Asthma

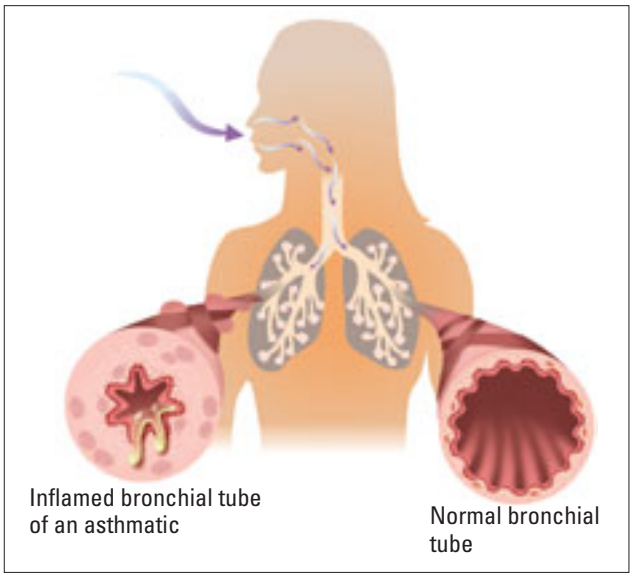
Biotech is bringing forth new products against an ancient disease.

BY EVELYN B. KELLY

A 3500-year-old Egyptian book known as the Ebers Papyrus shows pictures of people gasping for air and panting. The Greek poet Homer wrote about a similar disorder affecting sailors and leaving strong men weak and breathless. But it was Hippocrates who named the condition known today as *asthma*, meaning "breathing hard" or "panting."

Many treatments have emerged to assuage the frightening attacks. The Romans recommended owl's blood mixed with wine. In *Regimen of Health* from 1190, the first book to write about asthma, Maimonides recommended chicken soup and abstinence. Because of the sudden onset, physicians of the 17th century called asthma "epilepsy of the lungs" and devised powder concoctions for inhaling. In the 1960s, researchers discovered inflammation was part of the process and that exposure to certain environments might trigger an attack. This revelation brought an arsenal of drugs to treat the symptoms and causes of inflammation.

According to data from the Centers for Disease Control and Prevention's 2002 National Health Interview Survey, 14.7 million adults in the United States suffered from asthma in 2000. The *Global Burden of Asthma* report, issued in February at the Fourth Asthma Meeting in Bangkok, revealed 300 million sufferers worldwide. That figure is expected to catapult to 400 million in 20 years, as the report points out that "the rate of asthma increases in urbanized communities that adopt Western lifestyles." Thus, despite increased clean air standards and awareness campaigns, the numbers continue to climb. Approximately 5600 patients die of the condition each year in the United States. With the number of cases climbing, the market for long-term and emergency medications is strong. At present there is no cure.



Inflammatory disorder makes breathing difficult.

Understanding asthma

Asthma is a chronic inflammatory disorder involving coughing, wheezing, chest tightness, and shortness of breath. During an asthma attack, several things happen. Airways narrow as muscles around the bronchial tubes tighten. This response is called bronchospasm or bronchoconstriction. Inflamed bronchial tubes swell, and thick mucus is produced within the tubes. Attack triggers include a variety of allergens; irritants in the air, such as pollutants and tobacco smoke; infections; exercise; medications; foods; emotional anxiety; and comorbid conditions such as gastroesophageal reflux disease.

Although the underlying pathophysiology of asthma is not completely understood, scientists know the chronic inflammatory disorder does involve white blood cells (eosinophils), mast cells, epithelial cells, macrophages, and T lymphocytes. Recent elucidation of cellular pathways and molecular mechanisms in asthma has altered the understanding of this respiratory disorder. Immune-system factors—such as immunoglobulin E (IgE) and T-helper type 2 (TH2)-cell derived cytokines such as interleukin-4 (IL-4), IL-5, and IL-12—are thought to be involved in allergic responses. The variety of subtypes may indicate that the conditions are separate disorders.

Sally Wenzel, a professor at the National Jewish Medical and Research Center in Denver, says, "People who develop asthma as children may have a different disease than those who develop it as an adult." Wenzel and colleagues have found that the presence or absence of eosinophils makes the difference among patients. "The findings add to a growing body of knowledge that asthma is not a single disease, but a group of syndromes with different origins and biological characteristics."

Joe Spahn, professor of pharmacology at the National Jewish Medical and Research Center, explains that current therapies include long-term control medications and quick-relief rescue medications. "Taken regularly, these medicines reduce the constriction or underlying swelling and irritation in the airways in most patients," Spahn says.

Fast-acting medicines include bronchodilators or puffers, such as albuterol, that open airways quickly and are taken only when sudden symptoms occur. Approved in 1982, albuterol sulfate is marketed as Ventolin, Proventil, Salbutamol, and Volmax and continues to be an effective rescue medication. A new variation is levalbuterol hydrochloride, sold by Sepracor as Xopenex. This medication has an effect on β-2 receptors in bronchial smooth muscle.

Long-term medications

Three types of long-term medications—

glucocorticosteroids, leukotriene-modifying agents, and long-acting β-agonist bronchodilators—are currently available.

The glucocorticosteroids, or corticosteroids, are effective in reducing inflammation and mucus production in the lungs. Referred to as "maintenance medicines," they help prevent symptoms from occurring in the first place and reduce constriction and inflammation. According to Spahn, six different corticosteroid compounds are commonly prescribed.

Both Schering-Plough's Vanceril, an inhaler approved by the FDA in 1997, and GlaxoSmithKline's Beclovent are beclomethasone dipropionate and provide direct anti-inflammatory action. Meanwhile, Ivax's Qvar—also beclomethasone dipropionate, approved in May 2002—is an old drug with a new delivery system. When chlorofluorohydrocarbons were banned globally, no exception for medicines was made. Qvar uses smaller-sized particles of this generic drug propelled by a hydrofluoroalkane, an ozone-friendly preparation.

"This enables the drug to be delivered more distally into the deeper reaches of the lungs," Spahn says. "Asthma is a difficult condition to treat because we not only have to treat it, we have to deliver the medications. Qvar does this effectively."

Other inhaled steroidal products include Aventis's Azmacort (triamcinolone) and Forest Laboratories' Aerobid (flunisolide) for nasal inhalation or Aerobid-M for mouth inhalation. And AstraZeneca has developed Pulmicort (budesonide); Pulmicort Respules is the only FDA-approved corticosteroid for maintenance treatment in children 12 months to 4 years of age. The most commonly prescribed inhalant, however, is GlaxoSmithKline's Flovent (fluticosone), first approved in 1996.

"Steroid pills and syrups are good at reducing swelling and mucus and are often necessary for treating severe respiratory symptoms. These include several preparations of prednisone and prednisolone," Spahn says. "But the routine use of steroid pills can cause a number of side effects, including repression of the adrenal glands."

In 2003, momentasone, marketed by Schering-Plough as Nasonex, was approved as a once-a-day maintenance medicine. And on December 30, 2003, Aventis and Altana submitted a New Drug Application for Alvesco (ciclesonide). This drug represents a new generation of inhaled corticosteroids with novel distribution properties, and it isn't activated until it enters the lungs.

Leukotriene modifiers act against leukotrienes, one of many substances with a role in causing asthma constriction and swelling. "These oral medications have been available about five years and block a specific chemical pathway of asthma inflammation. They work in 40 to 50% of asthmatics and are not often used. However, in some patients, they work very well," Wenzel says. Currently, three drugs have been approved for use: Abbott Laboratories' Zyflo (zileuton), which is recommended four times a day and not often used; AstraZeneca's Accolate (zafirlucast); and Merck's Singulair (montelukast).

Stuart Green, a research scientist at Merck Research Laboratories, Rahway, NJ, believes that leukotrienes play a key role in acute asthma. "Activation of their pathways is accompanied by an increase in detectable levels of urinary leukotriene E4 (LT4). This substantiates the important role of leukotrienes as key mediators in the clinical spectrum of asthma," he says. "Effective treatment strategies to combat leukotrienes in acute asthma should be pursued."

PHOTO: PHOTODISC

Childhood asthma sufferer using an inhaler.

The last of the long-acting drugs are β-agonist bronchodilators, which treat airway constriction by relaxing muscles and keeping airways open for up to 12 h or longer. They make the patient feel better quickly but do not treat the underlying disease. GlaxoSmithKline's Serevent (salmeterol) and Foradil (formoterol) are often used in combination with an inhaled steroid and in patients with more severe symptoms. GSK's Advair is a dry-powder inhaler that combines fluticosone and salmeterol, a long acting β-agonist.

In October 2003, the FDA required three GSK products—Serevent Inhalation Aerosol, Serevent Diskus (powder), and Advair Diskus—to have warnings citing "a small but significant increase in asthma-related death." The Salmeterol Multi-Center Asthma Research Trial had shown life-threatening episodes in 2003, especially among African-Americans and those not taking corticosteroids.

Respiratory disorders offer large market

Many major drug players are researching respiratory disorders, and several of them already have profitable blockbusters. Schering-Plough's sales of Nasonex, a once-daily inhaled steroid, were $500 million in 2003, down 4% from the previous year. Nasonex is battling intense competition in the corticosteroid market, but as of December 2003, it had a 25.5% share of the market.

GSK's sales of the asthma drug Seretide/Advair (also sold as Advair Diskus), the company's biggest product, increased by 39% in 2003 to reach $3.9 billion. In the United States, sales were up 54% to $2.1 billion. The drug has also been approved for use in chronic pulmonary obstructive disease, and Seretide/Advair is now one of the 10 top pharmaceutical products in the world.

Worldwide sales of Merck's Singulair, prescribed for both chronic asthma and seasonal allergic rhinitis, grew 35% in 2003 to reach $2.0 billion for the year. The company says sales were driven by strong performance in the asthma market as well as a new indication and formulation. During the fourth quarter, Singulair became the second-most-prescribed product in the overall U.S. respiratory market, Merck notes.

New biotech drugs

Using knowledge of cellular and genetic pathways, biotechnology has created new products targeting asthma-related receptors. Genentech, Novartis, and Tanox jointly developed Xolair (omalizumab), the first biotech molecule for treating asthma. This injectable product is a humanized mouse monoclonal antibody that binds to the IgE receptor. The drug was launched in July 2003, and as of mid-September, Genentech reported that more than 1500 physicians, or 15% of the target market, had prescribed it. For all of 2003, Genentech's sales of Xolair reached $25.3 million.

Other targets under investigation are several cytokines—IL-4, IL-5 (eosinal growth factor), IL-9 (which induces mucus expression), and IL-13 (which induces airway hypersensitivity)—and phosphodiesterases.

Genetics and proteomics are revealing complex pathways in asthma. Michael Kahn of the Pacific Northwest Research Institute and pathobiology professor at the University of Washington, and colleagues have used chemogenomic techniques to show that asthmatics have a complex inflammatory response of airway infiltration of immune cells. These cells undergo a process known as respiratory burst activation, which releases reactive-oxygen specifics (ROS).

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"The process of respiratory burst can be caused by IgE interaction with its receptor—essentially initiated by an allergen. This creates inflammatory cells, such as mast cells, to degranulate and eosinophils to release inflammatory mediators and ROS," Kahn explains. Transcription factors for ROS, activator protein (AP)-1, and nuclear factor κB lead to the expression of the cytokines IL-4, IL-5, and IL-13, the hallmarks of asthma. Drugs that inhibit these pathways are therapeutic targets for asthma.

"We are using this type of cell-based assay system extensively to screen our proprietary libraries, and are finding many interesting new leads," Kahn says. An institute to capitalize on their lead discoveries is in the planning stage.

Despite effective therapies, asthma has emerged as an epidemic. Combination treatments and biotech drugs will continue to be developed, but Kahn sees chemogenomics as "a very powerful tool for finding the most effective way to treat asthma, which will come into its own probably in 10 to 20 years."

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