Asthma: Separating Facts from Fiction

The Annapolis Center for Science-Based Public Policy

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EXECUTIVE SUMMARY

This report defines asthma, evaluates trends, and reviews how it is studied. It reviews potential triggers of asthma attacks and their proper management, which can dramatically decrease morbidity and prevent mortality. The report recommends prudent steps that decision-makers, doctors, and patients should take in combating the disease.

Several major points of the report are as follows:

- Asthma is a serious disease, with a great impact on public health and the economy;
- Asthma has a disproportional impact in the United States on minorities, the poor, and children;
- Asthma is a complex disease. We do not have a complete picture of asthma because we have an insufficient understanding of all the interacting mechanisms. Because of this, there is no universally accepted definition of the disease;
- Because of the lack of a completely acceptable definition of asthma, it may be under-diagnosed or over-diagnosed;
- We do not yet know all the causes of asthma. Genetic factors play a role but these alone do not explain the disease. The strongest (but incomplete) evidence exists for interactions between genetic factors, indoor environmental allergens and tobacco smoke; however, finding "the cause" (or causes) of asthma will take time and money;
- Underlying causes, unlike immediate triggers, are speculative, or highly speculative, requiring much more research.
- A national asthma registry is needed.
- Action strategies aimed at eliminating some suspected environmental risk factors may reduce the prevalence of asthma attacks but are not guaranteed to reduce the incidence of new cases of asthma. There is evidence that dust mites, cockroaches, cat dander, spores of the common airborne mold, and Alternaria (a type of fungus) play an important role. It seems reasonable to clean homes, workplaces, and schools to reduce exposure to these triggers. This may not prevent all asthma attacks, but it may lessen their frequency and/or severity;
- Asthma is a very manageable disease. Much of the current morbidity and mortality is avoidable;
- Many asthmatics and their doctors do not take the disease as seriously as they should;
- Clinical guidelines for asthma treatment need to be followed;
- Better disease management is the strategy most likely to yield benefits for asthmatics at this time. Better disease management will result from specific programs to educate physicians and patients along with programs to ensure better access to care for all asthmatics.

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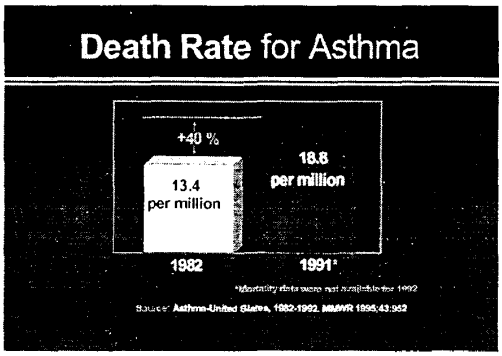
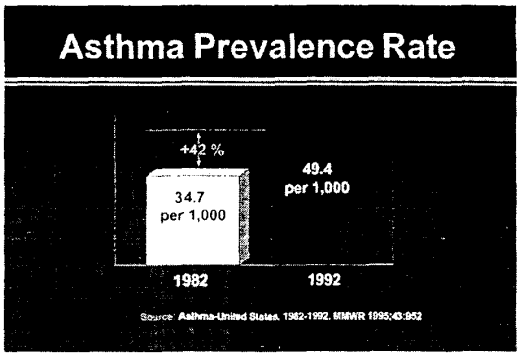
Introduction

"I know when an asthma attack is starting. I cough, then my chest feels tight. I struggle for each breath and I get tired. I feel like I am suffocating. I fear my next breath will be my last . . . between attacks I feel fine."





Asthma is a condition characterized by wide and sometimes rapid fluctuations in a person's ability to move air in and out of their lungs. For some patients, symptoms are intermittent, while for others they are chronic. It is a very serious disease.

In the United States, where according to recent accounts its prevalence is increasing, asthma has a disproportionate impact on minorities, children, and the indigent. The number of deaths attributed to asthma increased in the 1980s and 1990s, and asthma attacks contribute to nearly 500,000 hospital admissions each year. Asthma-related medical costs now exceed $14.5 billion[1] each year, for what has become the sixth-ranked chronic condition in the U.S., and the leading serious chronic illness in children.

History

In many asthmatics, especially children, an important causal factor may be atopy, a clinical hypersensitivity state more commonly known as allergy. (The first records of atopy date from the 18th Century with a description of allergic asthma, while the U.S. Centers for Disease Control began tracking the prevalence of asthma in 1979.) In many other asthmatics, however, the causal connection between atopy and asthma may not be clear or cannot be established. Importantly, although 50 percent of adult asthmatics and 80 percent of childhood asthmatics may experience allergies (atopy), these pre-existing conditions should not be considered *the* only cause of asthma because many atopic persons do not have asthma and many asthmatics have no detectable allergies. (For additional information on the history of asthma, see Appendix B.)

Asthma: A Very Complex Disease

No Firm Definition

Medical students are taught, "all asthmatics do not wheeze and all that wheezes is not asthma." (This statement defines in simple terms the problems faced in understanding this condition.) They are also taught that the acutely ill asthmatic suffering an attack with a "silent" chest has a far more precarious and dangerous condition than one who is short of breath with a noisy, wheezy chest. Consequently, physicians learn not only that asthma is a multi-factorial disease, but also that asthma provides a generic term for a set of symptoms. In this chronic, sometimes progressive condition, the major airways usually, but not always, become temporarily constricted. The diagnosis of asthma typically requires objective evidence of variable, measurable, reproducible, and at least partially reversible, airway obstruction.

We still have an insufficient understanding of the mechanism of asthma. Further, there is no universally agreed on definition of asthma. The lack of consensus creates significant challenges for those who seek reliable data on the incidence, prevalence, etiology, and epidemiology of the disease. The Institute of Medicine (IOM) offered the following definition of asthma using guidelines of the National Institutes of Health (NIH), but this definition should be considered evolving and not static:

Definition of Asthma

Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role, in particular, mast cells, eosinophils, T-lymphocytes, macrophages, neutrophils, and epithethial cells. In susceptible individuals, this inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment. The inflammation also causes an associated increase in the existing bronchial hyper-responsiveness to a variety of stimuli[1].

Asthmatics have an inherited or acquired defect in the ability of major airways to remain open when exposed to certain physical and immunologic stimuli. An asthma attack caused by allergen exposure typically occurs in two phases: first, an initial acute constriction of the bronchi with swelling of the airway linings; and second, with some stimuli (especially allergens), a more slowly developing, inflammatory phase with cellular infiltration (late asthmatic reaction)

Criteria for Diagnosis of Asthma

Asthmatics quickly learn to cope and to tolerate significant degrees of disability, and often do not seek medical attention during an attack. Some patients with compromised lung function have poor perception of their altered breathing status. This decreased ability to appreciate an altered breathing status further complicates a physician's

management plan and limits the value of questionnaires. Such patients may not be counted or captured in studies of incidence or prevalence of asthma.

Experts agree that asthma is characterized by reduced airflow in the lungs and reversibility of symptoms with use of a bronchodilator (relievers) or administration of corticosteroids. The diagnosis of asthma is not established, however, until the physician follows an individual over time and determines that airway obstruction recurs. If obstruction does recur, the likelihood is that a diagnosis of asthma is correct, versus a one-time airway obstruction episode.

Physicians sometimes incorrectly report an episode of airway obstruction (*i.e.*, wheezing) as asthma. Thorough assessment of the background upon which symptoms occur, however, will enhance accurate identification of the true asthmatic. Administration of a "challenge agent" also may be required to make the correct diagnosis. (Challenge testing involves measurement of lung function before and after inhalation of increasing concentrations of methacholine or other agents that are known to constrict airways. A 20 percent decline in the one-second forced expired volume after inhalation of methacholine at concentrations of 8 milligrams per milliliter (or less) is considered abnormal.)

The accuracy and reliability of incidence and prevalence data for asthma may be further compromised by the fact that primary care physicians with training in pediatrics, family practice, or internal medicine may hesitate or be unwilling to document in the medical records that a child or adult has asthma because they want to avoid or postpone any possibility of discrimination by employers or insurers.

Opinions of Workshop Physicians Involved in Asthma Research

Typically a diagnosis of asthma is based on the patient complaining of coughing, spasms or shortness of breath and that using an asthma medication made them feel better.

Most epidemiological studies are based on subjective, self-reported symptoms such as whether or not a patient wheezes, or by being told that they have asthma. Such cases need to be confirmed by measurable objective criteria.

Airway obstruction can be easily documented in everyone except very young children.

We are using the same technology to diagnose the existence of asthma or of airflow obstruction that we used 30 years ago.

There needs to be more than subjective reporting of symptoms to define an asthma episode. We need objective criteria for diagnosis; it should not be based solely on "feeling" – one can measure lung function and airway obstruction. A physician can AND should measure obstruction.

Lung function studies that measure airflow demonstrating that it decreases with attacks or that the process is reversible is the optimal way of establishing a diagnosis of asthma. (This is not a practical recommendation in very young patients who are unable to cooperate.) Many individuals can be made to wheeze with large amounts of physiologic (not immunologic) stimuli like very cold air, even though they don't have asthma.

Unfortunately, many asthmatics and even some doctors do not take asthma seriously, possibly because it is not viewed as life-threatening as other chronic diseases like diabetes or heart disease.

Airway obstruction can be triggered in young children (under 3 years of age) by certain viral respiratory infections. "Hyperactive airway disease" may be a more appropriate diagnosis than "asthma" if a physician is uncertain about recurrence and family history. Self-reported symptoms of asthma need to be confirmed. Diagnosis is dependent on the recurring nature of symptoms.

It is important to identify populations at risk and focus our efforts on them.

Asthma Trends

The number of Americans suffering from asthma increased from 6.7 million in 1980 to 17.3 million in 1998 [ii], while the total population rose from 220 million in 1980 to 280 million in 2000. Of potentially greater public health significance is the observation that the prevalence of asthma in U.S. children appears to have doubled during the past 15 years. Importantly, decision-makers desperately need more abundant and more reliable data for valid computation of the incidence and prevalence of asthma. Unfortunately, the lack of a consensus document on asthma not only makes acquisition of reliable data difficult, but also makes interpretation of current epidemiological reports highly problematic.

Prevalence
The total number of cases at a designated time in a designated area
Prevalence rate per 1,000 = (number of cases present within a population during a period of time) / (number of persons in the population at that specified time)

Incidence
The number of new cases in a given period in a designated area
Incidence rate per 1,000 = (number of new cases within a population during a period of time) / (number of persons at risk during that period of time)

For example, in the United Kingdom a change in disease labeling has caused both an increase in the number of cases of asthma and a decrease in number of cases of chronic bronchitis (another condition associated with wheezing). Consequently, changes in labels may alter apparent numbers of cases of asthma without there being a real change in asthma prevalence. Another potential, but only partial explanation for the apparent increase in asthma prevalence is the availability of more and better pharmaceuticals. People who simply tolerated symptoms in the past (without seeking medical attention) may now appear on the "asthma radar screen" as they seek pharmaceuticals for prevention as well as relief.

Asthma afflicts some groups more than others. There is no difference by gender, but in the US, the black population has a higher prevalence than whites.

Children seem to be more "at risk", but children living in rural areas of Europe seem to be less likely to be affected.

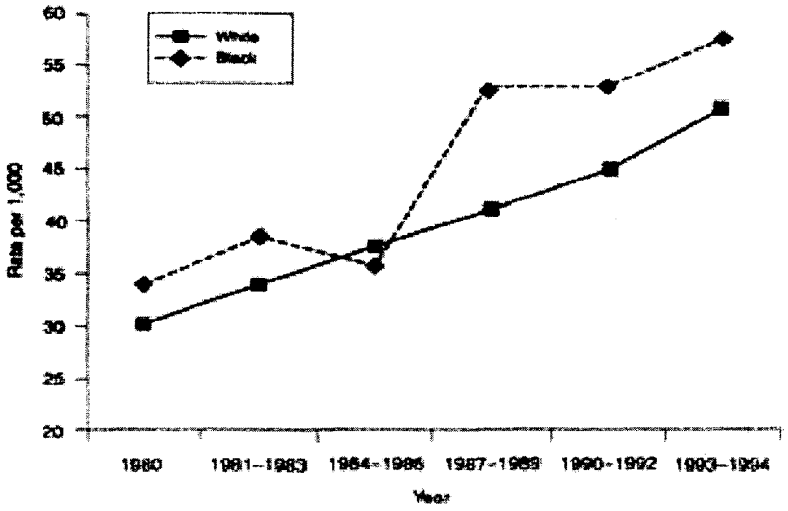


FIGURE 3-3 Asthma prevalence by race, 1980–1994. SOURCE: Mannino et al., 1998.

To obtain valid and reliable data on asthma trends, we need improved research methods that include standardized questionnaires and central registries. Appropriate study designs used for decades in research on diabetes, cancer, and heart disease can and should be adapted for the study of asthma.

We need the results of longitudinal studies of asthma patients from childhood through adulthood in order to determine if asthma is a lifelong disease. Some children with asthma are not symptomatic as adults but for many, asthma may be a life-long condition. Two-thirds of asthmatics are adults; one-third are children. (Currently more than 10 such longitudinal cohort studies are underway around the world.)

Prevalence of Asthma

Many epidemiological studies have sought to determine the incidence or prevalence of asthma or its symptoms. Unfortunately, in many of the larger studies, investigators have relied on nothing more than the treating physician's diagnosis to determine presence or absence of the asthmatic condition.

During the large International Study of Asthma and Allergy in Children (ISAAC) (see graph on page 11.[iii]), patients in different countries were interviewed using consensus translations and videotapes. Interviewees were asked whether they experienced wheezing, breathlessness, or coughing after exercise. They were also asked whether or not their symptoms were unrelated to the common cold. The prevalence of asthma symptoms was greater in developed countries than in less developed nations, but the prevalence of asthma symptoms also was greater in nations with good air quality (*e.g.*, Barbados, New Zealand, and Australia) than in nations with poor air quality (*e.g.*, Indonesia, China and Mexico.)

In 1998, the forecasted estimate of the prevalence of self-reported asthma across all U.S. age groups stood at 6.4 percent (±1.0 percent) (see Appendix A). Among U.S. residents of Puerto Rican descent, the prevalence of reported asthma in children ranges between 17-20 percent[iv].

There is a need for a national asthma registry. **Conclusions on prevalence will be more accurate when there is consistency of data. (Such information should be kept private and not be used to discriminate against an individual when applying for insurance or employment.)**

A consistent definition of what is being reported is needed. **The right questions need to be asked. Diagnoses need to be confirmed with appropriate testing. Studies should state and accept limitations.**

Selected sampling populations may skew the results through selection bias. **Populations of convenience, such as people with telephones, are often studied. This can skew the data by leaving out important populations with higher or lower prevalence of asthma.**

There needs to be a consistent definition of hyper-responsiveness. **Sensitization (the development of specific antibodies, or in the case of allergy, IgE) indicates that the individual has developed antibodies. The threshold dose that leads to sensitization may differ from the dose that produces symptoms. Not all persons who have been sensitized (have antibodies) to pollen, dust mites, or animal dander will have symptoms when exposed. However, once a person is sensitized, most will respond when exposed.**

Causes of Asthma

A lot of things are on the suspect list as causes of asthma or of being capable of triggering an attack. But, scientific evidence to support many of these suspicions is not conclusive. It is strong for some suspected causes while others are only speculative. The answers to "why" or "how" people get asthma will unfortunately take time and money to learn.

We cannot say with certainty what "causes" asthma.

Some advocacy groups with specific agendas try to assert that "pollution" causes asthma. While this may be politically popular, it is important to remember that much of the evidence supporting this contention is weak and often contradictory.

Similar to diabetes, asthma is a complex disease. Many studies have demonstrated a strong familial association. (A study of college students indicated that only about 15 percent of the students with no family member affected had asthma or hay fever. If one parent was affected about 38 percent had either or both of these conditions. If both parents were affected 65 percent had either or both conditions.) Genetic studies have identified areas on several chromosomes containing genes strongly associated with asthma, bronchial hyper responsiveness or both. In many populations, a gene that controls levels of the antibody responsible for allergy (immunoglobulin E) is associated with the development of asthma. The beta-adrenergic receptor gene is the first gene that has been associated with the presence of increasingly severe asthma, *e.g.*, accentuated nighttime asthma or poorer response to adrenergic drugs. However, more work in this area is needed.

We know that babies born to mothers who smoke during their pregnancy are more likely to have asthma. The reasons for this are obscure. The link of asthma to passive maternal exposure to environmental tobacco smoke (ETS) is more tenuous.

Pollution, especially air pollution, is often mentioned as a cause of asthma but this suspicion has to be balanced against what is known about air quality and trends in asthma prevalence.

Since 1970, total emissions of the six criteria pollutants[v] that the Clean Air Act requires the EPA to track and report have decreased about 31 percent. Today most Americans are breathing cleaner air than they have at any time in their lives. Yet despite these improvements in outdoor air quality, the prevalence of asthma appears to be increasing.

The USA is not alone with this trend of increasing asthma prevalence and clean air. Asthma has also been increasing in New Zealand and Australia, countries with very low levels of air pollution. In contrast Indonesia, Mexico, and South Korea, countries with high levels of air pollution have relatively low asthma rates. Because both asthma and air

pollution are so complex, it is difficult to draw a simple conclusion from these statistics. The most accurate statement seems to be that gross levels of air pollution currently measured, if they are a cause of asthma, cannot be a major cause of asthma.

Prevalence of Asthma by Nation (ISSAC)

Prevalence of asthma symptoms (percentage) from written questionnaires in the ISAAC database. Source: ISSAC Steering Committee (1998).

Since the oil embargoes of the early 1970's "tighter" homes and offices have been built in efforts to conserve energy. Indoor air is recirculated rather than "exchanged" with outdoor air. We know little about the air quality in our homes, office buildings and schools. What we do know is that the average American spends about 90 percent of his

or her time indoors. We breathe the same indoor air over and over with everything that is in it. While it is strongly suspected this has contributed to an increase in asthma prevalence, this has not been proven.

Other factors have also been implicated including sedentary lifestyles and obesity. There may be a connection between the rising prevalence of asthma and obesity. Obesity is increasing dramatically in the USA because of increasingly sedentary life-styles. Obese children are generally less physically active and this may have an effect on their lung capacity and immune system. More research is needed before conclusions can be drawn.

Triggers of Asthma

"It is amazing what we know, but more amazing what we don't know."

Asthma triggers can be categorized as non-specific (e.g.: pollution, etc.) and specific (e.g.: involving an immune reaction such as that to dust mites). To determine whether a substance is a potential trigger, we need to analyze existing studies and evaluate risk factors, looking for proven cause and effect. Often, in our desire to understand the disease and its triggers, we oversimplify what triggers asthma attacks.

The amount of allergen in the airways that triggers disease is often miniscule. Exposing the nose of someone who is appropriately sensitized to an allergen in the nose is enough to trigger the allergic inflammatory cascade that starts with the degranulation of cells in the nasal mucosa known as mast cells and ends with typical allergic symptoms (a stuffy and runny nose), A little bit of antigen might cause a big allergic attack if the person is highly sensitive. Allergic reactions are very specific, in that someone allergic to cats may have no reactions to dogs, and someone allergic only to mites may have no reaction to mold.

This report does not attempt to examine in detail each trigger. The following is a brief discussion of some of the major triggers and some of the issues that are associated with them:

Specific (Naturally Occurring) Triggers

Many of the following triggers are thought to be involved in producing asthma. Obviously, what triggers asthma in one individual or in one locality depends on the presence of a particular type of exposure. Thus, cockroaches are involved in inner city US asthma but are not so important in suburban areas. Dust mites are very important in some parts of the world, but not in mountain areas (like Colorado), since dust mites can't survive at high altitudes.

Animal dander

Cats are kept as pets in 27 percent of U.S. households while dogs are kept in 31 percent.[vi] Allergy to cats is about twice as common as for dogs. Many asthmatics are allergic to cats, while fewer are allergic to dogs. Dog and cat dander is easily aerosolized and widely disseminated through the community, even in places where dogs and cats have never been.[vii] Animal dander, especially from cats, may be a major risk factor as an asthma trigger for individuals who are cat or dog sensitive. Data is less strong for dogs. More research is needed before definite conclusions are drawn between animal dander and asthma.

Cockroaches

Cockroach antigen exposure can elicit a strong allergic response. Infants exposed to cockroach allergen are more likely to wheeze during infancy. It appears that children

exposed to cockroach antigen in the winter are more affected than those exposed during other months. Acute asthmatics living in the inner city who make emergency room visits are more likely to be both allergic and exposed to cockroach antigens. These allergens are excreted from the roaches and are found on discarded body parts. Thus the allergen remains in the home after successful extermination.

Dust mites

The following four conditions must exist for dust mites to live:

(1) multiple sites that provide harbors (i.e., pillows, carpets, sofas, etc.);

(2) the presence of humans that guarantees an abundant food source in the form of skin scales;

(3) an optimal temperature for growth; and,

(4) humidity

While many believe the data on dust mites being a major asthma trigger is compelling, asthma still occurs in areas where dust mites are not a factor, so that these are not the only cause of asthma (Most would believe that where mites are present, they are a major factor in triggering asthma. Other factors may be important where dust mites are not present in abundance.) More research is needed before definite conclusions are drawn between dust mites and asthma.

Fungi (molds)

People are routinely exposed to at least 200 different types of the more than 300,000 known species of fungi (molds).[viii] Fungi are attracting a lot of attention because many asthmatics are allergic to fungi. Some studies estimate that as many as 50 percent of inner-city asthmatics are allergic to fungi.

Not only are the numerous types of fungi a major issue, but so are the complex exposure issues. *Aspergillis* is a well-known mold that can trigger asthma attacks and cause serious lung infections. Allergy to Alternaria, a common outdoor fungus, has been linked to severe asthma attacks. Florida has higher levels of fungal spores than New York yet New York has a higher prevalence of asthma, again, illustrating the multi-factorial nature of this disease and the difficulty in implicating any one factor in its causation. Fungi are suspected to be one of the most important factors in asthma exacerbations; however, more research is needed before definite conclusions are drawn on the relationship of fungi to asthma.

Pollen

Like fungi, there are numerous types of pollen that can be carried by the wind up to fifty miles. In some areas, the peak of asthma attacks coincides with peak pollen levels. This has been reported with early spring pollens like trees, late spring pollens like grass, and

with fall pollens like ragweed. On the other hand, other studies have found no association between pollen counts and asthma exacerbations. Peak pollen levels often coincide better with allergic rhinitis than asthma.

More research is needed before definite conclusions are drawn between asthma and pollen.

Respiratory Viruses

Wheezing is often a component of viral respiratory infections in young children, especially with respiratory syncytial virus (RSV), which virtually all children get by age 3 years. There is suspicion that more severe cases of RSV may play a role in asthma.

Children in daycare tend to get earlier and more frequent infections. However, some infections in infancy may result in a decreased tendency to develop asthma and allergies later in life. There are conflicting studies on this point.

A very common way that asthma presents in adults is following a viral upper respiratory infection. What the virus does to the respiratory tract to bring on the hyper responsiveness and symptoms of asthma is unknown.

Food

Food allergies do not appear to play a major role as asthma triggers. Testing to identify a single type of food that may trigger asthma is difficult. More research is needed before definite conclusions are drawn.

Non-Specific (Environmental) Triggers

Environmental exposures should not be equated with biological exposures.

Biologic compounds

Some biological elements have a role in triggering asthma attacks. Endotoxins, compounds present in some bacterial cell walls, are released when bacteria die or when the cell wall is damaged. Endotoxin is ubiquitous in the outdoor environment. It is also present in home humidifiers.[ix] Little is known about the relationship between endotoxins and asthma.

Low Birth Weight (again, a risk factor, perhaps associated with smaller lungs or with the high risk of new born lung disease and lung damage)

With advancements in medicine, survival of babies born prematurely (usually less than 37 weeks gestation) or with low birth weights (usually under 2500 grams) have increased dramatically. One of the consequences of these births is the under development of the child's respiratory system. More research is needed before definite conclusions are drawn between low birth weights and asthma.

Outdoor Air Pollutants

As mentioned earlier, the trend for most air pollutants in the U.S. is downward while asthma is increasing. Nevertheless, there have been over 20 epidemiological studies that have been conducted to examine if there is an association between asthma and air pollutants including ozone, particulate matter, carbon monoxide, oxides of nitrogen, and sulfur dioxide. Most of the studies found a statistically significant relationship between asthma and one or more of the pollutants. A few of the studies found no relationship. However, even in the ones that found a positive relationship, the results were inconsistent and the associations very weak, as described below.

Some studies found the best association with ozone, while others found the best association with one of the other pollutants. In all studies, the association was very weak with the 95% confidence interval of the relative risk barely exceeding 1.00. The most commonly associated pollutant with asthma is ozone. EPA extrapolated one of these ozone studies and estimated that when ozone exceeds background concentrations, it is responsible for 1.3% of the annual hospital admissions for asthma in New York City.

There are three types of studies designed to look at health effects of air pollution: chamber studies, time series type studies, and animal (causality) studies. Chamber studies have not been performed on children because of reluctance to place children at risk. However, the response of the young lung is significant. (Most asthma develops before age six.)

A time series studies involve relating the number of physician visits, emergency room visits, medication use, etc., on a given day to outdoor air quality measurements on the same day or preceding days after adjusting for weather and season. These studies tended to consider only one pollutant at a time. Since these studies have rarely considered more than one pollutant jointly and since levels for all pollutants tend to increase and decrease together, it is difficult to specify which pollutant(s) are the ones most responsible for the observed associations between air pollution and asthma indicators. These studies would also be more useful if they considered a greater set of pollutants than have been considered to date.

Animal studies represent a third type of study. These studies can be difficult to interpret because it is not always clear whether the responses observed/induced in animals are the same as those associated with asthma in humans; in fact it is unclear whether there is any animal species that develop the same type of asthma as humans. Secondly, it is difficult to extrapolate from these studies to humans in the real world, where exposures are so much more complex.

Diesel and gasoline engine exhaust

Diesel emissions are a combination of heavy hydrocarbons, nitrogen oxides, carbon monoxide and "soot-type" particles, whereas gasoline emissions from exhaust and evaporation are primarily lighter hydrocarbons, nitrogen oxides and carbon monoxide. Hydrocarbons and nitrogen oxides react in the presence of sunlight to form ozone. Diesel emissions, however, due to their often-visible particulate exhaust, are suspected to

contribute to respiratory events in heavily congested city areas. Another potential effect of diesel exhaust particles is their ability to act as adjuvants by increasing the potential development of IgE (allergic antibodies) to pollen allergens.

These emissions have been suggested as a factor that increases asthma symptoms, *i.e.*, exacerbations, although the evidence supporting this connection is highly controversial. Recent data suggest that diesel exhaust particles can increase allergies in the bronchial airways and promote the bronchial inflammation that produces asthma. Mandated cleaner diesel fuel and improved emission controls on diesel engines should help reduce this potential as newer vehicles come into use. The manner in which diesel vehicles are used, especially in urban environments, could also be important as overloaded and/or cold-operating vehicles could emit smoke particles independent of modern emission controls. Gasoline and diesel emissions contributions to air pollution will continue to decrease in the U.S., but developing countries with older vehicle populations may be subject to higher levels; however, lower asthma prevalence is currently reported in these areas. The major factor in assessing vehicle contributions to asthma exacerbation is the fact that emissions from these sources have been reduced considerably over the last two decades while asthma prevalence has been increasing.

Indoor Air Quality

Since the relationship between outdoor air pollutants and asthma is ambiguous, one would not expect to find a relationship between outdoor air pollutants that are inside of a building because the efficiency in which they penetrate inside is less than 100 percent so their indoor concentrations will be lower. However, indoor sources of chemicals and solvents or poorly maintained combustion sources (*i.e.*, stoves, furnaces, and fireplaces) are potential sources that should be cause for concern for sensitive individuals.

Small Family Size

A highly speculative hypothesis is that small family size prevents cross-infection between young family members. The reduced rate of infection might explain an increased prevalence of asthma. However, more research is needed before definite conclusions are drawn between family unit size and asthma.

Thunderstorms

Thunderstorms can lead to "epidemics" of asthma attacks. This is due to the dispersal of grass pollen allergens that can precipitate asthma attacks in patients with grass pollen allergy.

Tobacco Smoke

The IOM committee found sufficient evidence for a causal association between maternal smoking during pregnancy and subsequent development of asthma in the child. However, one study has shown that exposure to ETS may trigger asthma attacks, while another study done in inner cites of the US, showed very little evidence that ETS made

asthma worse in children. As for the effect of ETS on lung function, people complain a lot, but any change is hard to document.[x]

Conclusions

Asthma prevalence is increasing in the United States, particularly in children. There are many studies suggesting this trend, but lack of a standard definition for asthma makes quantification of the trend difficult. There is a need for a national asthma registry. Conclusions on prevalence will be more accurate when there is consistency of data.

Asthma is a complex disease and we do not know what causes it. We know that genetics play a role but genetics alone does not explain the disease. The strongest (but incomplete) evidence exists for interaction between genetic factors, indoor environmental allergens and tobacco smoke. Our understanding of environmental triggers for asthma exceeds that of delineating any particular environmental causes for asthma. Causes, unlike triggers, are speculative, or highly speculative, requiring much more research and time. Some highly publicized "causes" of asthma (i.e., air pollution) may in fact be triggers for acute asthma symptoms but may have a minimal, if any role at all in causing the initial development of asthma.

Clinical guidelines for asthma treatment need to be followed. Not all physicians who treat patients with asthma know the latest recommendations for disease management and treatment. A most effective target in this regard would be education of primary care physicians (internists, pediatricians, and family physicians) in the importance of keeping the Goals of Therapy as recommended by the "Global Initiative for Asthma", which are the following:

- Minimal or no chronic symptoms including nocturnal symptoms
- No or infrequent acute episodes
- No Emergency Room visits or missed days in school
- Infrequent need for beta2-agonist type of medication
- No limitations of activities – even sports
- Near normal lung function
- Minimal or no adverse effects from anti-asthma medications

An Enigma

Why is it that our collective results treating Hypertension, which is a silent disease treated with drugs that make one feel bad, are far better than the collective results of treating Asthma, which is a disease with troublesome symptoms that can be treated with drugs that make one feel much better?

Better education for patients and their families are needed. Asthma can be managed and a lot of hospital admissions and even deaths avoided. Patients must be taught about their disease, what triggers attacks, and how to manage it. They must accept personal responsibility for compliance with proper disease management. Specifically, many patients must know the use and value of home peak flow measurements and how to use

the devices that deliver their medications correctly. Failure to do this will result in unnecessary lost time from school or work, hospitalizations and even death. Health care payers would gladly trade a decade's pharmaceutical costs for just one day's intensive care unit (ICU) bill.

- **Patient and physician "Steroid-o-phobia"**
- **Asthma is an emotional illness**
- **Asthma is an acute disease**
- **Asthma medications are addictive**
- **Asthma medications become ineffective if they are used regularly**
- **Asthma is not a fatal illness / It does not kill**

Better access to medical care is needed. We need better, more confident ways to define people at risk and a better understanding of the barriers to medical care they face.

Triggers of which we are more certain need to be removed where possible. There is evidence that sensitivity (allergy) to dust mites, cockroaches, cat dander, and/or Alternaria play a role in at least triggering asthma attacks. It seems reasonable to clean homes, workplaces, and schools to reduce exposure to these triggers. This may not prevent all asthma attacks, but it may lessen their frequency and/or severity at least in patients where these substances are known to trigger an asthmatic reaction. Finally, eliminating tobacco smoking by expectant mothers and by mothers of young children also makes sense.

Studies of how to reduce antigen burden and how it affects asthma incidence are needed. Are we removing the triggers that cause an asthmatic attack?

Disease management

The management of asthma is a complex issue depending on the frequency and severity of any given patient's symptoms or "attacks" of asthma. Presently, there are guidelines published by the NIH and other national and international asthma organizations. Physicians need to be familiar and up-to-date with these guidelines and management strategies. They also must involve their patients in the management plan.

In addition, asthmatic patients need to be able to discuss with their doctors a strategy that is appropriate for them. Self-management involving patient education reduces emergency room visits, hospital admission, unscheduled visits, lost school days, and lost workdays.

Appendix A

Forecasted Estimates of Self-Reported Asthma Prevalence by State, 1998

State	Number Of cases	Estimated Prevalence	95% Confidence Interval %	Standard Error (%)
Northeast				
Connecticut	215,900	6.6	5.6-7.5	7.2
Maine	80,300	6.4	5.4-7.4	7.8
Massachusetts	401,000	6.5	5.6-7.5	7.2
New Hampshire	78,500	6.6	5.5-7.6	7.8
New Jersey	540,400	6.7	5.7-7.6	7.2
New York	1,236,200	6.8	5.8-7.8	7.3
Pennsylvania	800,900	6.6	5.6-7.5	7.2
Rhode Island	64,400	6.5	5.5-7.4	7.3
Vermont	39,500	6.5	5.5-7.6	7.8
Total	3,241,200	6.7	5.7-7.6	7.3
Midwest				
Iowa	190,100	6.6	5.6-7.6	7.5
Illinois	795,200	6.7	5.7-7.6	7.5
Indiana	398,400	6.7	5.7-7.7	7.3
Kansas	174,900	6.7	5.7-7.6	7.3
Michigan	642,300	6.7	5.7-7.7	7.5
Minnesota	318,600	6.7	5.8-7.7	7.1
Missouri	362,300	6.1	4.7-7.4	11.3
Nebraska	112,100	6.7	5.7-7.7	7.4
North Dakota	43,600	6.7	5.7-7.6	7.3
Ohio	748,200	6.7	5.7-7.6	7.4
South Dakota	51,000	6.7	5.8-7.7	7.3
Wisconsin	350,800	6.7	5.7-7.7	7.2
Total	4,187,600	6.6	5.6-7.6	7.4
South				
Alabama	280,500	6.0	4.8-7.1	9.5
Arkansas	162,600	5.9	4.9-6.9	6.9
District of Columbia	31,400	5.9	3.6-8.2	19.7
Delaware	44,300	5.9	4.9-6.9	8.5
Florida	863,900	5.8	4.9-6.8	8.0
Georgia	458,700	6.0	4.9-7.2	9.7
Kentucky	232,800	5.9	4.9-6.9	8.2
Louisiana	265,500	6.1	4.8-7.3	10.5
Maryland	307,300	6.5	5.6-7.5	7.2

Forecasted Results of Self-Reported Asthma Prevalence by State, 1998

State	Number of Cases	Estimated Prevalence	95% Confidence Interval	Standard Error (%)
Mississippi	167,900	6.1	4.7-7.4	11.3
N. Carolina	447,200	5.9	4.9-7.0	8.9
Oklahoma	191,700	5.8	4.8-6.7	7.9
S. Carolina	228,600	6.0	4.8-7.2	10.1
Tennessee	328,300	5.9	4.9-6.9	8.3
Texas	1,175,100	6.0	5.0-7.0	8.2
Virginia	403,400	5.9	4.9-6.9	8.6
W. Virginia	108,600	5.8	4.9-6.8	8.2
Total	5,697,800	5.9	4.9-7.0	8.8
West				
Alaska	42,500	6.7	5.7-7.7	7.7
Arizona	316,200	6.9	6.0-7.9	6.9
California	2,268,300	7.1	6.1-8.0	6.8
Colorado	283,700	7.1	6.1-8.0	6.8
Hawaii	73,100	6.0	4.1-7.8	15.3
Idaho	86,100	6.7	5.7-7.8	7.6
Montana	61,600	6.6	5.7-7.6	7.4
Nevada	125,700	7.2	6.3-8.1	6.4
New Mexico	121,800	6.8	5.8-7.8	7.2
Oregon	225,900	6.9	5.9-7.8	6.9
Utah	141,200	6.7	5.6-7.8	8.1
Washington	391,900	6.9	5.9-7.8	6.8
Total	4,172,400	7.0	6.0-8.0	7.0
U.S. total	**17,299,000**	**6.4**	**5.5-7.5**	**7.8**

Note: Persons were considered to have asthma if asthma had been diagnosed by a physician at some time in their life and they reported symptoms of asthma during the preceding 12 months.

Source: Rappaport and Boodram, 1998

Appendix B

History

The first known descriptions of a condition that might have been asthma, an association between feathers and wheezing, date from the 16th Century. Henry Hyde Salter documented the correlation of asthma with cold air, dust, and animals in 1911.

The first appreciation that asthma might be caused by a reaction to external factors was in 1552 when Girolamo Cardano relieved a prolonged severe episode of airway obstruction in the Archbishop of St. Andrews by removing his featherbed and leather pillows. Two centuries later, Van Helmont identified some of the causes of hypersensitivity in asthma, notably inhaled dust and foods. He also reported the hereditary susceptibility of the disease, the effects of climate and weather, and the impact of emotional upsets.

Also in the 17th century, Benardino Ramazzini, the father of occupational medicine, was the first to detail the occupational asthma seen in bakers, starch makers, animal handlers, and in those working with vegetable matters. Asthma caused by exercise was formally described by Sir John Floyer in 1698.

In 1864, Henry Hyde Salter described the correlation of asthma with cold air, vapor and fumes in the air (smoke, dust, pungent fumes, etc.) and inhaled animal and vegetable particulate matter. From 1900 onward, asthma came to be regarded as the pulmonary response to previous sensitization to a variety of allergens. In 1910, Meltzer suggested that asthma could be the result of an allergic phenomenon and eight years later, Walker presented the classic classification of asthma based upon skin test sensitivity. The latter remains in use in some form even to the present day.

From these remarks it is obvious that asthma is not a new disease. It has been around for centuries and so have the efforts of the medical profession to find cures or at least ways to minimize the symptoms. The first class of drug used in the treatment of asthma was the anticholinergics (atropine-like). These were used from the 1850's in the form of cigarettes and burning powders. The isolation of theophylline in 1888 and epinephrine in 1889 enabled the regular use of these agents for asthmatics in the early 1900's.

The first half of the 1900's saw many advances with the development of ephedrine for oral use (1925), and aminophylline, synthesized in 1908, for intravenous use (1937). Aminophylline was the staple for emergency treatment from 1937 into the 1970's.

It was not until 1950 that corticosteroids were found helpful in asthma and not until 1972 that the first inhaler of a corticosteroid came into regular use. That same year saw the first derivative of atropine, which lacked its unacceptable side effects. The next major advance in the therapy of asthma did not occur until 1997 when a new class of agents, leukotriene modifiers, became available.

The future can only be noted by the expression "hang on to your hats" as the scientific community has heeded the call for help and are developing a large array of new classes of agents designed to modify the inflammatory process and to help maintain normal airway tone and function in the face of whatever is causing the increase in incidence and prevalence which is seen.

Asthma Therapy - Historical Perspective

Year	Event & Drug name	Class of agent
4000 BC	Datura (Indian herbal remedy)	Anticholinergic
3000 BC	Ma Huang (Ephedra sinica)	Sympathomimetic
1802	Datura smoking introduced to UK	Anticholinergic
1833	Atropine isolated	Anticholinergic
1850 -1950	Asthma cigarettes, burning powders	Anticholinergic
1850 -1865	Atropine methonitrate (+/- isoproterenol)	Antichol Adrenergic
1859	Major benefit of strong coffee (H.H.Salter)	Methylxanthine
1861	Caffeine isolated from coffee	Methylxanthine
1887	Ephedrine isolated	Sympathomimetic
1888	Theophylline isolated from tea	Methylxanthine
1898	Epinephrine isolated	Sympathomimetic
1903	Epinephrine first used for asthma	Sympathomimetic
1907	Osler's "Modern Medicine" Amyl nitrate, Stramonium, Belladonna, Lobelia, Tobacco!, Morphine, Heroine, Strychnine, Atropine, Cocaine, adrenal extract	
1908	Aminophylline synthesized	Methylxanthine
1922	Aminophylline rectally used in asthma	Methylxanthine
1925	Ephedrine orally used for asthma	Sympathomimetic
1929	Epinephrine nebulised for asthma	Sympathomimetic
1933	Adrenal cortical extract tried in asthma	Corticosteroid
1936	Compound E (cortisone) isolated	Corticosteroid
1937	Aminophylline given intravenously	Methylxanthine
1940	Isoproterenol by inhalation	Sympathomimetic
1940s	Oral theophylline +/- ephedrine	Xanthine/Sympathom
1948	Anti-inflammatory effect of corticosteroids	Corticosteroid
1948	Allquist - α and β receptors described	Sympathomimetic
1950	Corticosteroids found effective in sthma	Corticosteroid
1952	Hydrocortisone, prednisone, ...	Corticosteroid
1954	Choline theophyllinate	Methylxanthine
1957	Nebulised corticosteroids useful	Corticosteroid
1958	Cromoglycate developed	Cromone
1960	Metered dose inhalers introduced	All types
1967	Landis - β_1 and β_2 receptors described	Sympathomimetic
1967	isoetherine and orciprenaline described	Sympathomimetic
1968	Salbutamol, the first $\beta_2 >> \beta_1$ agent	Sympathomimetic

1970s	Many slow release theophyllines developed	Methylxanthine
1972	Beclomethasone inhaler for asthma	Corticosteroid
1972	Ipatropium inhaler for asthma	Anticholinergic
1984	Nedocromil developed	Cromone
1990s	Salmeterol, Formoterol	Sympathomimetic
1994	Corticosteroid sparing and anti-inflammatory effect of theophylline described	Methylxanthine
1997	First leukotriene modifier available	LTRA

Project Participants

VADM Harold M. Koenig, Medical Corps, U.S. Navy (Retired), Project Chair

VADM Koenig became the thirty-second Surgeon General of the Navy and Chief, Bureau of Medicine and Surgery, on June 29, 1995. He retired from that position on June 30, 1998 after competing 32 years of active duty service. He currently serves as Chair and President of The Annapolis Center.

A native of Salinas, California, he attended the U.S. Naval Academy and received his Bachelor of Science Degree from Brigham Young University. He received his Medical Degree from Baylor University College of Medicine. He is certified by the American Board of Pediatrics in general pediatrics and pediatric hematology-oncology.

VADM Koenig is a Diplomate of the American College of Healthcare Executives. In 1994 the American Hospital Association named him "The Federal Health Care Executive of the Year".

VADM Koenig served in a variety of clinical roles in the Navy, including general medical officer, residency training program director, department chairman, hospital executive officer and commanding officer. His staff assignments before becoming the Navy Surgeon General included: command of the Naval Health Sciences Education and Training Command, Director of Health Care Operations in the Office of the Chief of Naval Operations, Deputy Assistant Secretary of Defense (Health Affairs) for Health Services Operations and Deputy Surgeon General and Chief of the Medical Corps.

VADM Koenig's personal awards include the Navy Distinguished Service Medal, Defense Superior Service Medal, Legion of Merit with Gold Star, Meritorious Service Medal with Gold Star, Navy Commendation Medal, and the Navy Achievement Medal.

Stuart L. Abramson, M.D., Ph.D.

Stuart L. Abramson is Assistant Professor of Pediatrics and Immunology at Baylor College of Medicine in Houston, Texas. He is Associate Director for Clinical Research and Health Professional Education at the Children's Asthma Center at Texas Children's Hospital and Chief of the Pediatric Allergy and Immunology Clinic at Ben Taub General Hospital in Houston. Dr. Abramson is an active clinician, teacher, and researcher and is currently Principal Investigator or Co-Investigator on several NIH and CDC-funded grants pertaining to asthma. Areas of focus include new approaches to asthma screening, medical management, self-management, and environmental control that can be generalized to community health providers and schools. Several projects involve computer-based technologies for education and physician decision-support.

Dr. Abramson is board certified in Pediatrics, Allergy and Immunology, and Diagnostic Laboratory Immunology. He is a fellow of the American Academy of Pediatrics, the American College of Allergy and Immunology, and the American Academy of Allergy, Asthma and Immunology. He has published over 80 peer reviewed articles, abstracts, and book chapters in the fields of allergy, asthma, and immunology and has served on several grant review panels. Other scientific memberships include the American Federation for Clinical Research, the Clinical Immunology Society, the American Association of Immunologists, the Society for Leukocyte Biology, and the Southern Society for Pediatric Research. Dr. Abramson currently serves as Chairman of the Regional Advisory Board for the American Lung Association of Texas, Southeast Region.

Dr. Abramson received his undergraduate B.A. in Biology, with honors, from The Johns Hopkins University and received his M.D. and Ph.D. degrees from Baylor College of Medicine as a graduate of the NIH-funded Medical Scientist Training Program. He completed his internship and residency in pediatrics at Baylor College of Medicine, Houston, Texas.. His allergy and immunology fellowship was at the National Institute of Allergy and Infectious Diseases, NIH, Bethesda, Maryland.

Patrick N. Breysse, Ph.D.

Patrick N. Breysse is a Professor at The Johns Hopkins University in the School of Hygiene and Public Health, Department of Environmental Health Sciences. He is also Director of the Center for Information Technology and Health Research (formerly known as - VDT and Health Center) at The Johns Hopkins University's School of Hygiene and Public Health.

Since 1993, Dr. Breysse has served as the Program Director of the Industrial Hygiene Training Program at The Johns Hopkins University's School of Hygiene and Public Health. Since 1999, he has served as Director of the Exposure Assessment Core of the Center for Childhood Asthma in the Urban Environment. Since 2000, he has served as Associate Director of the Center for Childhood Asthma in the Urban Environment.

A Board certified industrial hygienist, prior to coming to Johns Hopkins, Breysse was an industrial hygiene consultant to the Los Alamos National Laboratory in New Mexico.

Dr. Breysse is a member of the American Academy of Industrial Hygiene, the American Industrial Hygiene Association, and the American Conference of Governmental Industrial Hygienists. He has been elected Chairman of the American Conference of Governmental Industrial Hygienists (ACGIH), a four-year commitment to serve in the following capacity vice-chairman elect, vice-chairman, chairman, and finally past-chairman (2000 - 2004). He has written, reviewed, and consulted on numerous issues.

Dr. Breysse received his B.S. from Washington State University in Environmental Sciences, M.H.S. from The Johns Hopkins University in Occupational Safety and Health, and Ph.D. from The Johns Hopkins University in Environmental Health Engineering. He

received Postdoctoral training from the British Institute for Occupational Medicine, Edinburgh, Scotland.

Robert Bush, M.D.

Dr. Robert Bush received his M.D. from West Virginia University. He completed his training in internal medicine and allergy and immunology at the University of Wisconsin-Madison. After spending a year in private practice, he joined the faculty of the University of Wisconsin-Madison in 1978, where he is currently Professor of Medicine and Chief of Allergy at the Wm. S. Middleton VA Hospital. He is also co-director of the Allergy/Immunology Training Program. Dr. Bush also holds an appointment as Professor in the Department of Food Microbiology and Toxicology of the Food Research Institute at the University of Wisconsin-Madison.

Dr. Bush has been an active member of the American Academy of Allergy, Asthma, and Immunology. He is a former Chair of the Indoor Allergens Committee, and served on the Training Program Directors Executive Committee. He is a former Chair of the Environmental and Occupational Disease Interest Section, the VA Allergists Committee, and the Training Program Director's In-Training Examination Subcommittee. He is a Director of the American Board of Allergy and Immunology and serves on the Board of Directors of the American Academy of Allergy, Asthma, and Immunology.

Dr. Bush's research interests have centered on the ***Alternaria*** and fungal allergy and asthma therapy. He also has conducted research on food allergy issues and occupational asthma.

Raymond J. Campion, Ph.D.

Dr. Campion is the President and Executive Director of the Mickey Leland National Urban Air Toxics Research Center, which is located at the Texas Medical Center in Houston Texas. The Leland Center directs an environmental health research program focused on the role of the 188 air toxics in public health outcomes. It is supported via Congressional appropriations to the EPA, which provides assistance grants to the Leland Center. As a private/public research partnership, the Leland Center also receives funding from major US corporations interested in air toxics health effects.

Dr. Campion received the Ph.D. degree from Washington University in St. Louis and joined Exxon Research and Engineering Co. where he conducted research on photochemical smog formation and automotive emissions. He later joined Exxon Company USA in Houston where he served as Environmental Coordinator. In that capacity, he was responsible for air, water and waste issues for Exxon as well as interactions with federal and state governments and environmental groups

Dr. Campion became the Executive Director of the Leland Center with its formation in 1993, and later its first president. The Center has grown to an organization with

approximately two million dollars in peer-reviewed air toxics/health effects research and hosts annual scientific conferences and workshops focused on personal exposures to air toxics and respiratory health effects in urban areas. He is an adjunct associate professor of environmental sciences at the University of Texas and chairs the Advisory Board of the Southwest Center for Occupational and Environmental Health.

Peyton A. Eggleston, M.D.

Dr. Eggleston graduated from the University of Virginia Medical School. He began his Pediatrics training at Vanderbilt University and finished at the University of Washington. He trained in Allergy and Immunology at the University of Washington, and then took a faculty position at the University of Virginia. His research while at the University of Virginia concerned exercise-induced asthma and asthma associated with rhinovirus infections.

In 1981, he took a position in the Johns Hopkins University Department of Pediatrics. His research at Johns Hopkins has shifted to the relationship of asthma and airborne allergens. He conducted environmental challenge studies examining the effect of airborne particles containing animal allergens on sensitized volunteers. He also conducted trials to examine the health effects of reducing airborne allergens and participated in a trial of the effectiveness of allergen immunotherapy for chronic asthma. Dr. Eggleston has also directed projects to study the epidemiology of chronic allergic asthma in urban populations and a clinical trial of the reduction of cockroach allergen in urban homes.

Dr. Eggleston was promoted to Professor of Pediatrics in 1992, received a joint appointment in the Department of Environmental Health Science in 1998, and now directs the Johns Hopkins Center for the Asthmatic Child in the Urban Environment. He has served as President of several regional allergy societies, as a Director of the Board of Allergy and Immunology, and a Member of the Pulmonary and Allergic Diseases Committee for the U.S. Food and Drug Administration (FDA).

Alan Hedge, Ph.D.

Alan Hedge is a Professor in the Department of Design and Environmental Analysis, Cornell University. Since 1987, he has directed the Human Factors and Ergonomics in Environmental Design program. His research and teaching activities have focused on issues of work environment design, and workplace ergonomics, especially as these affect the health, comfort and productivity of workers. He actively researches several diverse but related issues concerning ways to improve facilities environmental design. His most recent project has focused on investigating the effects of indoor air quality and ergonomics on the sick building syndrome. Other research has included developing tools for visualizing information on behavior in buildings; evaluating the effects of breathing-zone filtration technology on office worker comfort, health and productivity; assessing the health risks of emissions from new carpet; and studying the reactions of facility managers and office workers to under-floor task-air ventilation.

He is a coauthor of a 1998 book, "Keeping Buildings Healthy", on the management of indoor environment issues. He has published extensively in books and refereed journals, and has presented papers at numerous national and international conferences. He has given testimony on indoor air quality and indoor environment design issues to several committees of the US House of Representatives and to OSHA in Washington, D.C., to the UK House of Commons, and to the New York State Assembly. He has served as a consultant and scientific adviser to several organizations and major corporations.

He is active in several professional bodies. He chairs the US TAG to ISO TC159 SC5 Work Environment Committee and the Work Environment Technical Subcommittee of the International Ergonomics Association. He is a founding member of the International Society for Indoor Air Quality and Climate and serves on the ISIAQ task force on survey tools.

David F. Lehmann, Pharm.D., M.D.

David Lehmann is Associate Professor of Medicine and Pharmacology at SUNY Upstate Medical University. He is also Executive Director of the Center for Health Outcomes Research at SUNY Upstate Medical University. In 1999, he was appointed Hospital Pharmacologist at the University Hospital at SUNY. In 1998, he was appointed Chief of the Division of General Internal Medicine and in 1998 he was appointed Chief of the Section of Clinical Pharmacology at SUNY.

Dr. Lehmann received his Doctor of Medicine at the Medical College of Wisconsin. He received a Doctor of Pharmacy at the University of Kansas City.

Dr. Lehmann participated in this project as a representative of the American College of Clinical Pharmacology.

E. Regis McFadden, Jr., M.D.

Dr. McFadden is the Argyl J. Beams Professor of Medicine and the Program Director of the General Clinical Research Center at the Case Western Reserve University School of Medicine. Dr. McFadden has a long and distinguished career during which he has served as Director of the Division of Pulmonary and Critical Care Medicine and the Director of Airway Disease Center at the University Hospitals in Cleveland, Ohio; an Associate Professor of Medicine at the Harvard University, Massachusetts Institute of Technology Combined Division of Health Sciences and Technology; an Associate Professor of Medicine at the Brigham and Women's Hospital at the Harvard Medical School; the Director of Pulmonary Function Laboratory at the University of Texas Medical Branch; Consultant in Pulmonary Disease at the Sidney Farber Cancer Institute; and, Director of the Adult Respiratory Diagnostic and Therapeutic Services of the University Hospitals of Cleveland.

Dr. McFadden has received awards such as the George W. Thorn Award for Teaching Excellence and the First National Asthma Education Program Award for Clinical Research from NIH. He has held offices and/or committee assignments in the American Federation of Clinical Research, the American Thoracic Society, the National Heart and Lung Institute (National Institute of Health), the National Institute of allergy and Infectious Disease (National Institutes of Health), and the Federal Drug Administration.

Dr. McFadden received his Doctor of Medicine from the School of Medicine at the University of Pittsburgh.

Clive P. Page, Ph.D.

Dr. Clive Page is Professor of the Division of Pharmacology and Therapeutics of the School of Biomedical Science at the King's College of London. Prior to this appointment, he served as a Lecturer and a Reader in Pharmacology at the King's College in London. He also did preclinical research for Sandoz Ltd. in Basle, Switzerland.

Dr. Page received his Ph.D. in Pharmacology at the King's College of London and a BSc (Honors) in Pharmacology at Chelsea College at the University of London.

Dr. Page participated in this project as a representative of the American College of Clinical Pharmacology.

Charles H. Pierce, M.Sc., M.D., Ph.D.

Dr. Pierce is Professor of Pharmaceutical Science in the College of Pharmacy and of Family Medicine at the College of Medicine at the University of Cincinnati. At this time he is also the Associate Director of the Office of Clinical Trials of the Children's Hospital Medical Center of Cincinnati and the Director of Clinical Research of the Research Division of RiverHills Healthcare in Cincinnati. He also Represents Harrison Clinical Research in the US.

Dr. Pierce has been an educator of students, practicing family physicians, and specialists for over 23 years and has been involved, often as the course director, in many CME courses aimed at the practical aspects of therapeutic problems. The condition where he has had the most prolonged interest and activity and where he has had the greatest impact has been in the field of asthma. Regarding the latter, he recently published an article of general interest entitled "Asthma Therapy from the Practice perspective: Changes in the Wind" (March, 1999, Journal of Clinical Pharmacology). He has chaired three national symposia regarding the problem of Asthma, its development, diagnosis and its management.

Dr. Pierce is an active fellow in the American College of Clinical Pharmacology (Regent 1995-2000, Chairman of the 2001 annual meeting) and the American Academy of Pharmaceutical Physicians. He is also a member of the American Thoracic Society, the Society, the European Respiratory Society, American Academy of Asthma, Allergy, and Immunology, and a long time fellow of the American Academy of Family Physicians.

Dr. Pierce received his master's degree in Pharmacology from the University of Minnesota and both his medical degree and doctorate, also in Pharmacology, from the University of Saskatchewan in Saskatoon, Canada. Dr. Pierce participated in this project as a representative of the American College of Clinical Pharmacology.

David L. Rosenstreich, M.D.

Dr. David L. Rosenstreich is a Professor in both the Department of Medicine and the Department of Microbiology and Immunology at the Albert Einstein College of Medicine. He also serves as Director of the Division of Allergy and Immunology at the Albert Einstein College of Medicine and Montefiore Medical Center.

After receiving his medical degree from the New York University School of Medicine, Dr Rosenstreich completed his residency in medicine at the Bronx Municipal Hospital Center of the Albert Einstein College of Medicine. He then joined the National Institutes of Health, where he did research in allergy and infectious diseases and cellular immunology. Dr Rosenstreich has received many awards, including the Danziger Distinguished Scholar Award in Microbiology and Immunology and a Public Health Service Commendation for his work with the US Public Health Service.

As a scientific investigator, Dr Rosenstreich has focused on the pathophysiology and etiology of allergic diseases, including asthma. His most recent studies concern the relationship between increased asthma and outdoor air pollutants. He has authored or co-authored over 160 original research publications in peer-reviewed journals, and invited articles, and is the editor of 3 books.

He is currently the editor of Practical Reviews in Allergy, Asthma, and Immunology and the Bronx Asthma Newsletter. He is also the Director of the Bronx Asthma Project, and serves as a consultant to the New York City Department of Health Citywide Asthma Initiative.

Dr Rosenstreich is a Diplomate of both the American Board of Internal Medicine and the American Board of Allergy and Immunology. He is also a fellow of the American Academy of Allergy, Asthma, and Immunology, the American College of Allergy, Asthma, and Immunology, the American Association of Physicians, the American Society for Clinical Investigation, and many other professional organizations.

Jack W. Snyder, M.D., J.D., Ph.D., DABT

Dr. Jack Snyder is a physician-attorney with training and experience in pharmacology, toxicology, pathology, and occupational medicine. Prior to assuming his new role, Dr. Snyder was a member of the full-time faculty in the departments of medicine, emergency medicine, and laboratory medicine at the Thomas Jefferson University in Philadelphia, Pennsylvania. He is a frequent lecturer, advisor, and consultant to corporate, academic, legal, and governmental organizations in matters involving legal medicine, forensic, sciences laboratory medicine, toxic torts, workers' compensation, hazardous waste, occupational disease, disaster planning, and adverse drug reactions.
Dr. Snyder received a B.S. in Chemistry and an M.D. from Northwestern University, a J.D. from Georgetown University, a Master of Public Health from Johns Hopkins University, a Master of Forensic Science from George Washington University, and a Ph.D. in Pharmacology & Toxicology from the Medical College of Virginia. He is the president of the American College of Legal Medicine, a member of the Board of Directors of The Annapolis Center, and serves as treasurer of the American Board of Legal Medicine. He is a member of the Florida, Virginia, and Pennsylvania bars, and is licensed to practice medicine in Pennsylvania, Virginia, Louisiana, and the District of Columbia.

Dr. Snyder has been certified by the American Boards of Preventive (Occupational) Medicine, Toxicology, Medical Toxicology, Toxicological Chemistry, Clinical Chemistry, Legal Medicine, Quality Assurance & Utilization Review, and Anatomic, Clinical, and Chemical Pathology, He has published widely in medical, scientific, and legal literature, and is recently the co-editor of the ninth edition of Conn's Current Diagnosis.

George T. Wolff, Ph.D.

Dr. George T. Wolff is a Principal Scientist with General Motors' Public Policy Center. He has a B.S in Chemical Engineering from New Jersey Institute of Technology, a M.S. in Meteorology from New York University, and a Ph.D. in Environmental Sciences from Rutgers University. He has been conducting research on air quality issues for over 25 years and has published nearly 100 peer-reviewed articles on air pollution and atmospheric science in the scientific literature.

Dr. Wolff is a member of U.S. EPA's Science Advisory Board and served as Chair of EPA's Clean Air Scientific Advisory Committee during the recent review of the ozone and particulate matter air quality standards. He also serves on numerous scientific/environmental committees for the automobile industry, the U.S. Environmental Protection Agency, the National Research Council, the Health Effects Institute, and the State of Michigan. He is a fellow member and former director of the Air and Waste Management Association and is a member of the American

Meteorological Association. Dr. Wolff is a member of The Annapolis Center's Board of Directors.

Ronald E. Wyzga, Sc.D.

Ronald E. Wyzga is the Technical Executive/Area Manager of Air Quality Health and Risk for the Electric Power Research Institute (EPRI). As such, his research interests are in environmental risk assessment and the heath effects of air pollution. Dr. Wyzga received an AB in Mathematics from Harvard College, a MS in Statistics from Florida State University, and a Sc.D. in Biostatistics from Harvard University. Prior to joining EPRI, he worked at the Organization for Economic Cooperation and Development in Paris where he co-authored a book on economic evaluation of environmental damage.

Dr. Wyzga serves on, and has chaired, several committees for the EPA Science Advisory Board and National Academy of Sciences (NAS), including the NAS committee that will oversee the EPA's particulate matter research program through 2002. Dr. Wyzga is a Fellow of the American Statistical Association.

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[ii] **Centers for Disease Control and Prevention (CDC), National Center for Environmental Health, Asthma Prevention Program**

[iii] ISAAC (The International Study of Asthma and Allergies in Childhood) Steering Committee. 1998. Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis and atopic eczema: ISAAC. Lancet 351(9111):1225-1232.

[iv] Carter-Pokras and Gergen 1993, Crain et al 1994, and Becket et al 1996.

[v] Carbon monoxide, sulfur dioxide, particulate matter, ozone (the precursor of which are "volatile organic compounds"), and lead

[vi] IOM, pages 106 and 114.

[vii] IOM, page 114

[viii] IOM, page 158

[ix] IOM, pages 150-151

[x] Strachan and Cook Thorax 1997;52:905 and Strachan and Cook Thorax 1998;53:117. Yunginger et al: A community based study of the epidemiology of asthma: incidence rates 1964-1983 Am Rev Resp Dis 1992;146:888.