aeruginosa*. In advanced disease, more than 80% of patients harbor *Pseudomonas*. It is of interest that atopic patients with cystic fibrosis are more likely to have persistent colonization with *Pseudomonas* than are non-atopic patients with cystic fibrosis.

Colonization by *Aspergillus* species is also common in cases of cystic fibrosis. In the presence of asthma and cystic fibrosis, it is difficult to make a diagnosis of allergic bronchopulmonary aspergillosis because of overlap in clinical and laboratory features. Studies suggest a 5% to 20% incidence of allergic bronchopulmonary aspergillosis in patients who have cystic fibrosis. Positive sputum cultures, eosinophilia, precipitins to *Aspergillus fumigatus*, immediate or dual skin test reactivity, elevated total serum IgE levels and IgG antibodies to *Aspergillus* antigens are useful screening tests for allergic bronchopulmonary aspergillosis in patients with cystic fibrosis. Aspergillosis should be considered whenever significant pulmonary manifestations of cystic fibrosis do not respond to antimicrobial therapy. Clinical improvement and improved pulmonary function following corticosteroid administration may suggest the diagnosis of allergic bronchopulmonary aspergillosis.

Some but not all investigators have reported depressed leukocyte locomotion in cases of cystic fibrosis. Circulating immune complexes were also found to be increased in this disease, particularly during acute infections. The relevance of these findings to the pathogenesis and course of cystic fibrosis remains to be defined.

It is important for all physicians to recognize the immunologic aspects of cystic fibrosis, the similarity of its early manifestations to atopy, the frequent coexistence of atopy and cystic fibrosis and the possible enhancing effect of atopy to fungal growth. Increased understanding of immunologic mechanisms in cystic fibrosis may lead to improved patient management in the future.

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β-Adrenergic Agonists 1984

IN THE PAST DECADE several new drugs have been developed and marketed for the treatment of bronchial asthma that have improved β_2-specificity (bronchodilation greater than cardiac stimulation), that can be given by several routes of administration (oral, inhalation and parenteral) and that have a more prolonged duration of action (four to six hours) than epinephrine and isoproterenol. These improvements have come about by altering the basic catecholamine molecule. Changing the catechol nucleus to a resorcinol, such as metaproterenol sulfate or terbutaline sulfate, or salicyl alcohol (albuterol) decreases the agonists' susceptibility to enzymatic degradation resulting in more prolonged action and effective oral absorption. Increasing the size of the amino side chain substituent increases β_2-selectivity. β_2-Agonists are thought to have several actions in addition to bronchodilation, which make them useful in asthma, including inhibition of lung mast cell degranulation, increased mucociliary clearance and decreasing fatigability of diaphragmatic muscle.

Several recent studies have compared β-adrenergic drugs with theophylline for both acute and recurrent asthma. β-Agonists are superior to theophylline in alleviating acute asthma, whereas they compare favorably in controlling asthmatic symptoms over a several-week trial. In addition, when given simultaneously the effect of these drugs may be additive. Corticosteroids appear to restore β-agonist responsiveness in those who have become refractory, possibly by an increase in the rate of β-receptor synthesis.

In the oral form the newer β_2 drugs are more potent, selective and longer acting than ephedrine, which currently has little place in asthma therapy. Terbutaline (5 mg), fenoterol (5 mg) and albuterol (4 mg) are all comparable bronchodilators and more potent and selective than metaproterenol (20 mg). Although the efficacy of these agents has been shown in children 6 to 14 years of age, only metaproterenol is currently approved by the Food and Drug Administration for this age group. Epinephrine remains the most commonly used injectable sympathomimetic whereas terbutaline is also effective subcutaneously. Although theoretically advantageous, particularly in those with cardiac disease, terbutaline has not proved superior in children with acute asthma. Isoproterenol given intravenously is a useful treatment in children with respiratory failure and has not yet been replaced by the newer β_2-agonists.

The aerosol route of administration provides the greatest selectivity and effectiveness for β_2-agonists. Thus aerosolized metaproterenol from a metered-dose inhaler produces greater bronchodilation than the orally given form, though the dosage is only 10% to 20% of the oral dose. The onset of action and peak response are more rapid than with the oral form and side effects are less common, possibly because less drug is needed. The aerosol is also superior to the orally given form for exercise-induced asthma. Aerosols can be delivered by metered-dose inhaler or compressed-air jet nebulizer. Recently, auxiliary delivery systems using the metered-dose inhaler with spacers or reservoirs have been developed and show promise particularly in younger patients. Metaproterenol, terbutaline and albuterol are available in the metered-dose inhaler form, while metaproterenol solution is available for the jet nebulizer and can be used at home.

The most common side effects for the β_2-agonists are tremor and tachycardia. Because tolerance to these phenomena may occur after several weeks, one can begin with a reduced dose and gradually increase to the recommended dosage. Tolerance to the bronchodilator

response does occur, but the degree is not usually clinically significant unless these agents are used excessively. Such abuse is more likely to occur with the metered-dose inhaler with occasional serious consequences.

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