Asthma: Clearing the Air

By
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- Asthma is a chronic lung disease caused by inflammation of the lower airways and episodes of airflow obstruction. Muscles surrounding the airways react and cause a bronchospasm.
- Medications for asthma include a variety of long-term controller drugs such as corticosteroids (CS), bronchodilators, and leukotriene-modifying β-agonists. Fast-acting or rescue medicines are used for emergencies.
- Novel delivery systems of old medicines as seen in hydrofluoroalkane (HFA) use in Qvar®, a corticosteroid, are promising.
- Biotechnology-developed medications will soon be used for asthma. Xolair® or omalizumab, a monoclonal antibody targeting IgE, is expected to be on the market in June 2003.
- Several genes are possibly involved in asthma including those on chromosomes 5, 6, 11, 12, 14, and 3.
- Improved understanding of cellular and molecular mechanisms mediating the pathogenesis of the disease will produce novel therapies for asthma.
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Introduction

The Egyptian Ebers Papyrus 3500 years ago described in hieroglyphics a terrible condition in which people panted like dogs to get air. Homer's *Iliad* also told how "labored breathing" affected some of the otherwise brave sailors. Hippocrates was the first to use the word "asthma," meaning "to breathe hard." The Greek name stuck.

Treatments for asthma throughout history have varied. The Romans treated the condition by giving owl's blood in wine. The Spaniard, Moses Maimonides, physician to Sultan Saladin, wrote the first book about asthma in AD 1190. His treatments included chicken soup and sexual abstinence.

Since the seventeenth and eighteenth centuries, physicians have known that asthma was due to spasms of the bronchi. One doctor even called the condition "epilepsy of the lungs," because of the sudden onset. However, in the 1960s physicians found the inflammatory property of asthma and that certain triggers create an attack. This started a revolution in treatment. Instead of just treating the constriction of the airways, now scientists could target the underlying causes of inflammation.

Physicians today have a vast arsenal of drugs and treatments, but still there is no cure for the disease. Yet, most people with asthma who carefully comply with their physicians' recommendations can lead normal and fulfilled lives.

What is asthma?

Asthma is a chronic lung disease, caused by inflammation of the lower airways and episodes of airflow obstruction. Muscles surrounding

the airways react and cause a bronchospasm. Airways are sensitive and inflamed in people with asthma at least to some degree all of the time, even when there are no symptoms. Episodes of asthma are called asthma attacks, flare-ups, or exacerbations.

In breathing, the bronchi became the smaller branches of the bronchial tree or bronchioles. These fine subdivisions are lined with circular muscles that through contraction or relaxation can change the diameter and control the air capacity of the lungs. In asthma a spasmodic contraction of the small muscles and swelling of the mucous membrane of the bronchioles amounts to a partial strangulation. Air passages are tight because of the airway muscle spasms, mucous obstruction, and swelling of the airway lining.

Symptoms related to the obstruction of airflow in the lungs result in shortness of breath at rest or with activity, wheezing, difficulty in getting air all the way out, coughing, and chest “tightness.” A great way to describe the condition is like breathing hard through a straw or through the nose with the mouth closed while running.

What Causes Asthma Symptoms and Attacks?

Symptoms of asthma may occur under the following circumstances:

1. Exercise-induced asthma. Drying out of airways, as well as temperature changes within airways caused by increased breathing, may result in this very common type. Symptoms may begin during the exercise or at the end. However, good body conditioning does help oxygen delivery.

2. Allergies and asthma. Environmental conditions such as dust mites, animal dander from pets like dogs, cats, hamsters, mice, etc.,

pollens, molds, and cockroaches and their waste may cause an asthma reaction. Another allergen is the house dust mite. Seventy to eighty percent of people with allergies are sensitive to the mite's droppings.

3. Nighttime asthma. Seventy-eight percent of all children and adults with asthma have nighttime chest symptoms. Changes in normal body chemicals and the normal rhythm of the body worsen the condition. Airways are more sensitive and less stable at night.

4. Asthma associated with infections. Another common problem is the cold that does not end or the cold that progresses to chest tightness. Viral infections, rather than bacterial infections, may cause the greatest problems. Influenza can cause significant asthma-like illness in any age group but especially with those who have had pre-existing asthma.

5. Irritants in the air. Tobacco smoke, wood fires, charcoal grills, strong fumes or odors from household sprays, paint, gasoline, perfume, and scented soaps may cause allergic reactions.

6. Weather. Dry wind, cold air, and sudden changes may evoke an attack.

7. Other. Co-morbid conditions like gastroesophageal reflux disease (GERD), obesity, emotional anxiety, and certain medications and food may trigger an attack.

Approximately 10 to 15 percent of Americans have asthma that can start at any age. It is not just a problem that children will "outgrow." Without proper treatment asthma can cause a dramatic change in lifestyle. It can decrease performance at work or in school, cause increased dependence on others, and lower self-confidence. See Table I- Asthma Report Card.

Diagnosis

To diagnose and establish treatment plans, allergists follow the *Guidelines for the Diagnosis and Management of Asthma* (1997). A thorough history is taken and a physical examination performed with special attention to the nose and sinuses. A spirometer is used to measure the amount of air inhaled and exhaled to determine the level of airway function. Allergy skin tests using tiny amounts of allergen pricked into the skin are conducted to determine what the person reacts to.

A problem with diagnosis is that there are subtypes that are not so well defined. Probably allergic eosinophilic reaction is seen across all levels. Eosinophils are a type of white blood cell important in immune response. High levels of these cells signal the presence of asthma. But there is an infection-related condition that does not seem to have the same allergic response. The people do not seem to have the same Th2 lymphocyte type of pattern and do not even have the same pathology. In looking at tissue under microscope, this may be the old intrinsic asthma that was in the textbook years ago and has fallen out of favor. People with aspirin-sensitive asthma do not seem to have allergies but they have asthma- and if they take aspirin they could die. These people tend to get the disease in adulthood as opposed to those with allergy who get the disease in early childhood.

Treating Asthma

Peebles, *et. al.* (2002 *Southern Medical Journal* 95(7):775 – 779) discussed strategies for treatment and management of asthma. They focused on pharmacology, environmental control, allergen

immunotherapy, and the importance of immunization for influenza and sometimes pneumonia.

Drugs for asthma therapy include both long-term controller medicine and fast-acting (rescue) medicines. The long-term controller medications, also called maintenance medicines, help prevent symptoms from occurring in the first place. Taken regularly, these medicines reduce the constriction or narrowing of airways in the lungs and/or the inflammation or underlying swelling and irritation in the airways. Many people need treatment for both the constriction and inflammation for the best asthma control.

These long-term controller medications are recommended for use daily for patients with persistent asthma. There are three types of medicines that are now available that appear as several brand names.

Glucocorticosteroids. Inhaled steroids are thought to suppress the inflammatory response that contributes to asthma and are the preferred treatment. Some people confuse these glucocorticosteroids or corticosteroids (CS) with the anabolic steroids that athletes use to build muscle mass. According to the National Institute of Health, these inhaled corticosteroids are the most effective long-term control medication for those who need fast-acting inhalers more than twice a week. They also may help prevent a long-term decline in lung function that could occur if asthma is left untreated.

Some studies have shown that compliance with taking these medicines according to the directions of physicians is a problem. Some may hear the word “steroid” and decide that it is not good for them to take it for along period of time. Some may decide not to use the medicine when they feel better.

Five different CS compounds exist in many brand names:

1. Beclomethosone dipropionate is marketed in three different brands: Vanceril®, Beclovent® and Qvar®. Qvar is a version of the drug with a new delivery of steroid. The global ban on chlorofluorohydrocarbons (CFCs) made no medical exception, even for inhaler devices. Qvar utilizes a hydrofluoroalkane (HFA) for delivery of a novel formulation of beclomethasone dipropionate, a CS that produces anti-inflammatory activity. HFA is an ozone- friendly propellant, and the steroid is dissolved in a suspension. The particle size is smaller and a larger fraction of the drug into lungs. Dr. Joe Spohn, National Jewish Center, Denver, Colorado, said, "This enables the drug to be delivered more distally into the deeper reaches of the lungs. Asthma is a difficult drug to treat because we not only have to treat it with medication, but we have to deliver the medications. How you deliver is just as important. Qvar is an old drug but a new delivery."

2. Triacinolone is marketed by Aventis as Azmacort®. The goal is to eliminate use of systemic CS or those that are taken orally.

3. Flunisolide is known as Aerobid® and Aerobid-M®. Manufactured by Forest Pharmaceuticals, it is available for either nasal and mouth inhalation.

4. Budescinide marketed by Astra-Zeneca is marketed as Pulmicort® in a turbuhaler.

5. Fluticosone or Flovent® by GlaxoSmithKline is the most commonly prescribed inhaled GS.

Two promising CS are in stages of development:

1. Mometasone by Schering is being reviewed now and will hopefully be ready soon.

2. Ciclesonide, developed by Aventis, is unique in that it is thought to have less potential for any systemic absorption, according to Dr. Spohn. “The reason we use inhaled as opposed to oral steroids is because the long term use of oral steroids results in multiple side effects. If we can deliver much smaller doses of steroid topically, then you can avoid a lot of systemic absorption. Inhaled steroids are safe to begin with, but if you use big doses, you could get into problems. This drug is different in that there is good delivery without any or little potential for systemic effects. It will be a couple of years before it is available.”

Although most patients respond to steroid therapy, a small subset of asthmatics is unresponsive and shows persistent airway obstruction and inflammation despite high doses. Leung ***et. al*** (2002 *Seminar of Respiratory Critical Care Medicine* 23 (4) 387 – 398) outlined subtypes of steroid resistance that requires a systematic approach to rule out underlying conditions that lead to treatment failure.

<u>Leukotriene- modifying agents antagonists</u> Leukotrienes are one of many substances that contribute to asthma symptoms. They have a role in causing airway constriction and swelling. Leukotriene-modifiers act to combat this action. They should not be used to relieve sudden asthma symptoms.

According to Dr. Sally Wenzel, National Jewish Center, “These medications available for about five years, now block a very specific chemical pathway of asthma inflammation. They work in 40 to 50 percent of asthmatics and are not used as often. However, in some patients, they work very well.”

Three members of this class are:

1. Zilueton or Zyflo® by Abbott is recommended four times a day and not used often.
2. Zafirlucast or Accolate® is a product by Astra-Zeneca.
3. Montelukast sodium or Singulair®, Merck's product, is very widely prescribed. This drug is not recommended for fast relief of acute asthma attacks or to prevent asthma. It is taken once daily.

These medications, thought to have some anti-inflammatory effect, are oral medications as opposed to inhaled. They are generally not as effective for most asthmatics.

Long-acting β-agonist bronchodilators. These drugs treat airway constriction and help keep the airways open by relaxing the muscles surrounding the airways for up to 12 hours or longer. This effect can also help prevent airway constriction from occurring in the first place. These drugs make one feel better quickly but do not treat underlying disease and should not be used to relieve sudden asthma symptoms. There are two:

1. Salmeterol or Serevent®
2. Formoterol or Foradil®

These broncho-dilators, similar to albuterol, belong to controller agents although they do not have anti-inflammatory effects. They provide long-acting bronchodilatation and are not usually used alone, but more in combination with an inhaled steroid and in patients that have more severe disease.

One newer product is a combination called Advair Diskus®. The product comes in a dry powder inhaler therefore avoiding CFC problems. This combination of fluticosone, an inhaled steroid, plus salmeterol, a long acting β-agonist, is a very popular. It provides the anti-inflammatory drug

and sustains symptom control for about 12 hours because it is a bronchodilator.

More combinations may soon be on the way. In Europe Symbicort®, a combination of an inhaled steroid budesoide and long acting β-agonist formaterol, is used. It has not been approved in the US. Another combination has been suggested using mometasone plus formaterol. See Tables II and III.

Fast-Acting (Rescue) Medicines Inhaled fast-acting bronchodilators, such as albuterol, which are also known as rescue inhalers or fast-acting "puffers," should be taken only when sudden asthma symptoms occur. They quickly open the airways by relaxing airway muscles. They do not provide long-term asthma control or help prevent future attacks.

For almost 20 years albuterol sulfate has been the bronchodilator or rescue medication of choice for most asthmatics throughout the world. Several brand names are used: Bentolin®, Proventil®, Salbutamol,® and Volmax®. It was approved in 1982 and was a great advance for its time. Other bronchodilators had powerful side effects and were good for only a short period of time. Albuterol extended the duration of effectiveness to six hours. Although other therapies can be used for long term, albuterol will remain a popular Rescue Medication for some time. New variations of albuterol, such as Xopenex®, continue its long history of effective interventions.

Pharmacological studies of albuterol have demonstrated it has a preferential effect on β 2-receptors, the predominant receptors in bronchial smooth muscle. The drug has an effect on the respiratory tract in the form of smooth muscle relaxation while producing fewer effects on the heart.

Cromolyn and nedocromil are mild anti-inflammatories that help make the airways less sensitive to irritants. Used in children, these drugs are not as common now. The theophyllines, oral bronchodilators in pill form, are also older medications. These help by relaxing the airways muscles for up to 6 hours or longer. Dosages must be monitored carefully by blood testing. These should not be used to relieve sudden asthma symptoms.

Agents from Biotechology A disease-modifying drug targeting IgE should be available in June, 2003. Xolair®, marketed by Genentech and Novatis, is the first biotech molecule for treatment of asthma. This product, a murine (mouse) monoclonal antibody that been humanized, binds to human IgE. Being a protein that cannot be given orally, it is injected twice a month subcutaneously. The drug sops up IgE that is circulating in the bloodstream. About 80 percent of asthmatics in this country have allergic asthma.

Another biotechnology product that targeted the IL-4 receptor looked promising in early trials, but the product that worked so well in mice did not work well in Phase 2 human trials.

Trends in Treating Asthma

Although there have been important discoveries in the treatment of asthma, still 17 million Americans suffer from the disorder. The prevalence continues to rise. Three trends are rocking the research community. Genetics of asthma.

Researchers are trying to find the genes that predispose to asthma in certain people. This is a difficult task as there are no universally accepted definitions of asthma, genetic criteria, or defined indicators as to why the

condition occurs only in certain people. Researchers in Arizona (1984 Lebowitz, *et. al Journal of Clinical Immunology* Feb,73(2):250-264) looked at 344 families and found that where neither parent had asthma, 6 percent of the children had the condition. In families where one parent had asthma, 20 percent had asthma; in families where both parents had asthma, 60 percent of children were asthmatics.

Another study of twins provided evidence that both genes and environment have a role in asthma. Sarafino, *et. al (*1995 *Archives of Disabled Children* Aug 73(2)112-6) found that in 39 pairs of identical twins 59 percent or 23 of 39 pairs had asthma; in non-identical twins, 24 percent or 13 of 55 pairs had the condition. If asthma were governed only by genes, then every one of the identical twins should have asthma. This indicates an interplay between genes and the environment. No single asthma gene exists, but combinations of several weak genes are suspects. Some genes increase the susceptibility and others lower it. Table IV lists the gene suspects and their roles.

Improved understanding of cellular mechanisms

Improved understanding of cellular and molecular mechanisms has helped design novel therapies for asthma. Several have promised to inhibit cellular pathways of the inflammatory response *in vitro* and in animal studies. Several studies focus on these factors. Presenting at the November 2002 68th Annual meeting of the American College of Chest Surgeons, Levine *et. al* reviewed approaches to the treatment of asthma.

Anti-IgE in asthma. IgE is a key antibody responsible for all allergic reactions. Using special techniques to create antibodies against IgE, scientists seek to disarm the cells and enable people to encounter allergens

without developing the sensitivity. Thus, reducing the IgE levels could reduce the T lymphocyte activations and inhibit IgE-mediated antigen-presenting cells. Busse*, et. al* (2001 *Journal of Clinical Immunology*; 108:184-190) found that omalizumab, anti-IgE recombinant humanized antibody reduced asthma exacerbations and improved symptoms.

Anti IL-4. IL-4 probably plays a key role in asthma through its ability to induce differentiation of ThO cells to Th2 lymphocytes that express several cytokines including IL-4, IL-5, IL-9, and IL-13. Inhibiting IL-4 would also stop these additional cytokines expressed by the Th2 cells. Soluble IL-4R was used in clinical trials to bind to IL-4 and inhibit its properties.

Anti-IL-5. IL-5 is responsible for accumulation and growth of eosinophils. Studies in animals and humans show this cytokine is an important feature of airway inflammation. Some studies showed a single intravenous infusion of anti-IL-5 antibody reduces blood and sputum levels of eosinophils more than 90 percent. However, this reduction in eosinphil levels did not show how this antibody protected them against late-phase decline in FEV1 (forced exhalation volume) and airway responsiveness. This suggests that the dose will need to be adjusted or it needs to be combined with other inhibitors.

IL-12. L-12 as a single infusion decreased eosinophils but has troublesome side effects that would preclude it use.

Antisense oligonucleotides. Another approach is introduction of antisense oligonucleotides. In mouse models of ovalbumin-induced asthma, this substance resulted in decresed IL-4 levels and bronchial responsiveness.

PDE4 Inhibitors. Some of the newest work present at the conference is unpublished. John Conderri, Professor of Medicine at the University of Rochester, presented data on new phosphodiesterase (PDE) inhibitors. He pointed out that there have been PDE inhibitory drugs developed for PDE-4 and PDE-3. These effect only the lungs and doe not effect other PDEs in the heart, brain, or platelets. These agents decreased histamine release, IL-2, 4, and 5 levels, and decreased chemotaxis.

Linkage of asthma with allergies

Another exciting trend is the linkage of asthma to allergies. Allergic rhinitis was shown to link to other respiratory diseases including sinusitis, middle ear infections, nasal polyps, and bronchial asthma. Researchers are investigating ways to determine why patients with allergic rhinitis are at great risk for asthma and why the relationship exists.

Conclusion

Although research has come a long way with many promising treatments, there is still no cure for asthma. New long-lasting drugs as well as new drug delivery systems will continue to develop. The trends that are stimulating great discussion will impact the future of the drug market. Using immunology techniques to block or shut down substances like IgE

so that people can come in contact with allergens without fear of allergic response is still in its infancy. Finding the links between other allergic reactions and asthma has encouraged continued investigations of cellular and molecular pathways. However, to find the genes and their pathways and then develop interventions will be the challenge of the 21st century.

Table I Asthma Report Card

Americans with asthma	17,000,000 (CDC,1998)
Children with asthma	4.8 million under age 18; 8 – 10 percent of all children
Total prevalence	24.7 million Americans have been diagnosed with asthma during lifetime
Pre-school prevalence	5.8 percent of children under 5- a 160 percent increase since 1980 (1996)
Increase by gender	From 1980 – 1996, 97 percent increase among women; 22 percent increase among men
Deaths	5300 deaths in 1997
Asthma-related hospitalizations	1,500,000 annually
Emergency room visit	1,997,000 in 1999
Health care costs	Direct $9.8 million annually; indirect $12.6 billion
Missed school days	10 million/ year in 1997; more than 14 million days missed in 2002
Loss of work for adults	3 million lost work days 2002
Prevalence African American to white children and parents	21.6 percent higher in 1999; 40 percent of children who have asthmatic parents develop asthma

Source: D&MD

Table II Long-term Controller Medications

Brand	Medication	Company	Type	Remarks
Vanceril	**Beclomethsone propionate**	**Schering-Plough**	**Inhalation aerosol corticosteroid (CS)**	**FDA approved 1999**
Beclovent	**Beclomethosone proprionate**	**Glaxo-Wellcome**	**CS**	**Direct inflammatory action**
Qvar	**Beclomethosome proprionate**	**Ivax**	**CS**	**Approved 1999; new delivery system using HFA**
Azmacort	**Triacinolone**	**Aventis**	**CS**	**Seeks to eliminate use of systemic CS**
Aerobid and Aerobid-M	**Flunisolide**	**Forest Pharmaceuticals**	**CS**	**Nasal and mouth**
Pulmicort Respules	**Budesonide**	**Astra-Zeneca**	**CS**	**FDA approved for children 12 months to 8**
Flovent	**Fluticosone**	**Glaxo-Smith-Kline**	**CS**	**Most commonly prescribed**
Zyflo	**Zilueton**	**Abbott**	**Leukotriene-modifying agent**	**Oral, Not used often; approved 1997**
Accolate	**Zafirlucast**	**Astra-Zeneca**	**Leukotriene-modifying agent**	**A non-steroid tablet**
Singulair	**Momentukast**	**Merck**	**LMA**	**Most prescribed oral medication**
Serevent	**Salmeterol**	**Glaxo-Smith-Kline**	**Beta-agonist bronchodilator**	**Long term; inhalation powder**
Foradil	**Formoterol**	**Schering-plough**	**Beta-agonist**	**Long term**
Advair	**Fluticasone propionate and salmeterol**	**Glaxo-Smith-Kline**	**Combination Inhaled CS and long acting beta-agonist**	**Does not replace fast acting medication**

Source: D&MD and Dr. Joe Spohn, National Jewish Center

Table 3 Pipeline Therapies

Brand name	Generic name	Company	Strategy	Remarks
	Mometasone	Schering-Plough	Corticosteroid	Once a day; in phase III
Alvesco®	ciclesonide	Aventis	CS	Less potential for systemic absorption
Symbicort®	Oxis and pulmicort	Astra-Zeneca	Combination CS and b-agonist	New Zealand-inhaled as turbuhaler
Xolair®	omalizumabi	Genetech/Novartis	Biotech IgE	Reduces asthma attacks and improved symptoms
			Anti-interleukin therapies	Binds to Il4 to inhibit production of cytokines

Source: D&MD

Table 4 Genes in Asthma

Gene Name	Chromosome	Comments
Beta-2 adregenic receptor	5	Mutations influence the severity but not the susceptibility to asthma; may control response to various medicine
Interleukin genes	5	This family of molecules controls inflammation. Five interleukin genes are found on the longer arm of this chromosome and probably relate to susceptibility
HLA class II	6	This complex of genes on the short arm may relate to allergy to dust mites and ragweed pollen.
TNF-alpha	6	This gene contributes to inflammation and sensitivity of airways. Variants lead to increased TNF-alpha and asthma.
IgE genes	11	As an important molecule in allergies, variations in these genes are assembled from

			the products of several genes. Many of these are on chromosome 11.
	Unknown	**12**	**Genes are indicated but not located .**
	TcR-alpha	**14**	**Genes are indicated but not located.**
	C-C chemokine receptor 5 (CCR5)	**3**	**May lower risk**

Source: D&MD