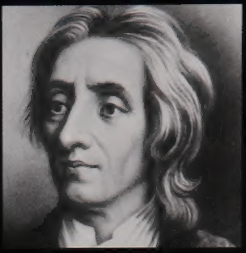

BREATH OF LIFE

An exhibition that examines the history of asthma, the experiences of people with asthma, and contemporary efforts to understand and manage the disease.

National Library of Medicine
National Institutes of Health
U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

BREATH OF LIFE

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National Library of Medicine
National Institutes of Health
U.S. Department of Health and Human Services
Bethesda, Maryland 20894

An exhibition March 23, 1999–March 28, 2001

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An exhibition that examines the history of asthma, the experiences of people with asthma, and contemporary efforts to understand and manage the disease.

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National Library of Medicine Director's Statement

The creation of the exhibition *Breath of Life* at the National Library of Medicine reflected not only the intellectual enthusiasm and involvement of so many of my colleagues, but also a gathering sense of urgency. We all came to realize that great strides had been made in understanding—at least in large part—the bodily processes and treatment of asthma, and yet we saw enormous numbers of new cases—especially in children—arising every day. Indeed, the basic incidence of asthma in the United States continues to soar.

Thus we began to see the exhibition as more and more urgently needed as a means to help children and parents to understand the real nature of this treatable and manageable disease.

Many distinguished administrators, scientists, and clinicians, and Congressman William Young, attended the opening reception of the exhibition on March 22, 1999. Joining the crowd were children from the National Institutes of Health Children's Inn, junior high-school athletes, local and national press, and a fascinated crowd of adults. Also in attendance were the Muppets, who introduced their asthmatic member, Dani, to the audience. In spite of being an event centered on medicine and science a good time was had by all.

Three American winners of Olympic gold medals (Tenley Albright, figure skating, 1956; Nancy Hogshead, swimming, 1984; and Jackie Joyner-Kersee, heptathlete, 1988, 1992) presided over the evening's events. They gave assurances to the audience that great athletic feats—such as winning Olympic gold medals—are possible for people with asthma who collaborate with their physicians in striving for excellent management of their own health. I have personally seen on many occasions that children and adults are consistently gratified and sustained by this message of *Breath of Life*.

The electronic (DVD) version of the exhibition has circulated widely and is available online at http://emall.nhlbihin.net. The DVD frequently offers a "gathering point" for conversation and planning by groups concerned about asthma and finding help for patients. This printed catalogue of the exhibition will also, I hope, find a wide audience. May it permit the unhurried and careful consideration of this vexing problem that a book affords.

Lastly I congratulate and thank all those who helped in creating this fine exhibition.

Donald A.B. Lindberg, M.D.
Director, National Library of Medicine


CURE
IN SARANAC LAKE

Breath of Life

In the United States, fifteen million people are affected by asthma, and five thousand die of the disorder or its complications every year. Between 1980 and 1996 the incidence of asthma more than doubled, with children under five years old experiencing the highest rate of increase.

Breath of Life is the story of our increasing knowledge and the continuing challenge of asthma, one of the oldest known human disorders. The causes of asthma are varied—some known, some unknown—manifested by symptoms of wheezing, shortness of breath, and tightness of the chest. The patient with asthma suffers from inflammation, constriction, and mucus plugging of the airways to and from the lungs—which obstruct the free flow of air through the bronchial airways. With air trapped in the lungs, the person with asthma has difficulty expiring air through the narrowed bronchial tubes. Forced air passes through mucus plugs like the reed of a wind musical instrument, producing the characteristic vibratory sound of wheezing.

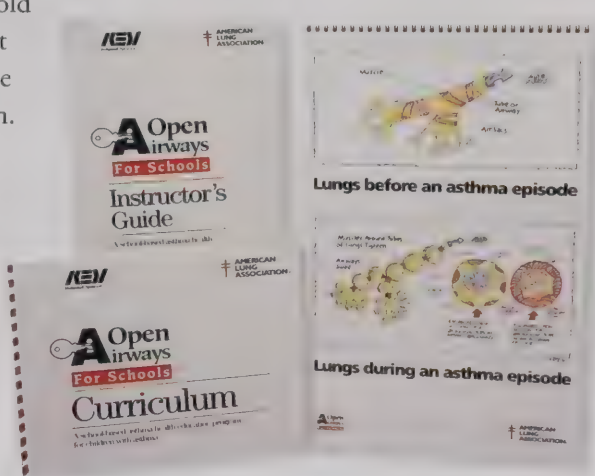
The Lord God formed man of the dust of the ground and breathed into his nostrils the breath of life; and man became a living soul.
—Genesis 2:7

In susceptible persons, this chronic disorder may be triggered by a variety of factors: respiratory tract infections, industrial air pollutants, environmental agents such as airborne pollens and molds, allergenic foods, household dusts, inhalant allergens, and even sudden changes in the weather. It is becoming increasingly evident that asthma is the outcome of these triggers and their common roles in effecting bronchial inflammation.

Four Perspectives of Asthma

The efforts to unravel the causes of asthma are challenging. Identifying the triggers of the disorder with precision remains elusive. Over the years, four distinct perspectives have evolved.

First, asthma has been viewed as a disorder of the lungs. Physicians have adapted the tools and techniques originally developed for anti-tuberculosis therapy for the treatment of asthma.



Open Airways for Schools flip chart, Curriculum Guide, and Instructor's Guide, 1998

The American Lung Association has conducted public education campaigns, health advocacy, and research since the early 1900s. Asthma and other chronic lung diseases are now the focus of their work.

Courtesy American Lung Association

Winter Carnival parade at Saranac Lake, New York, ca. 1900

In the late 1800s and early 1900s, Saranac Lake was one of the most prominent spa areas in the United States for patients with tuberculosis and other lung diseases.

Courtesy Adirondack Collection, Saranac Lake Free Library

Secondly, asthma has been viewed as an allergic condition. Consequently, researchers identified the character of the antibodies that cause allergic reactions and developed injection techniques for blocking and reducing antibody production by an immunization-like procedure known as immunotherapy.

A third perspective linked asthma to emotional distress. In the 1940s and 1950s, physician M. Murray Peshkin (1892–1980) of New York noticed that some of his most severe asthma patients markedly improved when they were removed from stressful situations. In the case of children, for whom he founded a retreat in a controlled environment at the Children's Asthma Research Institute and Hospital in Denver, he coined the term "parentectomy" to describe his therapeutic method involving separating children from their parents.

Finally, asthma was viewed as the result of exposure to environmental irritants—one reason why asthma sufferers sought refuge in clear mountain air, warm dry climates, and air-pollution free atmospheres. Certainly it is now appreciated that a healthy environment at home and at work is critically important in the control of asthma.

Each of these perspectives provided insights into causative, triggering, and exacerbating factors in asthma, and led to the design of corresponding approaches to managing the disease. Advances in the biomedical sciences have taken management of asthma beyond the historical panorama of balancing the four humors, the letting of blood, the smoking of tobacco, and the breathing of medicated aerosols. The search for the causes and treatment of this ancient disorder continues.

Seventy-five allergen patch test kit

When they began allergy injections in the 1910s and 1920s, allergists had to collect, purify, and sterilize allergen extracts themselves. In the late 1940s private companies began to manufacture extracts for skin testing and immunotherapy.

Courtesy Mütter Museum, The College of Physicians of Philadelphia

Skin Testing

When a patient undergoes a skin test, diluted extracts from allergens are injected under the skin. A positive reaction is indicated by a small, raised, reddened area (called a wheal). The doctor measures the extent of the reactions by drawing a line around each of the wheals on the patient's arm.

Courtesy National Institute of Allergy and Infectious Diseases

North Shore Health Resort, Winnetka, Illinois, late nineteenth century

People have long traveled to ocean or mountain locations—thought to have especially pure air or water—to improve their health. With widespread rail and steamship travel and extensive advertising, nineteenth-century spas and resorts opened in remote locations and attracted a broad clientele. People with tuberculosis, asthma, and hay fever often moved permanently to places thought to have air or water conducive to good health.

Construction worker

Bending over using a handsaw, this construction worker inhales a great deal of sawdust, which can trigger asthma as a general lung irritant or a specific allergen.

Courtesy National Institute for Occupational Safety and Health

M. Murray Peshkin and philanthropist Fannie E. Lorber with two children from the National Asthma Center (formerly the National Home for Jewish Children) in Denver, 1956

A founder and former president of the American College of Asthma, Allergy and Immunology.

Courtesy National Jewish Medical and Research Center


高大如天地
光明如日月
千億萬年後
其徳永不渇
寛政十年吉月冬至之日
大日本太盤令従五位下
朝散大夫大和守和氣成
美君人題書

Symptoms of Breathlessness

Virtually all cultures in all times have recognized the importance of breathing and have tried to identify the circumstances that inhibit airflow to and from the lungs. To cite one modern example, the student of yoga, learning to breathe properly during exercise postures, is practicing the spiritual discipline developed by ancient Hindu philosophers who linked adequate breathing, *prana*—to use the Sanskrit word—with the soul. The breath, they believed, builds a connection between the mind, the body, and the spirit.

Perhaps the earliest description of what is assumed to be asthma dates back to ca. 2700 BC. Shen-Nung, sometimes called the Fire Emperor of China and regarded as a founder of Chinese medicine, described remedies for the treatment of multiple disorders including those that affected the chest. As the first known herbalist, he recorded what he had learned about the medicinal effects of many plants.

***Ma huang* plant (*Ephedra sinica*): (female/male). Illustration from B.E. Read, *Chinese Medicinal Plants: Ephedra*, 1930**

Plants of the *Ephedra* genus are native to Asia and the Americas, but many varieties are not effective stimulants. Species from India and China are particularly potent; those native to North America are not.

Courtesy Harvard University, Cambridge, Massachusetts

***Three Chinese Emperors of Medicine*, 1798**
Artist unknown
Japanese painting

The legendary founders of Chinese medicine, Huang Di (r. 2697-2597 BC) (left), Fu Xi (center), and Shen-Nung (ca. 2700 BC), were thought to walk with the gods. In Chinese stories they are said to be among the first humans. Fu Xi is credited with introducing yin and yang, the principles that separate the universe into male and female, light and dark.

Courtesy East Asian Collection, The Library and Center for Knowledge Management, University of California, San Francisco

Female

Male

One of these was the plant *ma huang*, the botanical source of what is known today as ephedrine. Identified as a treatment for what Shen-Nung termed "coughing up," *ma huang* was used for centuries in China for the relief of cough and bronchial asthmatic symptoms. We believe that the condition described by Shen-Nung was asthma.

To the Chinese, breathlessness was a symptom of the body's balance falling into disorder. Relief could be found in the restoration of balance. According to the ancient Chinese concept, health and well-being are controlled by the flow of energy—the life force they call *ch'i*—and breathing difficulties are a symptom of its imbalance. Indeed, for centuries, traditional Chinese medicine has advocated treating asthma by "restoring the balance" of the body.

Lilly Syrup No. 110, Ephedrine Sulphate, 1932

Lilly Inhalant No. 20, Ephedrine Compound, 1932

Swan-Myers Ephedrine Inhalant No. 66, ca. 1940

Courtesy National Museum of American History, Smithsonian Institution

Ephedrine

Confirmation of Shen-Nung's observations of the therapeutic properties of *ma haung* came in the early 1920s when the Japanese investigator Jokichi Takamine (1854–1922) isolated ephedrine from the plant. Later, the research team of Ko Kei Chen (1898–1988), a Chinese physician, and American pharmacologist Carl F. Schmidt (1893–1988), conducted the first investigation of ephedrine's cardiovascular effects while working at the Peking Medical College in 1924. They found the effects of ephedrine and adrenaline on bronchial spasm to be similar, but they noted the advantages of ephedrine being taken by mouth compared to adrenaline, which required administration by hypodermic injection. For the relief of asthma, they suggested that it was reasonable to expect beneficial results from ephedrine, although the action of adrenaline was prompt and effective.

Ephedra mahuang [sic]
(Ephedra vulgaris)

Ma huang has been an ingredient in Chinese medicines for centuries.

Courtesy National Museum of American History, Smithsonian Institution


FLEGMATICVS ·3·
FLEGMATICI NVLLAS IN MENTIS ACVMINE VIRES ·
IDCIRCO MERITÆ NIL QVOQ LAVDIS HABENT

Asthma and Western Medicine

The word "asthma" derives from the classic Greek word for gasping. Greek and Roman physicians used the term to describe a shortness of breath believed to be the result of an imbalance between the four body humors that controlled health—yellow bile, black bile, blood, and phlegm. Imbalances in the humors determined an individual's propensity to sickness and the kinds of disorders to which he or she was susceptible. Asthma, characterized by coughing, wheezing, and respiratory congestion, was regarded as an excess of phlegm. Treatment of the condition involved adjusting the balance of the four humors. One effort to achieve this objective, blood letting, influenced medical practice well into the eighteenth century.

The first description of asthma as the disease we know today is attributed to a Greek physician, Aretaeus, who practiced in Rome after training at the Greek library and medical center in Alexandria. He noted the symptoms of "heaviness of the chest, difficulty of breathing when running or during other exertions, there is wheezing and hoarseness. The cheeks become ruddy, the eyes protuberant, there is a need for air, there is an incessant and laborious cough and if the symptoms persist, suffocation" (Aretaeus of Cappadocia. "On the Causes and Symptoms of Chronic Diseases." In Francis Adams, ed. and trans., *The Extant Works of Aretaeus the Cappadocian* [London: Sydenham Society, 1856] Book I, Chapter XI, pp. 316–18).

De Causis et Signis Acutorum et Diuturnorum Morborum, Libri Quatuor (Of the Causes and Signs of Acute and Morbid Disease)
Aretaeus of Cappadocia (81–138?)
Oxford, 1723

Aretaeus of Cappadocia carefully described asthma, attributing it to thick and viscid phlegm caused by coldness and humidity experienced by the patient.

Flegmaticus 3
Virgilius Solis, the Elder (1514–1562)
Engraving

An excess of phlegm made a person phlegmatic, and also lazy, sleepy, and languid. This was thought to be the most common cause of asthma in ancient Greek medical study.

Following the decline of the Roman Empire in the fifth century, progress in medicine slowed as Western medical practice became embroiled in alchemy and astrology. As the seat of medicine and culture moved eastward from Rome, Byzantine physicians played important roles in preserving the writings of the Greek physicians by translating their works first into Arabic, and subsequently into Hebrew and then Latin.

The first treatise on asthma was written in 1190 by Moses Maimonides. Born in Cordova, Spain, the philosopher, rabbi, and physician fled to Egypt to escape religious persecution by Islamic invaders. There, as physician to the court of Saladin, Sultan of Egypt and Syria, Maimonides was given responsibility for the care of Saladin's asthmatic son, Almalik Alafdal. From this circumstance, Maimonides wrote *De Regimine Sanitatis ad Soldanum Babyloniae (Regimen of Health for the Babylonian Sultan)*, in which he provided advice and recommendations for a program of prevention and treatment for the Prince to follow.

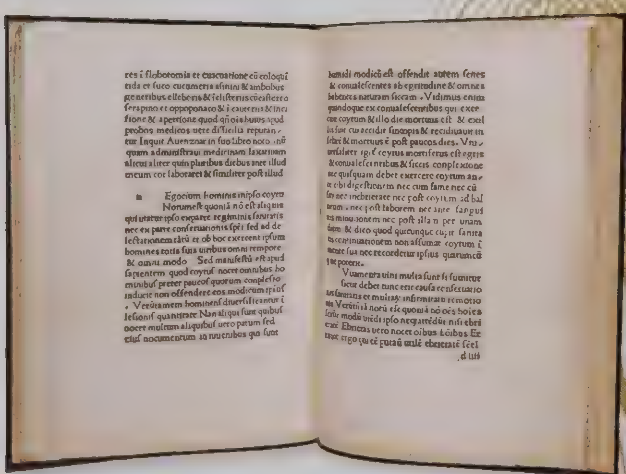
Recognizing that he did not have a cure for asthma, Maimonides recommended measures for living with the disorder. He noted that dry air was preferable to the humidity prevailing in Alexandria, situated as it is in the Nile delta, and thus suggested that the Prince live in Cairo. He counseled the Prince to keep an even temper, and adopt a moderate lifestyle in food, drink, and sleep. One of Maimonides' recommended remedies was chicken soup.

For all practical purposes Maimonides' advice was the only available course of action for the relief of asthma for the next several hundred years and in fact his advice is still given to the asthmatic patient today: avoid substances and factors that can trigger an asthmatic attack.

Aretaeus, the Cappadocian
Artist unknown
Illustration from Johannes Sambucus (1531–1584), *Icones Veterum aliquot ac Recentium Medicorum Philosophorumque (Images of Some Ancient and Recent Physicians and Philosophers)*, 1901

Maimonides
Artist unknown

Courtesy The Francis A. Countway Library of Medicine, Boston



De Regimine Sanitatis ad Soldanum Babyloniae (Regimen of Health for the Babylonian Sultan)
Moses Maimonides (1135–1204)
Florence, 1481

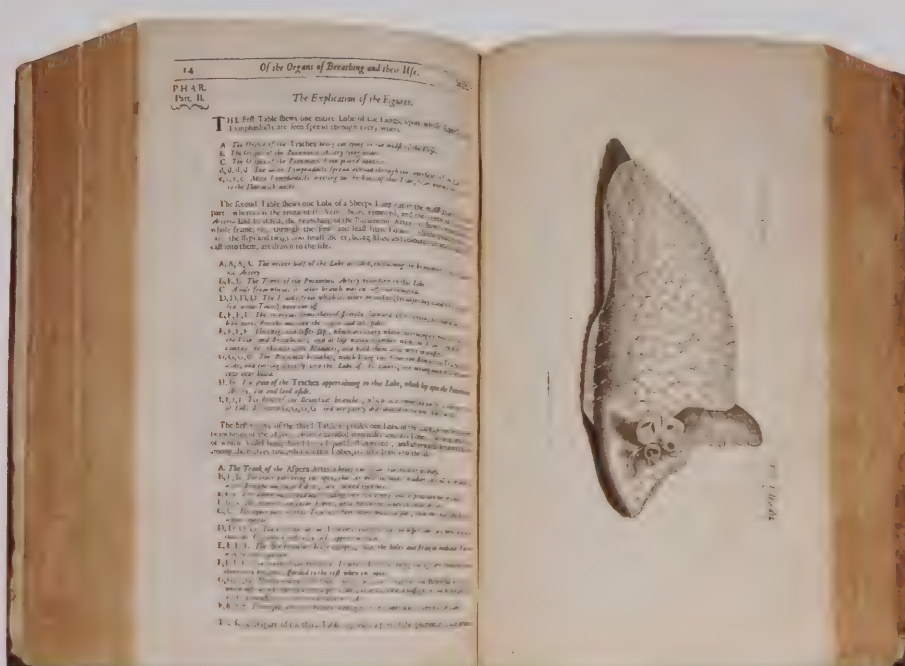
Asthma: From Symptoms to Disease

Following the Renaissance, with both the rediscovery of classical Greek thought and advancing knowledge of anatomy and pathology, asthma became more widely recognized as a specific disorder. The concept of its manifestation due to spasm of the bronchial tubes was proposed by the English physician and neuroanatomist Thomas Willis in about 1670. Willis had wide interests, among which were the convulsive and spasmodic nature of asthmatic paroxysms (from which he suffered) and their relationship to the innervation of the bronchi. These studies led to a better understanding of asthma as a bronchial disease.

A generation later another English physician, Sir John Floyer, identified asthma as an entity distinct from other pulmonary diseases, and as different from simple breathing difficulties. His definition revolutionized approaches to the mechanism and management of the disease.

Thomas Willis (1621–1675)
Dr. Willis's Practice of Physick
London, 1684

English physician Thomas Willis was one of the first European medical scholars to synthesize the observation of symptoms, which was the province of physicians, and the careful study of the dissected body, which had been the realm of the separate professions of surgeons and anatomists.

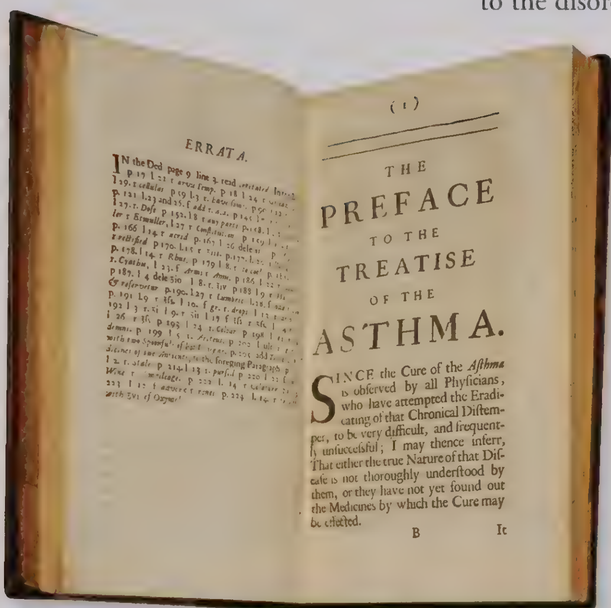


***Antoine-Laurent Lavoisier and His Wife*, 1788**
Jacques-Louis David (1748–1825)
Photographic reproduction of a painting

Antoine-Laurent Lavoisier, a French chemist, is pictured in his study with his wife, Marie-Anne, whose drawings illustrated all of his works. To the right of the quill pens is a gasometer of the type Lavoisier used to determine the composition of air in the 1780s.

Courtesy The Metropolitan Museum of Art, Purchase, Mr. and Mrs. Charles Wrightsman Gift, in honor of Everett Fahy, 1977. (1977.110) © 1989 The Metropolitan Museum of Art

Floyer is best known for his focus on counting the pulse. He used a watch to time different pulse and respiratory rates resulting from the influence of emotions, diet, climate, temperature, and various drugs and diseases. As an asthma sufferer, he wrote about his own experience after exercise, and after exposure to environmental factors such as tobacco smoke, dust, and specific foods. He noted the constriction of the bronchi and the wheezing that characterizes asthma, speculated on the causes, and was one of the first to note that asthma ran in families—that there was a heritable predisposition to the disorder.



Sir John Floyer (1649–1734)
The Treatise of the Asthma
London, 1698

Sir John Floyer, an asthmatic English physician, wrote his *Treatise of the Asthma*, which made the case for considering asthma a separate disease from other causes of breathlessness. The authoritative text on asthma for over a century, Floyer's book went through four English editions and was translated into French.

In his book, *The Treatise of the Asthma* published in 1698, Floyer described the condition: "I have assigned the immediate cause of asthma to the straightness, compression, or constriction of the bronchia. The slowness of inspiration and expiration depends on the stiffness or straightness of the lungs . . . which resist the action of the pectoral muscles: 'tis a long time before the air can be drawn in, and almost as long before it can be forced out, because of the constriction of the bronchia'" (Floyer, Sir John. *The Treatise on the Asthma* [London: Richard Wilkins, 1698]).

About the same time Floyer was working in England, an Italian physician, Bernardino Ramazzini, published *De Morbis Artificum (Diseases of Workers)*, his original observations on the sources and causes of illnesses among workers in a large number of occupations and trades. It was the first comprehensive account of occupational diseases. It is largely due to Ramazzini that many modern physicians note patients' social, environmental, and occupational circumstances as integral factors in recording and evaluating medical histories.

Bernardino Ramazzini (1633–1714)
De Morbis Artificum (Diseases of Workers)
Padua, 1713

Bernardino Ramazzini, an Italian physician, described "asthma" in bakers, miners, farmers, gilders, tinsmiths, glass-workers, tanners, millers, grain-sifters, stonecutters, ragmen, runners, riders, porters, and farmers. Ramazzini outlined health hazards of the dusts, fumes, and gases that such workers inhaled. The bakers and horse riders described by Ramazzini would today probably be diagnosed as suffering from allergen-induced asthma. The lung diseases suffered by most of the other workers would now be classified as "pneumoconiosis," a group of dust-related chronic diseases.

Among the occupations Ramazzini studied were baking and milling, and the conditions he referred to as bakers' and millers' asthma. He noted that those who worked with wheat, barley, and other grains could not help inhaling floating particles of the grains liberated during the measuring and sifting process. He envisioned the formation of balls of dough that clogged the bronchial tree. These particles, he said, "ferment in the salivary juice and stuff not only the trachea but the stomach and lungs with a sort of paste" producing coughs, shortness of breath, hoarseness, and finally asthma (Ramazzini, Bernardino. *Diseases of Workers.* Wilmer Cave Wright, trans., *De Morbis Artificum,* 1713 [New York, London: Hafner, ca. 1964]).

The Oxygen Revolution

In the eighteenth century, advances in chemistry shed new light on the understanding of the role and function of the respiratory system.

In 1774, the English chemist Joseph Priestley devised experimental techniques for preparing and collecting gases that included focusing sunlight through a lens to generate heat directed to a sample of mercuric oxide in a closed vessel. The released gas vigorously enhanced the burning of a candle. In Priestley's own words, "I have discovered an air five or six times as good as common air." He named this "good air" dephlogisticated air and estimated that it accounted for some 20 percent of the atmosphere. A decade later, the French chemist Antoine-Laurent Lavoisier, repeating Priestley's experiment, named the "good air" oxygen. Subsequently, he demonstrated the body's requirement for oxygen to convert food into energy.

Asthma is life-threatening when the disorder deprives the body's vital organs of oxygen. The shortness of breath in asthma is oxygen hunger.

Joseph Priestley
Artist unknown
Engraving

In 1791, the home and laboratory of English clergyman and scientist Joseph Priestley (1733–1804) were burned by a mob angered by his unconventional religious beliefs and support of the French Revolution. Priestley left England in secrecy in 1794, settling in Philadelphia, where he founded the first Unitarian church in North America. In 1804, he died in Northumberland, Pennsylvania.

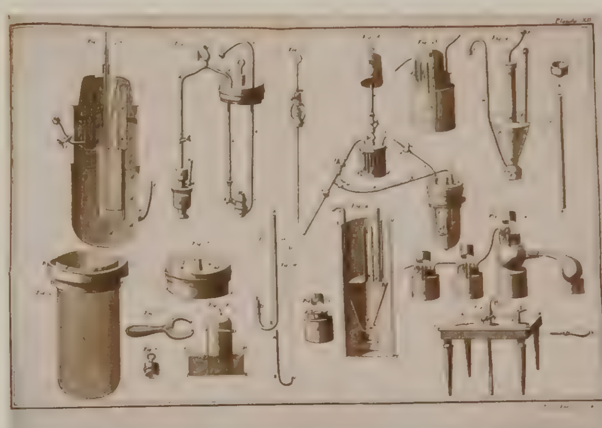


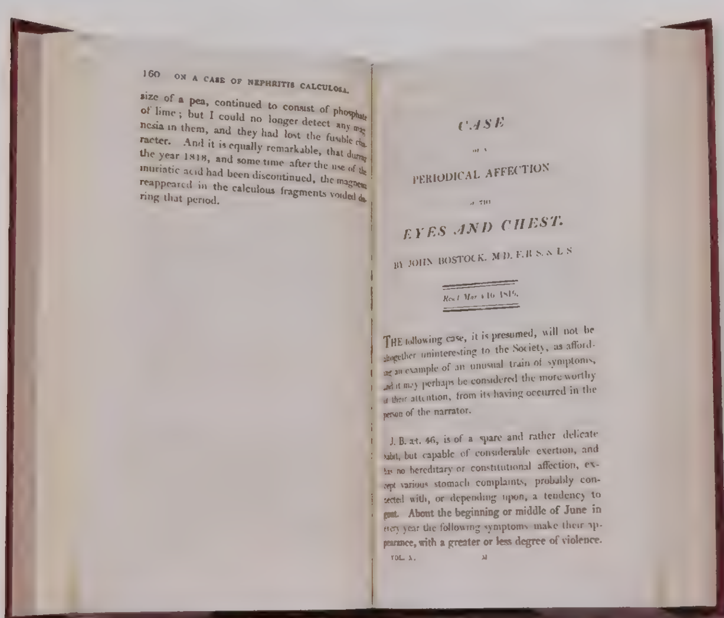
Plate 12
Marie-Anne Lavoisier's illustration from Antoine-Laurent Lavoisier (1743–1794), *Traité élémentaire de chimie (Elements of Chemistry)*, Paris, 1789

Lavoisier's gasometer was the first instrument to make accurate measurements of gases. Because gases can be compressed, in order to measure the amount of a gas used in an experiment, Lavoisier had to find a way simultaneously to measure both changing volume and changing pressure or to hold one constant while measuring the other. He used a piston to hold gas pressure constant while measuring the volume of gases used in his experiments. In the 1850s, British and Australian physician John Hutchinson (1811–1861) modified a gasometer to make the first spirometer for measuring the volume of a patient's breath.

"Almost all who make a living sifting or measuring grain are short of breath and cachectic and rarely reach old age," wrote Ramazzini. "The dust is so irritating that it excites intense itching over the whole body, of the sort that is sometimes observed in nettle rash. I have often wondered how so noxious a dust can come from grain as wholesome as wheat." Further, he suspected that the dusts these workers were exposed to harbored "minute worms imperceptible to our senses and that they are set in motion by the sifting and measuring of the grain and broadcast by the air; then they readily adhere to the skin and excite that great heat and itching over the body" (Ramazzini, Bernardino. *Diseases of Workers.* Wilmer Cave Wright, trans., *De Morbis Artificum,* 1713 [New York, London: Hafner, ca. 1964]). In conjecturing some hidden substance at work, he came close to the later concept of an allergic response. What Ramazzini attributed to plugging of the bronchial tubes by "dough balls" is recognized today as an allergic reaction to wheat and rye.

John Bostock (1773–1846)
Medico-Chirurgical Transactions
London, 1819

Hay fever or *allergic rhinitis* (known commonly as "allergies") can be brought on in sensitive individuals by many of the same substances that bring on asthma symptoms. In 1819, John Bostock described this condition as a "periodic affliction of the eyes and chest," presenting the details of the case of one "J.B."—himself.


160 ON A CASE OF NEPHRITIS CALCULOSA.

size of a pea, continued to consist of phosphate of lime; but I could no longer detect any magnesia in them, and they had lost the fusible character. And it is equally remarkable, that during the year 1818, and some time after the use of the muriatic acid had been discontinued, the magnesia reappeared in the calculous fragments voided during that period.

CASE

PERIODICAL AFFECTION

EYES AND CHEST.

BY JOHN BOSTOCK, M.D. F.R.S. & L.S.

THE following case, it is presumed, will not be altogether uninteresting to the Society, as affording an example of an unusual train of symptoms, and it may perhaps be considered the more worthy of their attention, from its having occurred in the person of the narrator.

J. B. æt. 46, is of a spare and rather delicate habit, but capable of considerable exertion, and has no hereditary or constitutional affection, except various stomach complaints, probably connected with, or depending upon, a tendency to gout. About the beginning or middle of June in every year the following symptoms make their appearance, with a greater or less degree of violence.

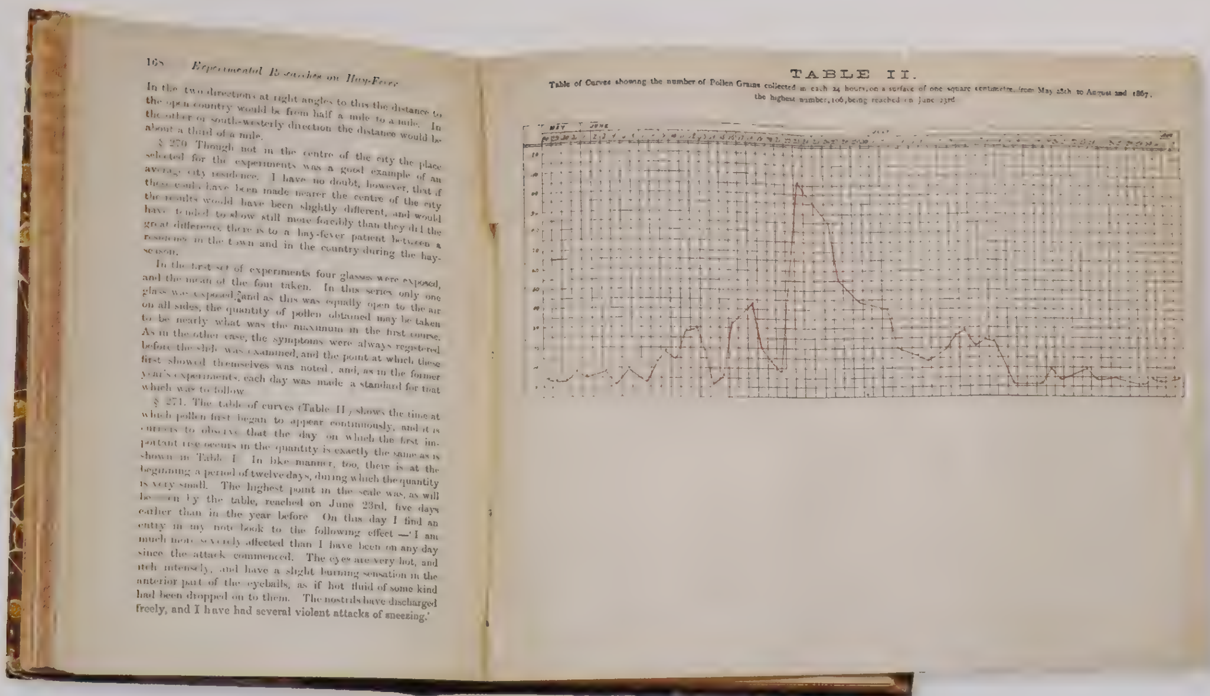
VOL. X.

The view that there might be extrinsic factors that could trigger an asthmatic attack was further explored by the Scottish physician William Cullen (1712–1790), founder of the medical school at the University of Glasgow and a professor of medicine and chemistry. Since the disorder could not be easily treated, he reasoned that the patient could only escape the disease by avoiding "exciting" causes.

Cullen noted that different asthmatic patients have different reactions to external factors: one asthma sufferer may find it easiest to live in the city, another cannot breathe except in the free air of the country. In also noting that asthmatic patients did better if the air was tolerably dry, Cullen could well have been reading Maimonides.

Because there were no specific medicinal measures for treating asthma, Cullen's recommendations for avoiding asthmatic triggers evolved into a mainstay of asthma management well into the nineteenth century. Indeed, as noted, avoidance of substances such as pollens, house dust, and perennial airborne inhalant allergens, as well as some foods, remains a major tool in managing asthma today. It is bolstered by modern-day tests for determining the specific allergens to which the patient is sensitive and reactive.

Although the term "allergic response" dates only from the earliest years of the last century, its general description goes back a century earlier. In 1819, English physician John Bostock linked excessive watering of the eyes and nasal congestion with the summer season. Since childhood, Bostock had had what is known as hay fever.



168 *Experimental Researches on Hay-Fever*

In the two directions at right angles to this the distance to the open country would be from half a mile to a mile. In the other or south-westerly direction the distance would be about a third of a mile.

§ 270. Though not in the centre of the city the place selected for the experiments was a good example of an average city residence. I have no doubt, however, that if these counts have been made nearer the centre of the city the results would have been slightly different, and would have tended to show still more forcibly than they did the great difference there is to a hay-fever patient between a residence in the town and in the country during the hay-season.

In the first set of experiments four glasses were exposed, and the mean of the four taken. In this series only one glass was exposed, and as this was equally open to the air on all sides, the quantity of pollen obtained may be taken to be nearly what was the maximum in the first course. As in the other case, the symptoms were always registered before the slide was examined, and the point at which these first showed themselves was noted; and, as in the former year's experiments, each day was made a standard for that which was to follow.

§ 271. The table of curves (Table II.) shows the time at which pollen first began to appear continuously, and it is curious to observe that the day on which the first important rise occurs in the quantity is exactly the same as is shown in Table I. In like manner, too, there is at the beginning a period of twelve days, during which the quantity is very small. The highest point in the scale was, as will be seen by the table, reached on June 23rd, five days earlier than in the year before. On this day I find an entry in my note book to the following effect:—'I am much more severely affected than I have been on any day since the attack commenced. The eyes are very hot, and itch intensely, and have a slight burning sensation in the anterior part of the eyeballs, as if hot fluid of some kind had been dropped on to them. The nostrils have discharged freely, and I have had several violent attacks of sneezing.'

TABLE II.

Table of Curves showing the number of Pollen Grains collected in each 24 hours, on a surface of one square centimetre, from May 28th to August 2nd 1867, the highest number, 106, being reached on June 23rd.

About the middle of June every year, he reported, a sensation of heat and fullness of the eyes developed into an acute itching and smarting. This was followed by nasal irritation, sneezing, tightness of the chest, and difficulty in breathing. Although Bostock did not know the cause, he conjectured these symptoms came from flowering plants, thus establishing a seasonal connection to asthmatic attacks.

The allergenicity of grasses and ragweed was established later in the century by two physicians with very different backgrounds working on opposite sides of the Atlantic.

In Manchester, England, Charles Blackley established the cause of what we today call hay fever.

Like Bostock, Blackley suffered from hay fever and asthma. Not content just to describe the condition, he designed an instrument to count pollen at different locations: at ground level and at various heights, which he investigated using a kite. In his home and office laboratory setting, he conducted systematic experiments into the role of pollen in triggering attacks of hay fever. In his greenhouse, Blackley cultivated various plants and grasses, and induced them to flower out of season, in the winter. Then, subjecting himself to inhaling their pollen, he showed that such exposure triggered the symptoms of hay fever.

Charles Harrison Blackley (1820–1900)
Hay Fever: Its Causes, Treatment, and Effective Prevention, Experimental Researches
London, 1880

Charles Blackley invented the pollen counter in the late 1860s. The first pollen counter was simply a glass slide smeared with a sticky substance. Blackley used it to collect pollen from the air. He then counted the grains of pollen under a microscope. (Current models use the same principle.) Blackley and others used the pollen counter to collect extensive data on seasonal variations in airborne pollen in order to show why hay fever, asthma, and other allergic diseases were more severe at particular times of the year.

Experimenting on himself, Blackley conducted what amounts to the first skin test for an allergic response. He put pollen on the abraded skin of his forearm and, recognizing the need for a control, also abraded an area of skin on his other forearm but did not apply pollen. Within a few minutes, on the arm that had been treated with pollen, a hive-like wheal appeared, along with intense itching. But the untreated arm experienced no such reaction. Blackley's studies were not widely recognized at the time, largely because he was a private medical practitioner in Manchester, not associated with a university. Also, as a homeopathic physician, he was not part of mainstream medical practice, and his work was not disseminated.

Morrill Wyman (1812–1903)
***Autumnal Catarrh* (Hay Fever)**
New York, 1872

American physician Morrill Wyman's pollen maps of the United States helped physicians and patients select places (shaded area) for vacations or migration where hay fever and asthma sufferers might be less likely to encounter allergens.

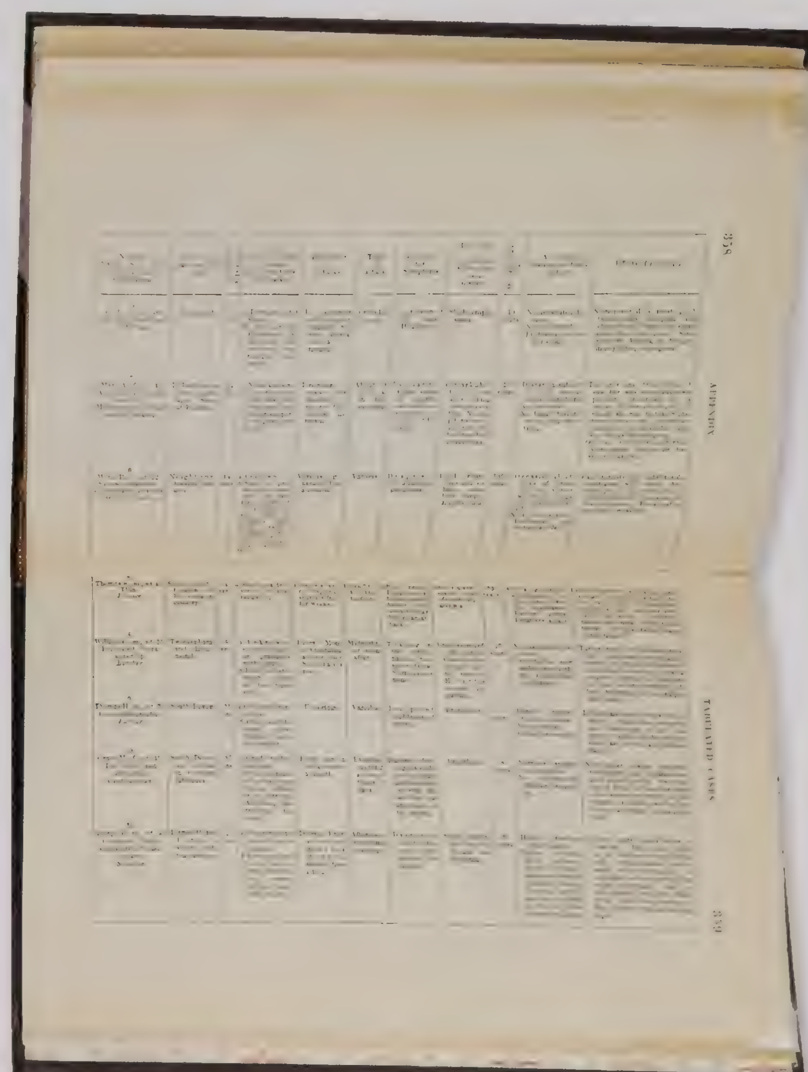
Concurrently, on the other side of the Atlantic, a contemporary of Blackley's, Morrill Wyman, initiated a similar line of investigation. Wyman suffered from hay fever. When studying the effects of another pollen source obtained from Roman wormwood, a plant member of the ragweed family, he identified it as the agent of what he termed "autumnal catarrh."

Wyman noted that there was no hay fever in the White Mountains of New Hampshire and believed that its absence was due to the fact that Roman wormwood did not grow in the area. He collected and packed pollen from flowering plants in Cambridge, Massachusetts and took them to New Hampshire, where the packages were opened and both he and his son sniffed the pollen. He reported that they were both "seized with sneezing and itching of nose, eyes, and throat . . . my nostrils were stuffed and my uvula swollen" (Wyman, Morrill. *Autumnal Catarrh* [New York: Hurd and Houghton, 1872]). Serving as a control, his brother Jeffries Wyman, who did not have a history of autumnal catarrh (hay fever), did not develop any symptoms when he sniffed the pollen.

Wyman further observed that some families were more affected by autumnal catarrh than others; in his own family his father, two of his brothers, his sister, and his son were all affected. He also recognized that nonseasonal inhalants, such as the fumes of sulphur from burning matches or the gases emanating from burning coal, could induce difficulty in breathing because of what he described as a "peculiar sensitiveness of the respiratory nervous system." His observation may be one of the earliest on hyper-reactivity of the bronchial airways, appreciated today as a common pathophysiologic disorder of asthma sufferers.

In 1860, the English physician Henry Hyde Salter wrote *On Asthma: Its Pathology and Treatment*, the most authoritative text on asthma at that time. His book was widely read well into the twentieth century and was considered the basic treatise on asthma. As an asthma sufferer himself, Salter recorded various triggers that could induce an attack, including animal dander, impure air, hay fever, and foods. He thought of asthma as a spasmodic disease, represented by constrictions of the bronchial tubes. In later years, it was discovered that the pathogenesis of asthma was more likely due to swelling, rather than constriction of the airways. Salter's concept led to attempts at therapy with antispasmodic drugs that included the use of *ma huang*, or ephedra, thus explaining the benefit derived from the plant the Chinese had identified for managing breathing difficulty millennia before.

Salter and the French physician Armand Trousseau (1801–1867) agreed that one way of controlling an asthmatic attack was to deliver an antispasmodic agent via bronchial intake through the breath, by smoking or inhalation. They studied several different medications for depressing irritability of the bronchial passages; one method investigated was the inhalation of smoke from burning paper that had been dipped in a chemical solution of nitrate. Additionally they found that one of the more effective treatments for controlling an asthmatic attack was to smoke a cigar—likely due to its nicotine content, which had pharmacological activity.



Henry Hyde Salter (1823–1871)
On Asthma: Its Pathology and Treatment
London, 1860

Salter made the interesting observation that cigar smoking helped those who were non-smokers, but not patients who were habitual smokers. He was noting the fact that the treatment only worked for those who had not developed tolerance through frequent smoking. Largely because of Salter's authority, inhalation therapy for asthma (although not necessarily cigar smoking) became widely practiced, and indeed is still used today.

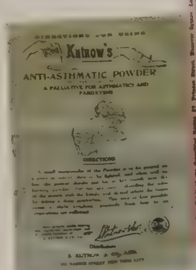
Another therapeutic agent Salter recommended was coffee, based on his observation that asthmatic attacks were preceded by drowsiness and were often triggered when the patient was asleep. Drinking strong, hot coffee would keep the patient awake, he argued, thus avoiding an asthmatic attack. Additionally the caffeine of coffee or tea had the pharmacological property of relaxing bronchial spasms; the chemical analogs of caffeine, for example theophyline, worked even better in treating asthma.

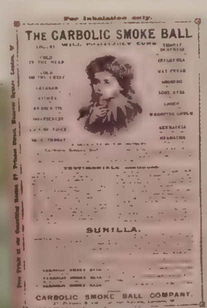
Asthma Remedies

The development of modern chemistry in the nineteenth century encouraged ingenious initiatives to uncover and define agents to relieve airway constriction and reduce the excess mucus and bronchial swelling that produce the shortness of breath, wheezing, and chest tightness typical of asthmatic attacks. Most early measures were aimed at reducing symptoms and were refinements of traditional, partially efficacious, herbal remedies.

Pharmacists and physicians derived and compounded their own medicaments until chemists in the nineteenth century isolated what they believed to be the active ingredients of traditional agents for alleviating asthmatic symptoms. By the latter part of the century, these agents were being produced in quantity for the commercial market, and often extravagantly advertised. Drug companies promoted their products to asthma sufferers without the need for a physician's prescription.

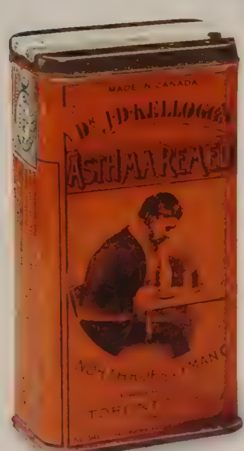
It is questionable whether most of these agents did in fact relieve asthma. Many contained alcohol or narcotics such as cocaine or morphine, which, in addition to having pharmacologic actions, were more likely to mask asthmatic symptoms and permit the patient to feel better than to play a true therapeutic role. There could also be untoward side effects of morphine derivatives, such as depressed respiration.





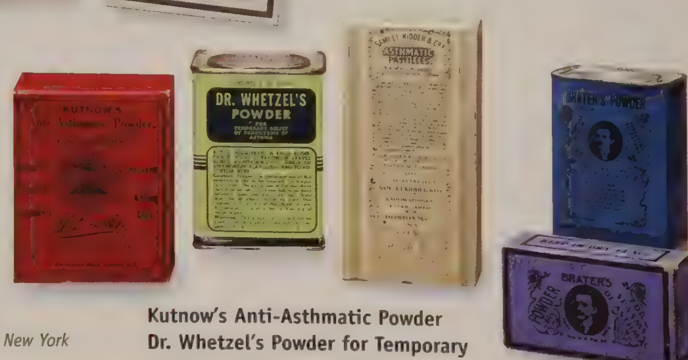
Directions for Using Kutnow's Anti-Asthmatic Powder and The Carbolic Smoke Ball
Courtesy William H. Helfand Collection, New York

Marshall's Prepared Cubeb Cigarettes, ca. 1882
Courtesy William H. Helfand Collection, New York



Pastilles Salmon
Courtesy William H. Helfand Collection, New York

Dr. J. D. Kellogg's Asthma Remedy
Courtesy William H. Helfand Collection, New York



Kutnow's Anti-Asthmatic Powder
Dr. Whetzel's Powder for Temporary Relief of Paroxysms of Asthma
Samuel Kidder & Co.'s Asthmatic Pastilles
Brater's Powder for Spasms of Asthma and Brater's Powder
Courtesy National Museum of American History, Smithsonian Institution

Early Epidemiological Research

The measures recommended for managing asthma in the nineteenth century, of necessity, relied on material gleaned from individual case reports, and represented the experiences of physicians involved in treating asthma. There were, however, some investigators, among them Salter, who innovatively searched for common features of asthma and tabulated information gathered from observations of large numbers of patients. Salter noted familial associations with asthma in 84 of 217 patients surveyed. This type of statistical investigation represented a divergence from the case-study approach to studying disease, which concentrated on each individual's experience rather than trying to understand the traits common to all sufferers.


Henry Hyde Salter (1823–1871)

In the late nineteenth century, New York physician George Beard, looking for a common factor in hay fever and asthmatic disorders, sent out a detailed questionnaire to patients. Beard received two hundred replies and used the responses to assess the impact of such respiratory symptoms on the population. He observed that more men than women and more tradespeople than professionals were affected, that symptoms occurred more frequently among married persons, and that symptoms occurred more frequently in "persons of nervous temperament."

These efforts represent early steps toward epidemiologic investigation of hay fever and related respiratory disorders. While case studies of individual patients are always useful, epidemiology adds to knowledge of a disease through the study of its effects on populations. By Beard's time, it had long been recognized that without a good measure of the incidence and prevalence of a disease it is difficult to mount effective attacks against it. Adequate epidemiologic study of any disorder is the cornerstone of effective public health practice and a useful guide for the clinician.

By the nineteenth century, epidemiologic investigation was well established as a means of measuring the impact and discovering the cause of disease. In 1740, Percivall Pott (1714–1788) identified soot as the cause of scrotal cancer among London chimney sweeps, and in 1857, John Snow (1813–1858) linked cholera to the water supply from the Broad Street pump. Adequately performed surveys of diseases such as asthma had not yet been mounted. It was only in the mid-twentieth century that data began to provide a more reliable picture of the impact of asthma on the general population.

2ND MED

NEW YORK HOSPITAL OUT-PATIENT DEPARTMENT

NAME Calder Joseph AGE 35 SEX M. M.W. DATE Nov 25/16 NATIONALITY

ADDRESS 437 E 35 OCCUPATION Cook.

Last winter operated for empyema in NYH
O.K. until this winter
9 days ago dyspnea & cough came on rather suddenly c fever & chills
Cough continued
Dyspnea lasted 4-5 day fever 2 days

T 98.6
Slight dulness R base where operation was but no rales

Nov 21 Still pain R side where was operation

June 27 - 1921:
Pt. complains of having had Asthma for 10 years. Attacks occur throughout the year, but especially during November - cannot work steadily from Nov. to May: during this period the attacks mostly occur weekly.

Family history - neg.

Pt. spent the last winter in Fla. - i.e. from Oct. to Mar. - and was free from attacks for 1st time in 10 years.
2 or 3 days after returning to N.Y.C. the attacks

A New Century and New Knowledge

At the turn of the twentieth century, a distinguished Philadelphia physician, Solomon Solis-Cohen (1857–1948) proposed that the immediate mechanism resulting in an asthmatic attack was the obstruction of respiration from a swelling of the bronchial mucosa, related to angioneurotic edema. Suggesting that increasing the bronchial vascular tone might prevent these attacks, he introduced a therapeutic extract of adrenal glands from animals to treat his own hay fever. He reported that it cut short an asthmatic paroxysm, was useful in preventing a recurrence, and relieved the fear of attack. Solis-Cohen proposed the use of adrenal extract as a "measure applicable in certain cases."

The real importance of Solis-Cohen's preliminary work with adrenal extract lay fifty years in the future. His was probably the first use of an agent to modify an immune mechanism in asthma. In 1949 the work of Philip Hench (1896–1965) and Edward Kendall (1886–1972) made it possible to use adrenal gland-derived cortisone in treating autoimmune disorders when they isolated the adrenal hormone. Solis-Cohen's finding also marked the beginning of an increasing interest in the immune system—the body's reaction to foreign invaders—which furthered much of twentieth-century biomedical research.

By the last years of the nineteenth century, largely due to Louis Pasteur's (1822–1895) work on germ theory, an increasing interest developed in the mechanisms by which the immune system recognizes and rejects disease-causing invaders such as bacteria. To many researchers interested in asthma, it must have seemed a natural step from studying bacterial pathogens and the efforts to neutralize them, to studying the adverse reactions of asthmatic patients to plant pollens and animal proteins.

Robert A. Cooke's patient notes, 1916

Robert Cooke set up the first allergy clinic in the United States at New York Hospital in 1920. Patients' skin was exposed to concentrates of common allergens to learn which substances brought on each individual's allergic responses. Patients could then either avoid the substances that made them sick or undergo "immunotherapy," periodic injections of specific allergens designed to reduce the immune response that caused asthma and other symptoms.

Courtesy Sheldon G. Cohen, M.D.

In the late 1870s, a German physician, Robert Koch (1843–1910), working with the tubercle bacillus, pioneered the development of techniques for staining pathogenic microorganisms, thus marking them for identification by microscopic visualization. His work made possible the identification of microbes associated with infectious processes and the diagnosis and treatment of several bacterial diseases. Information thus gained stimulated efforts to develop antisera against disease-causing organisms and their toxins.

Anaphylactic Shock

One of the earliest antisera, anti-streptococcal horse serum, had been developed to treat the complications of scarlet fever. In the early years of the twentieth century, the Viennese physician Clemens von Pirquet (1874–1929) noted the development of altered reactivity in some persons treated with the anti-streptococcus serum produced in horses. After they had been sensitized by a previous injection, they manifested evidence of hypersensitivity to horse serum proteins.

Clemens von Pirquet coined the word "allergic"—from the Greek words *allos* meaning "other" and *ergon* meaning "work"—to describe this altered reaction and pointed out that horse-derived allergens, the substances that induced this adverse effect, were antigenically different from the substances that stimulated antibody production against the streptococci. "The term allergen is far more reaching," he wrote. "The allergens comprise, besides the antigens proper, the many protein substances which lead to no production of antibodies but to super-sensitivity" (von Pirquet, Clemens. "Allergie," *Munch Med Wochenschr,* 1906; 53:1457. C. Prausnitz, trans. in P.G.H. Gell and R.R.A. Coombs, eds., *Clinical Aspects of Immunology* [Oxford, Blackwell, 1963]). He went on to note that allergens included mosquito bites, bee stings, the pollen that causes hay fever, and the swelling and itching caused by substances such as strawberries and crabs. He would later learn that allergens do engender production of antibodies of a different type, not detectable by test-tube techniques, but identifiable only by their untoward reaction against susceptible tissue cells.

In addition to a hypersensitivity serum-sickness reaction which may take as long as ten days to develop, another type of allergic reaction became known as immediate hypersensitivity. Within minutes, seconds sometimes, a sensitive individual after exposure is struck with symptoms of hives, itching, swelling, respiratory difficulty, even a precipitous drop in blood pressure and shock. If the situation is not immediately neutralized, it may lead to death. This immediate systemic allergic reaction is called anaphylaxis. The reaction was initially observed in experimental animals by two French physicians, Charles R. Richet (1850–1935) and Paul J. Portier (1866–1962). The manner of their discovery is a colorful story of scientific research.

When Portier and Prince Albert I of Monaco became friends, the Prince often invited Portier to cruises on his yacht. On one of these occasions Richet was also invited and the Prince asked them to try and solve a problem for him. He was concerned that visitors to Monaco were unwilling to swim in the Mediterranean because it was becoming overpopulated by stinging jellyfish. He was losing tourists and in Monaco, then as now, tourism was its lifeblood. He asked them to develop a vaccine against jellyfish stings.

The idea of a vaccine was then popular because in the 1870s Pasteur had shown the protective effect of an attenuated strain of anthrax bacillus in sheep, similar to the action of English physician Edward Jenner's cowpox vaccine against the development of smallpox. The idea that one might be able to prevent illness by immunization against jellyfish toxin had some appeal, especially in the light of Emil von Behring's (1854–1917) development of an effective diphtheria antitoxin.

Edward Jenner

The body's ability to neutralize foreign pathogens has been utilized therapeutically for centuries. As early as the eleventh century, the Chinese, noting that patients who had once experienced smallpox were immune to subsequent attacks, inoculated persons against the disease with small amounts of fluid or powdered scabs recovered from skin lesions. From China, the method spread westward to Turkey, then to England and to other parts of the world. The procedure was risky, in that it could induce a full-blown case of the disease and deaths sometimes occurred. It was considered an acceptable risk only because smallpox was such a serious disease in which a quarter of those infected died.

A safer method of inoculation was developed by the English country physician, Edward Jenner in a 1796 experiment. Following the experience of English milkmaids, Jenner inoculated a boy with cowpox, a milder disorder related to smallpox. He subsequently tested this method of inoculation with fluid from smallpox pustules and found that the tested recipient did not develop smallpox.

Edward Jenner (1749–1823)

Jenner, although unaware of the specific mechanism, was making use of what we now recognize as an antigenic similarity between two biologically related disease-causing microorganisms: i.e., through shared chemical character, the ability of one to induce an immune response to another. For example, the recent introduction of childhood immunization against chickenpox virus also carries the potential for preventing or at least mitigating the occurrence of herpes zoster (shingles) in later life since the two agents are antigenically similar.

The Prince had outfitted a laboratory on his yacht for the two scientists to extract the incriminated component of the jellyfish toxin, which they then injected into dogs in increasingly potent doses to test for a possible vaccine. Although some of the animals died from the poisonous effects, those that survived were given a second injection of the toxin to see if they were protected.

"At this point an unforeseen event occurred," wrote Portier and Richet. "The dogs which had recovered were intensely sensitive and died a few minutes after the administration of small doses." In one experiment they reported that a few seconds after the second injection "the animal became extremely ill, breathing became distressful and panting; it could scarcely drag itself along, lay on its side, was seized with diarrhea, vomited blood and died in twenty-five minutes" (Portier, Paul and Richet, Charles, "De l'action anaphylactique de certain venins," *Comptes rendes Societe de Biologie (Paris),* 1902; 54:170). The animals had experienced, a newly recognized phenomenon, anaphylactic shock.

The two essential and sufficient requirements for inducing this response, Portier and Richet noted, were "increased sensitivity to a poison after previous injection of the same poison and an incubation period for this increased sensitivity to develop." For this pioneering discovery of anaphylaxis, Richet (not Portier) received the 1913 Nobel Prize in physiology or medicine.

During this same decade, in 1905, two physicians working in the Laboratory of Hygiene in Washington, D.C., the predecessor of today's National Institutes of Health, were studying a very similar response in guinea pigs. Milton J. Rosenau (1869–1946), the laboratory's director, and John F. Anderson (1873–1958), the assistant director, were following up on reports of severe reactions, some fatal, in patients who had been treated with diphtheria and tetanus antitoxins. In addition to the studies by Poitier and Richet, anaphylaxis had by this time been reported by others.

In carefully controlled experiments with guinea pigs, using horse serum-derived diphtheria and tetanus antitoxins, Rosenau and Anderson studied anaphylaxis in great detail. They demonstrated the requirements for specific antigen-antibody interaction, the amount of the dosages, and the time intervals between the first sensitization dose and the second challenging injection. Their studies eliminated a long list of possible cofactors on the anaphylactogenic properties of sera such as aging, drying, heat, irradiation, filtration, dialysis, and treatment with enzymes.

They noted that reactions differed between species, indicating some distinction in species-specific target organs. In one demonstrated example, they found that while a guinea pig suffers bronchial spasm and dies of respiratory failure, a rabbit, by contrast, dies of cardiac arrest. Nevertheless, they concluded: "The fact that humans, guinea pigs, and other animals react to a second injection of horse serum would seem to indicate that we are dealing with one and the same action."

During this period, related studies led some investigators to believe that immunology was a useful model for studying human asthma. Theobold Smith (1859–1934), a microbiologist at the Rockefeller Institute, reported findings that guinea pigs get bronchial spasms when pre-sensitized to an antigen and then challenged. Although the guinea pigs had respiratory deaths, their pathology was not similar to human asthma, in which there is also inflammation of the bronchial membranes and sputum formation.

American investigator William Schultz (1873–1953), a member of the Laboratory of Hygiene in Washington, D.C., described an experiment of suspending sensitized guinea pig ileum in a physiologic solution. He noted that, as susceptible target tissue, it would contract when the corresponding antigen was added to the solution. The following year, Sir Henry Dale (1875–1968), working at the Wellcome Physiological Research Laboratories in England, took up the study of anaphylaxis—an immediate and severe systemic reaction to antigens—in guinea pigs.

Dale, interested in the chemical transmission of nerve impulses, then used a smooth muscle strip taken from another target organ, sensitized uterine tissue. He exposed it to a chemical, beta-iminazolylethylamine, otherwise known as histamine, and showed that the muscle contracted when histamine was added to the solution in which it was suspended—the reaction is known today as the Schultz-Dale phenomenon. Dale concluded that released histamine was the cause of anaphylaxis. In 1936 Dale shared the Nobel Prize for physiology or medicine with the German physician-physiologist Otto Loewi (1873–1961) for their work on the chemical transmission of nerve impulses.

Today histamine, along with other chemical mediators, is known to be released from a class of cells—named mast cells in 1877 by Paul Ehrlich (1854–1915)—following stimulation by an allergen reacting on its surface membrane. Histamine plays an important role in some immediate allergic responses, such as the swelling and itching experienced by hay fever sufferers, but it plays a lesser role in asthma. Histamine was later synthesized, and in 1933, another Nobel Prize winner, Daniel Bovet (1907–1992), developed the first antihistaminic drug. However, antihistamines only relieve symptoms and do not prevent or remove the underlying cause of the allergic state or its reactions.

The concept that allergens such as ragweed and grass pollens are foreign bodies much like bacteria and could, therefore, be countered by mounting an immune response was the driving force behind an experiment in London in 1902. Sir Almroth Wright's (1861–1947) Inoculation Department at St. Mary's Hospital became world-famous for its studies in immunization. The department was particularly recognized for Wright's immunization of the British Army in India against typhoid fever.

Robert Anderson Cooke, 1940

Wright had assembled a small group of investigators, among them Leonard Noon (1878–1913) and John Freeman (1877–1962). Noon, an immunologist, had studied tetanus toxins and antitoxins and, believing that the causative agent of hay fever was a toxin in pollen similar to those in microbes, prepared extracts of grass pollen with which he attempted to immunize affected subjects by subcutaneous injection. There was some success in that, as his coworker and successor, Freeman, later reported: "Where a patient has been inoculated for one year he has in the next year complete, or almost complete, immunity, but in the third year he has only slight immunity left. Where patients have been successfully inoculated for two years they have, as might be expected, complete immunity during the third year, and time will show how long this complete immunity will last" (Freeman, John. "Vaccination against hay fever: Report of results during the last three years," *Lancet,* 1914; 1:1178).

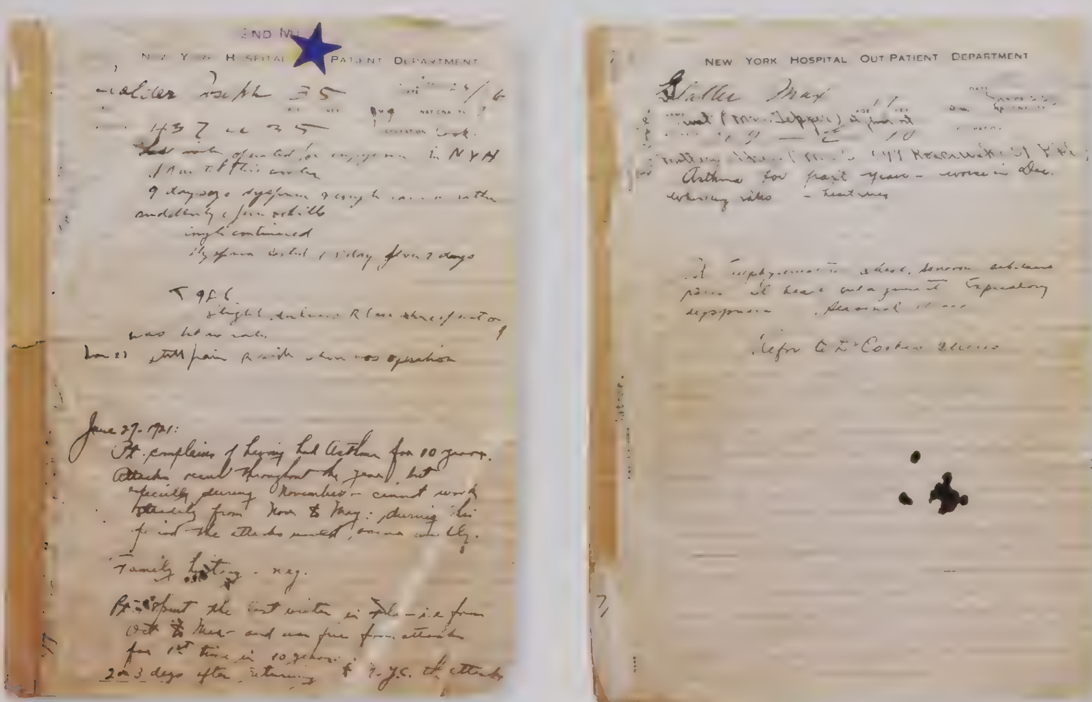
Noon and Freeman believed they were producing a protective immune response, that is immunizing their patients against pollen toxin. But, reexamination showed that they were inducing a lessening of a hyposensitization of their patients, a form of immunotherapy. Regardless of their misunderstanding of the cause, their work had a major influence on the clinical management of allergic disorders for the next several decades. The injections of pollen extract were the beginnings of what are popularly called today "allergy shots."

Noon's and Freeman's approach was adopted by many clinicians, most notably two American physicians, I. Chandler Walker (1883–1950) in Boston and Robert Cooke in New York, who figured prominently in taking this idea further. Walker and Cooke were among the first to set up allergy clinics using injection treatments for asthma and allergic diseases. Between them they popularized the treatment of asthma by desensitization.

Robert Cooke (1880–1960)
Allergy in Theory and Practice
W.B. Saunders Company,
Philadelphia and London, 1947

In 1916 Cooke began seeing patients and in 1920 set up a laboratory and allergy clinic at New York Hospital where he developed standards for diagnosis and treatment and for training programs in allergy. In that setting, he was responsible for training a large number of physicians who then returned to their home cities to develop their own clinics along similar lines. He became a dominant force in the field and through his leadership created the subspecialty of allergy in internal medicine in the United States.

Cooke himself suffered from asthma, a factor that, as with so many other earlier investigators, influenced his professional interest. His investigations covered a broad spectrum of problems in allergy in addition to asthma. He developed a system for standardizing the protein extracts used in hyposensitization therapy, examined drug reactions, and studied the role of heredity. He noted that sensitized individuals transmitted to their offspring, not their own specific sensitization, but the unique hereditary capacity for developing a reaction to foreign proteins. Cooke was getting close to the underlying factor of allergic disorders in general, and asthma in particular, when he found that there was a genetically transmitted aberration that made the subjects susceptible to sensitization to foreign proteins.



Robert Cooke's patient notes, 1916 and 1919
New York Hospital Out-Patient Department

Courtesy Sheldon G. Cohen, M.D.

Another influential member of the select New York study group that founded the Society for the Study of Allergy and Allied Conditions was Francis M. Rackemann (1887–1973), the Society's second president after Cooke. Early in his career, Rackemann became interested in research in experimental anaphylaxis and the developing field of clinical allergy. On returning to Boston and joining the staff of the Massachusetts General Hospital and the Faculty of Medicine at Harvard University in 1916, he turned his attention to asthma. Two years later he published his noteworthy study of 150 patients with asthma. In a monumental effort he followed some of them for up to thirty years.

From this work came his most frequently quoted conclusion: that bronchial asthma was a symptom that might have multiple causes, which he defined as either "extrinsic" or "intrinsic." Extrinsic causes related to allergenic, skin test-positive agents; intrinsic causes of asthma were the result of some constitutional disorder.

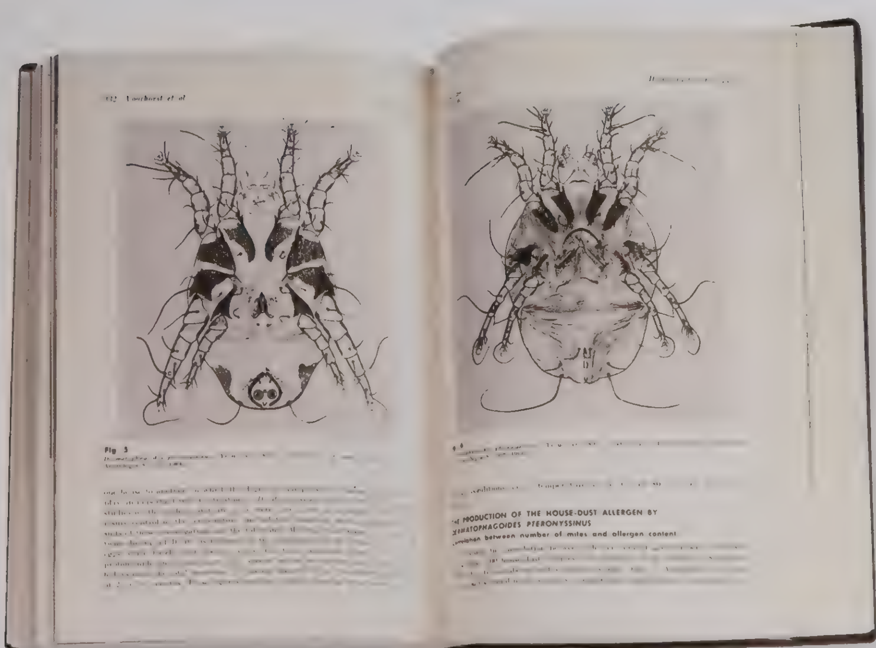
One of Cooke's associates, Oscar M. Schloss (1882–1952), a pediatrician, developed the scratch test as a diagnostic procedure for detecting hypersensitivity, using it to detect diagnostic leads in studies of patients sensitive to various foods. Schloss had become interested in von Pirquet's scratch test for tuberculosis and Bela Schick's (1877–1967) intracutaneous test with diphtheria toxin. Concerned over what he called the alarming reactions to toxic foods, he reasoned that a skin test, rather than actual feeding of the suspected food, was needed to identify adverse reactions.

Schloss found that, within five to fifteen minutes after an active substance was rubbed into the skin, like Blackley's study years before with pollen, a distinct wheal was raised at the inoculation site. The reaction was always immediate and disappeared within thirty minutes to an hour. He did extensive experiments that showed the reaction was specific for the test food and not caused by chemical or mechanical irritation.

For many years the scratch test and the intracutaneous modification were the bases for the investigation and treatment of allergic disease: first, skin testing for allergens to which the patient was suspected to be sensitive, then development of injection treatments designated to hyposensitize the patient.

At first glance it might seem as if these and the continuing studies on allergic responses had little to do with asthma. Persons who have experienced skin reactions from substances to which they are allergic do not necessarily have coexisting or complicating asthma. There is, however, an association. Studies during the latter half of the twentieth century have demonstrated that sensitization among those genetically susceptible to some indoor allergens, such as house dust mites, animal dander, and cockroaches, poses a risk for developing asthma, particularly in children. There is less risk from outdoor pollens, although grass and ragweed pollen have been associated with seasonal asthma. It has also been found that sensitivity to perennial inhalant allergens as a cause of asthma declines with age. Food allergens may, but do not commonly, give rise to symptoms of asthma. Even those who are highly susceptible and may experience anaphylaxis as a result of eating certain foods do not have lower respiratory tract symptoms.

There is also clinical evidence that an allergic reaction in the airways, as a result of exposure to allergens, leads to an increase in inflammatory responses, increased airway hypersensitivity, hyperreactivity, and an increase in eosinophils, white blood cells contained within the bronchial effusions that play a role in effecting immune-mediated allergic reactions. These findings are bolstered by evidence that when exposure to allergens, such as house dust mites, is reduced, asthmatic symptoms in those predisposed to allergies are also reduced. These and similar studies emphasize the importance of minimizing or eliminating exposure to allergens in treating hypersensitivity-related respiratory tract disorders, and they open doors to new knowledge of asthma.



R. Voorhorst, F. Th. M. Spieksma, H. Varekamp, M.J. Leupen, and A.W. Lyklema "The house-dust mite (Dermatophagoides pternyssinus) and the allergens it produces. Identity with the house-dust allergen," *The Journal of Allergy*, June 1967

In 1967 the Dutch research team of R. Voorhorst, F. Th. M. Spieksma, H. Varekamp, M.J. Leupen, and A.W. Lyklema explained why millions of allergic and asthmatic patients were sensitive to common house dust—their pillows, mattresses, couches, curtains, and clothes were infested with millions of invisible dust mites.

Courtesy Mosby Publishing Company

Immune System Research Clarifies Asthma

Recent research into the mechanisms of allergy has thrown new light on the role of the immune system. Researchers have discovered that when the immune system deviates from normal function, there are powerful secondary, inflammatory, and constricting effects on bronchial tissues. Hence, studies on immune function and hypersensitivity mechanisms in allergic individuals have played major roles in clarifying some of the causes of asthma.

The immune system is the body's defense against the microbial world. Without adequately functioning immune systems, animal populations could not survive infection. We live in a world of potentially deadly germs—viruses, bacteria, fungi, protozoa, and parasitic worms. We survive because the body has evolved a complex defense system able to recognize these invaders; attack, destroy, or neutralize them; and keep them under control.

As we have seen, the existence of the immune system has been recognized for hundreds of years and through intervention has been manipulated to control disease, by Jenner and others. But not until after Pasteur advanced the germ theory of disease did the specific components of the immune system come under close study. The last half of the twentieth century has seen remarkable progress in our understanding of the components and products of the immune system and their function. As a result, the diagnosis, prevention, and treatment of many disorders, including asthma, have improved.

Kimishige Ishizaka (1925–) and Teruko Ishizaka (1926–)

Working together, in 1967 husband-and-wife team Kimishige and Teruko Ishizaka showed that people with allergic disease have a type of antibody that healthy people do not have. Every person with a healthy immune system has antibodies to many different substances, and these antibodies begin the process of immune response to disease-causing microbes. People with allergies and allergic diseases, though, have IgE antibodies, a kind that healthy people do not normally possess. IgE antibodies are the key to allergic asthma because allergic people form these antibodies upon exposure to common and harmless substances, resulting in immediate and chronic symptoms of the disease.

Courtesy William Coupon

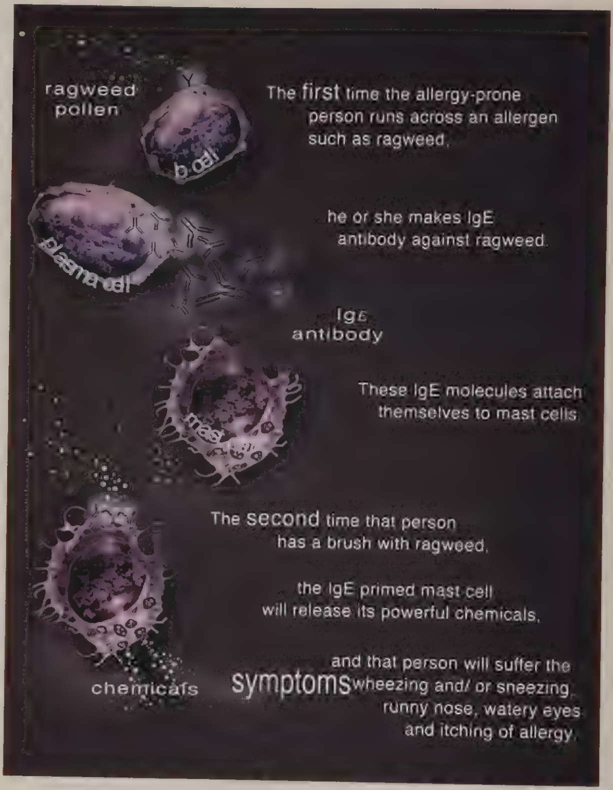
Sometimes the immune system malfunctions and mounts an attack on the host's own tissues. The result is an autoimmune disease, examples of which include rheumatoid arthritis, systemic lupus erythematosus, and glomerulonephritis. It has been suggested that, in some instances, asthmatic syndromes may also be the result of such an aberrant immune response. Whether autoimmune reactivity plays a role in asthma remains to be determined.

The Immune Response

The immune response in allergic disorders such as hay fever and asthma begins with exposure to a causative agent, the allergen, an inhaled, injected, or ingested foreign protein. When the allergen reaches the lungs, it encounters a macrophage, which engulfs the foreign molecular particle. As the macrophage ingests, degrades, and processes the allergen, it undergoes changes on its surface through expressed proteins that send out a signal to attract a precursor of the T lymphocyte called the T-helper cell.

The T-helper cell picks up the signal carrying the imprint of the allergen from the original encounter, and, in an evolving maturation process, migrates to a lymph node where it encounters a B lymphocyte and transmits the allergen-derived imprinted message. This begins the transformation of the B cell into a mature immunoglobulin-producing cell known as the plasma cell, which generates antibodies that switch on and off depending on the need.

In essence, the T-helper cell's job is to try and keep the foreign agent, whether infectious or allergenic, under control and localized as much as possible, while the other arm of the immune system, the B cell, creates antibodies directed against the antigen.



When allergic people are exposed to allergens, their immune system responds by producing antibodies called IgE.

The symptoms of asthma result from a series of cellular events in the human immune system. There are several specific cell types involved: the macrophage, so named because of its large size and its ability to ingest particles from outside its own cell walls; the lymphocytic T and B cells; the plasma cells which evolve from the B cells and produce different classes of antibodies; and, finally, the mast cells, a particular type of cell whose intact granules contain chemicals that on release are capable of inducing inflammation, a reaction that plays a role in allergic asthma.

Antibodies belong to a group of proteins known as immunoglobulins (Ig), of which there are five major classes: IgA, IgD, IgG, IgM, and IgE as identified by their molecular structures and sites of formation and action. Each plays a role in forming defenses against foreign substances that challenge the body.

The immunoglobulin of most interest to the study of asthma is IgE. It is now known that IgE is responsible for the majority of allergic reactions of the immediate skin test positive type. The main protective immune function of this immunoglobulin is to protect against or repel invasion by tissue-invasive parasitic worms. Thus IgE levels in the blood of those who live in those parts of the world where these tissue–invasive parasitic worms are common are generally elevated. In persons not normally exposed to such parasites, IgE is present in very small amounts. Allergic persons synthesize IgE against allergens such as extrinsic or atmospheric pollen, dusts, animal danders, molds, and certain foods. When IgE was identified in 1966 by Kimishige Ishizaka and his wife Teruko Ishizaka, it opened a door to an approach to asthma therapy through efforts to suppress or modify IgE formation.

Working as an immunology team at the Children's Asthma and Research Institute in Denver, Colorado, they isolated the antibody responsible for the skin sensitivity in specifically allergic people. The Ishizakas showed that IgE was, by molecular structure and by its demonstrable effect on allergically susceptible tissues, a "distinct class of immunoglobulins," unrelated to any of the other immunoglobulins. It could be differentially identified in test tube reactions. They named it immunoglobulin E.

New Discoveries: Leukotrienes

Not all allergic reactions are mediated by agents from mast cell granules. A group of chemicals known as leukotrienes are produced by the action of antigen on sensitized tissue. They are of special interest to the study of asthma because they are potent constrictors of the small bronchial airways.

Leukotrienes have only recently been chemically characterized, but the discovery of their role in allergic reactions dates back to 1930. An American physician-investigator, Joseph Harkavy (1890–1980), working at the Institute of Pharmacology in Leiden, The Netherlands, discovered a substance in the sputum of asthmatics that caused spasms in isolated smooth muscle strips. In experiments, somewhat similar to those of Sir Henry Dale with histamine, he recorded the pattern of the contractions of the suspended test muscle strip. The contractions were immediate, suggesting, he said, that there were two substances responsible for the spasms. Histamine was one; the other remained unknown.

Harkavy's studies were followed up in the late 1930s by two Australian investigators, Charles H. Kellaway (1889–1952) and Everton R. Trethewie (1913–1984). Studying the antigen-antibody reaction of anaphylaxis, they showed that the substance Harkavy had postulated was present in the sputum of asthmatic patients and caused a slow, long-lasting, and profound constriction of the bronchial airways. They called it the slow reacting substance of anaphylaxis or SRS-A.

Its exact nature remained a mystery until forty years later, when Bengt I. Samuelson (1934–), of the Karolinska Institute in Stockholm, identified and chemically characterized SRS-A. He named the group of component chemicals leukotrienes because they are made by leukocytes (white blood cells). He and his associates demonstrated the role of leukotrienes in asthma, showing that they are potent bronchial constrictors, cause increased vascular permeability, stimulate mucus secretion, and have pro-inflammatory effects. In 1982 Samuelson shared the Nobel Prize in medicine or physiology with scientists working in the same biomedical area, Sune Bergström (1916–) and the English scientist, John Vane (1927–).

Leukotrienes originate from the breakdown products of cells that are disrupted following injury, infection, hormonal stimulus, or an allergic response. The membranes of the cell are converted by enzymatic action into a substance called arachidonic acid. This in turn is broken down into biologically active compounds, one of which forms the leukotrienes.

When Samuelson summarized his studies in 1983, he noted that their discovery opened the way to developing new and more specific agents designed to antagonize the key inflammatory-producing leukotrienes. In fact, at least two such agents have since been developed that function in this way and are now available. They represent a major advance in the management of asthma.

When allergic persons respond to an allergen to which they are sensitive, they produce specific IgE antibodies. This first encounter does not produce an allergic reaction but it primes the sensitive individual so that when that individual re-encounters the same antigen it triggers an allergic response. Thus an individual who is allergic to horses, dogs, or cats makes IgE in response to a particular protein in horse or dog dander or cat saliva, although that individual may tolerate exposures to other animals perfectly well. Similarly a person allergic to oysters makes IgE that recognizes and interacts with a protein in oysters, but that person is able to eat non-mollusk foods without any reaction.

IgE does not mediate the allergic reaction itself; rather it primes an effector cell—the mast cell first identified in 1877 by Paul Ehrlich. Ehrlich noted that these cells were stuffed with large granules. It was assumed at the time that the granules had been engulfed by the cells, hence, the name "mast" from the German word for a fattening feed. However, it is now known that the granules are produced within the cells and are filled with histamine and other chemical mediators of the allergic reaction.

When an IgE antibody on the mast cell encounters its specific corresponding allergen, the granules move to the surface of the mast cell, and, through a process known as degranulation, release chemical mediators into the surrounding tissue.

50%
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1 ml + 1 ml/litre
8h fun
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Max fall - Original Base line = 12.5%
.. - Final Base line higher = 17.3%
.. .. Lowest. = 14.5%

5 mins

K84 (82 Hydroxy-ethyl)
0.5% 10L/m

? Hurrah!

Mw

5 mins

K82
0.5%
10L/m

26-27%
fall.

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Effective Medicines for Treating Asthma

While one of the best methods for treating asthma and allergic disorders is careful management of the environment to avoid substances that trigger reactions in sensitive persons, there are a number of effective drugs available for treating and, in some cases, preventing asthma.

Some drugs have been derived from remedies used in the past. In recent years scientists have isolated the active chemical components from many of the botanical agents favored by the ancient healers, and constructed synthetic versions of them.

One such agent is sodium cromoglycate, known by its trade names Intal® or Cromolyn. It is an anti-inflammatory agent that inhibits the release of histamine and thus prevents swelling and inflammation of the airways, allowing air to flow more freely.

The leading figure in the development of cromoglycate was Roger E.C. Altounyan, an Armenian physician who worked in England. He is recognized for his determined pursuit of a single idea—the development of an anti-allergic, anti-asthmatic agent from a weed called khellin, derived from a herb indigenous to Egypt and North Africa. A soup made from khellin was used 5000 years ago in ancient Egypt to relieve spasmodic muscular contractions. Reasoning that khellin might relieve the bronchial contractions that occur during an attack of asthma, Altounyan and his associates decided to try and improve on its action by isolating and synthesizing derivative compounds.

May 9, 1963 chart

Roger Altounyan (1922–1987) tested hundreds of extracts of khellin on himself, taking it before and after exposing himself to a solution of guinea pig hair—to which he was allergic. Extract K84, which would later be shown to contain sodium cromoglycate, reduced his response to the allergen, and he wrote "Hurrah!" on his chart.

Courtesy Mrs. Hella Altounyan and Family, Cheshire, England

Intal® Inhaler inhalation aerosol, 1998
Rhône-Poulenc Rorer Inc.

Courtesy Robert Aronowitz, M.D.

Altounyan suffered from asthma and, like many medical researchers throughout history, experimented on himself. He would induce asthmatic attacks by inhaling mixed pollen antigens to which he was allergic and then determine if the compounds isolated by the chemists had any mitigating effect. Over the course of eight years, he tested 670 compounds. While most of them failed to relieve his asthma during an actual attack, he found one compound that, if inhaled before he induced an attack, stopped the attack from developing. The compound was identified as sodium cromoglycate.

Cromoglycate is delivered by inhalation into the airways. Altounyan developed a device called the spinhaler to move the drug efficiently. The device works on the same principle as an airplane propeller, with whose mechanism Altounyan was familiar, having been a Royal Air Force pilot during World War II. Inside the device is a miniature propeller. When the patient breathes in, the propeller rotates and this releases the drug into the air stream. Thus there is an automatic coordination between the drug's entry into the airways and the patient's intake of breath.

Cromoglycate prevents or at least slows the release of chemical mediators, such as histamine, which are released by the degranulating mast cell and trigger an attack of asthma. Once degranulation occurs, treatment has to be directed at blocking the effects of the mediators on their target tissues or otherwise counteracting them. In this respect, theophylline, a bronchial muscle relaxant; the corticosteroids, which have an anti-inflammatory effect; and the long-standing first choice in an emergency, epinephrine, which enlarges the bronchial airways, are all useful.

May 9, 1963 chart

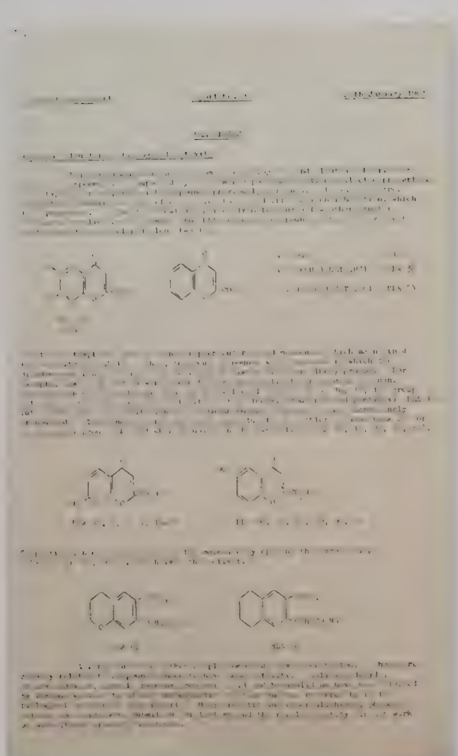
Courtesy Mrs. Hella Altounyan and Family, Cheshire, England

Unfortunately most of these agents have side effects. Theophylline, a chemical analog of caffeine (thus explaining the beneficial effects some asthma sufferers obtain from coffee), needs strict monitoring. Too high a dose and gastrointestinal effects, headaches, and high blood pressure can occur. Too low a dose and it is ineffective.

Side effects of epinephrine include an increased heart rate, central nervous system symptoms such as anxiety, and sometimes nausea and vomiting. However, newly developed drugs known as beta adrenergic agents have an epinephrine-like action. They are longer acting and have fewer side effects than epinephrine itself.

Corticosteroids reduce inflammation and airway irritability, and decrease mucus production and swelling. Unfortunately, if taken orally over the long term, steroids cause severe side effects, including the characteristic "moon face," osteoporosis, acne, and cataracts, as well as increased blood pressure and elevated blood sugar levels. They can also suppress the normal growth pattern in children. Some of these undesirable systemic effects can be avoided by the use of inhaled steroids, which primarily act locally on respiratory tract tissue.

Asthma can be a life-threatening disease but with the correct use of medications, patients may look forward to leading symptom-free lives.



Report No. 18, January 20, 1961

Physician Roger Altounyan's first report on the khellin extract project includes diagrams of some of the molecules he thought might prevent or treat asthma attacks.

Courtesy Mrs. Hella Altounyan and Family, Cheshire, England

Spirometer, mid-twentieth century

Altounyan used this spirometer from 1959 to 1967 during his tests to find the active ingredient of khellin, a Middle Eastern folk remedy for asthma. It measures the volume of air entering and leaving the lungs.

Courtesy Rhône-Poulenc Rorer Ltd.

Asthma and Genetics

Studies suggest that humans develop asthma because of an interaction between their predisposing genes and the environment in which they live. The earliest students of asthma, such as the seventeenth-century English physician Sir John Floyer, noted that the condition runs in families. In the coming years, the data anticipated from the Human Genome Project at the National Institutes of Health, supplemented by findings by other institutions, will help to elucidate the mode of inheritance of asthma. A recent report from the University of Southampton, England, reported a gene for asthma located on chromosome 5. However, the current thinking is that there is likely to be more than one gene involved. Identifying a person who is genetically susceptible to asthma is not expected to be a simple matter.

One reason is that not everyone who carries the familial susceptibility to allergy expresses it clinically. A study of twins in Sweden suggests that about 18 percent of the population carries a genetic susceptibility to allergy but that less than half of that number are clinically affected.

Another indication of the variability of the genetic expression of such disorders as asthma comes from a study in the United States that found that two clinically allergic parents had a 58 percent chance of having an allergic child. Where one parent was clinically allergic the risk of an allergic child was 38 percent and where neither parent was clinically allergic the risk was only 12.5 percent.

Courtesy National Institute of Allergy and Infectious Diseases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The Future of Asthma Research

Asthma affects fifteen million Americans, and causes, directly or indirectly, five thousand deaths annually, but what especially concerns public health authorities is the increasing number of people with the disease. Between 1980 and 1994 the incidence of asthma rose by 75 percent. In children under the age of five, asthma increased by 160 percent.

The need to manage and control asthma is urgent. From an economic standpoint, the disorder is a major burden on the population. In the United States alone, it is estimated that the costs of asthma to the health care system are over six billion dollars a year. Nearly 500,000 persons are admitted to hospitals and 1.9 million visit hospital emergency rooms for asthma-related conditions each year.

The National Institutes of Health has mounted a major effort to discover effective ways to manage and treat asthma by supporting and funding scientists conducting research on the disease throughout the world. Three Institutes lead the effort: the National Heart, Lung, and Blood Institute, the National Institute of Allergy and Infectious Diseases, and the National Institute of Environmental Health Sciences. Some examples of specific research projects currently underway include a study of the role of respiratory infections in childhood asthma, a study on the origins of asthma in early life, and a study on environmental intervention in the primary prevention of asthma in children.

Asthma affects persons of all ages, races, and ethnic groups but not equally. In the United States, low income, minority, and disadvantaged inner city populations have significantly higher numbers of emergency room visits, hospital admissions, and fatalities due to asthma. This may be because of a higher level of exposure to environmental allergens and air pollutants. But it is also likely to reflect a number of complicating socioeconomic problems, such as the reduction in use and availability of health care services, a lack of education and guidance on management needs, and difficulties maintaining a management program, rather than a greater susceptibility to the disease.

Courtesy National Institute of Allergy and Infectious Diseases

It is not only in the United States that the prevalence of asthma is increasing. Asthma is on the rise practically everywhere in the world, with rates increasing in all age groups, but particularly in children. It is probably the most common chronic disease in children, according to World Health Organization (WHO) data.

The most striking increases are occurring in Australia, where about one-quarter of primary school children are diagnosed with asthma, a prevalence higher than in any other nation. In Western Europe asthma has doubled in the past ten years. In Switzerland 8 percent of the population suffer from asthma compared with only 2 percent twenty-five to thirty years ago. In Finland, from 1981 to 1996, the number of asthmatic sufferers increased threefold. In the Latin-American countries of Brazil, Costa Rica, Panama, Peru, and Uruguay, the prevalence of children with asthmatic symptoms is between 20 and 30 percent. In Japan there are an estimated three million asthma sufferers, in India there are fifteen million. The worldwide cost of the disease is greater than that of tuberculosis and AIDS combined, according to WHO.

The situation is raising widespread concern among public health officials throughout the world, because the reasons for the increase in asthma are unknown. The WHO describes it as one of the "biggest mysteries in modern medicine."

There is a general consensus that the increase is not a result of improved diagnosis, although that may account for some of it, according to the U.S. Centers for Disease Control and Prevention.

Certainly there is no lack of hypotheses attempting to account for the increase. They include exposure to diesel fuel exhaust, diet, smoking, viral infections, cold air, the increase in obesity, changes in nutrition, and alterations in living patterns that have reduced physical exercise.

One conjecture is that something has occurred in industrial countries in the past four decades that has resulted in some new environmental exposure. For example, housing construction practices have changed since the 1970s. People are more likely to be exposed to allergens at higher critical concentrations than in the past. At the same time, though, there are no reliable data on what these allergens might be.

One view gaining increasing support is that there's been a change in the kinds of exposures that children are now experiencing early in their lives. This sets the juvenile immune system on track for an increased allergic response.

Another theory includes an increase in air pollution and what has sometimes been called the hygiene hypothesis. In terms of chemical pollutants, it has been clearly demonstrated, for example, that components of diesel particles enhance allergic responses. The hygiene hypothesis focuses on the early treatment of infectious diseases and argues that it is to the benefit of infants and children to be exposed to endotoxins and to undergo some experience with infections, which have the potential to move them away from the allergic phenotype—susceptibility and aberrant immune responses to environmental allergens.

The present consensus is that there are at least three factors that underlie asthma: the allergic response, viral infections, and air pollution. They can act singly or in concert in ways that are not yet fully understood.

The story of our search for the causes of asthma is far from complete. There are basic biomedical and clinical aspects of the disorder that are obscure and need active investigation. Certainly, there are new tools available to scientists today, such as developments in molecular biology that allow detailed study of the immune response. Ultimately the results of such studies will help us understand the immune system and will put new therapies and avenues of management at the disposal of physicians and patients.

But laboratory science, by itself, is unlikely to provide all the answers. To be successful, the attack on asthma will need scientific research, environmental studies, public health investigations, and improvements in health and medical services. Based on accumulating evidence, society will have to be willing to implement measures and adopt policies aimed at minimizing the disease.

Courtesy National Institute of Allergy and Infectious Diseases

The Faces of Asthma

Asthma has many different faces: it is more than just the symptoms that patients experience. Asthma is also about people—individuals and their families, communities, health care providers, and medical scientists.

Some people who have asthma benefit from current asthma treatments and achieve great honors in their chosen profession. Others learn to manage their asthma and lead full and productive lives. The faces of asthma are many and varied—some of these people may be your family and friends.

Baruj Benacerraf (b. 1920)
American immunologist and Nobel Prize winner

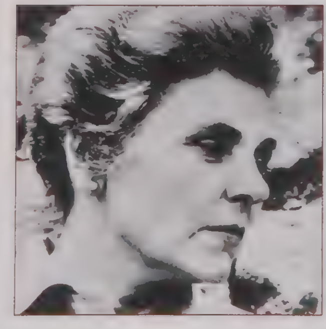
Baruj Benacerraf shared the 1980 Nobel Prize in medicine for his discovery of the genetic basis of autoimmune diseases. His childhood experiences with asthma fostered his interest in immunology. Benacerraf continues his work at Boston's Dana-Farber Institute.

Courtesy Baruj Benacerraf, M.D.

Leonard Bernstein (1918–1990)
American composer, conductor, and pianist

As a sickly infant, Leonard Bernstein sometimes turned blue from asthma. He became a prodigious pianist, conductor, composer, and lecturer, although he suffered from asthma throughout his life. Audiences often heard him wheezing above the orchestra.

Courtesy Carl A. Koenig



Elizabeth Bishop (1911–1979)
American poet, teacher, and author

Elizabeth Bishop won almost every important literary prize of her day, while battling asthma unsuccessfully throughout her life with injections of adrenaline, calcium, and antihistamines. Her treatments also included transfusions, electroshock, cortisone, and alcohol—all to no avail.

Courtesy Prints and Photographs Division, Library of Congress

Bruce Davidson (b. 1949)
American equestrian champion

Bruce Davidson manages his allergic asthma with medications so he can continue to compete in equestrian events. He has won a silver and a gold Olympic medal, seven American and two world championships.

Courtesy Bruce Hewitt/Getty Images

Charles Dickens (1812–1870)
British novelist

Charles Dickens found relief from his "chest troubles" only with opium, a popular asthma remedy of his day. Mr. Omer, one of the asthmatic characters in the autobiographical novel, *David Copperfield*, reflects Dickens's own suffering.

Courtesy Prints and Photographs Division, Library of Congress

Benjamin Disraeli (1804–1881)
British statesman and author

For Benjamin Disraeli's disabling asthma, Queen Victoria's physician prescribed mustard poultices and a change of scene. Other physicians recommended arsenic, a popular new remedy, but all treatments were unsuccessful.

Courtesy Prints and Photographs Division, Library of Congress

Tom Dolan (b. 1976)
American swimming champion and spokesperson for asthma

Despite severe chronic asthma, Tom Dolan is a fierce competitor and often trains to exhaustion. He is an Olympic gold medallist and a world champion swimmer.

Courtesy Reuters/Gary Hershorn/Archive Photos

Robert Donat (1905–1958)
British stage and screen actor

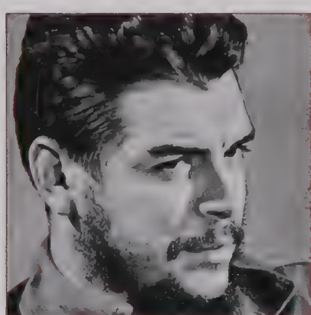
Sudden explosive asthma attacks shortened Robert Donat's career and life, despite the efforts of physicians around the globe. Donat starred in dozens of films and plays, sometimes with oxygen tanks ready to treat his asthma.

Courtesy of the Academy of Motion Picture Arts and Sciences

Kurt Grote (b. 1973)
American swimming champion

Kurt Grote's doctor recommended he start swimming at age fifteen to help his chronic asthma. He won an Olympic gold medal in 1996 in the breast stroke.

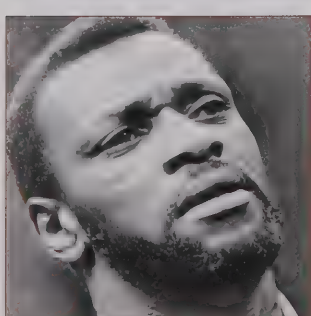
Courtesy Tony Duffy/Getty Images



Ernesto (Che) Guevara (1928–1967)
Argentine physician and freedom fighter

Although he was weakened by asthma from infancy, Ernesto Guevara fought in three revolutions, sometimes using his rifle as a crutch. During a skirmish in Bolivia, he suffered an asthma attack, was captured by government troops, and executed shortly thereafter.

Courtesy Prints and Photographs Division, Library of Congress



Moses Gunn (1929–1993)
American actor

Moses Gunn won nominations for a Tony and an Emmy award for his work on stage and television, in addition to awards for his Off-Broadway theater performances. During his final years, he required annual hospitalizations for asthma, and he died of complications of the disease.

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Helen Hayes (1900–1993)
American actress and author

Helen Hayes, often called the "First Lady of American Theater," made frequent trips to hospitals because of asthma attacks aggravated by backstage dust. When asthma ended her theatrical career, Hayes wrote books and raised funds for organizations that fight asthma.

Courtesy Culver Pictures, Inc.

Nancy Hogshead (b. 1962)
American swimming champion and spokesperson for asthma

Despite breathing difficulties, Nancy Hogshead won three gold medals and one silver in the 1984 Olympics. When a bronchial spasm kept her from winning medal number five, a physician discovered the problem was asthma.

Courtesy Tony Duffy/Getty Images

Robert Joffrey (1928–1988)
American dancer, choreographer, producer, and teacher

Robert Joffrey began dancing at age six to counteract his asthma. Founder of the Joffrey Ballet, a world-renowned innovative modern dance company, Joffrey battled lifelong asthma with acupuncture, herbs, and medications, but hardly ever missed a performance.

Courtesy ©Herbert Migdoll 2002

Jackie Joyner-Kersee (b. 1962)
American track and field champion

Olympic triple gold medalist Jackie Joyner-Kersee became the world's top woman athlete in the heptathlon and long jump competitions despite severe asthma. She retired from track competition after the 1996 Olympic Games.

Courtesy Tony Duffy/Getty Images

John F. Kennedy (1917–1963)
Thirty-fifth president of the United States of America

Asthma resulting from allergies to dogs, horses, and dust troubled John F. Kennedy throughout his adult life. Steroids prescribed to treat his Addison's disease probably also helped control his asthma.

Courtesy John Fitzgerald Kennedy Library

Alyce King Clarke (Alyce King) (1915–1996)
American singer

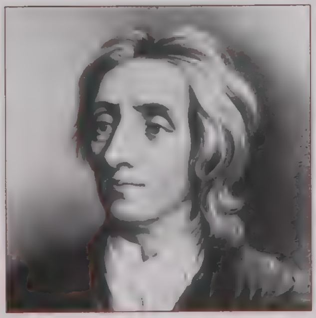
Best known as one of the four King Sisters, Alyce King performed for six decades with members of her musically gifted family. Asthma plagued her as a child and caused life-threatening attacks in her sixties and seventies.

Courtesy Brown Brothers

Bill Koch (b. 1956)
American cross-country skier

The only American ever to win the World Cup overall cross-country title, Bill Koch also won a silver medal at the 1976 Olympic Games. He manages his asthma with medications.

Courtesy David Cannon/Getty Images



John Locke (1632–1704)
British physician, philosopher, and scientist

As a political leader, John Locke was drawn to London, the seat of English government. But persistent asthma, unrelieved by physicians, forced Locke to live in the country, away from London's polluted air and political life.

Ernest (Dutch) Morial (1929–1989)
American political, legal, and civil rights leader

Ernest Morial, a two-time mayor of his native New Orleans and pioneer in civil rights and government, broke the color barrier at every stage of his municipal and national career. Twenty-five years of asthma led to his untimely death at age sixty.

Courtesy Marc H. Morial

George Murray (b. 1947)
American wheelchair marathon champion

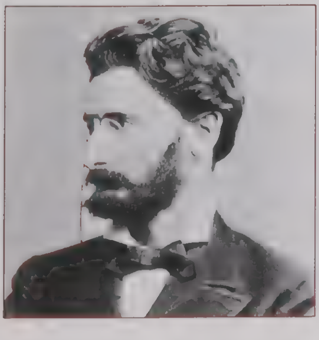
George Murray began racing in his chair to manage his asthma. He became world wheelchair marathon champion, was first to break the four-minute mile, and first to cross the country in a wheelchair.

Courtesy AP/World Wide Photos

Peter the Great (1672–1725)
Russian czar

An ambitious ruler with an insatiable drive to reform Russia, Peter the Great seemed unhindered by health problems. But during his last ten years, severe asthma and other diseases seriously hampered his ability to function and govern.

Courtesy Hulton Getty/Liaison Agency



Joseph Pulitzer (1847–1911)
American publisher and philanthropist

Although Joseph Pulitzer consulted physicians worldwide, none was able to remedy his asthma. After forty-three years of suffering, he died on the yacht the breezy deck of which often alleviated his breathlessness.

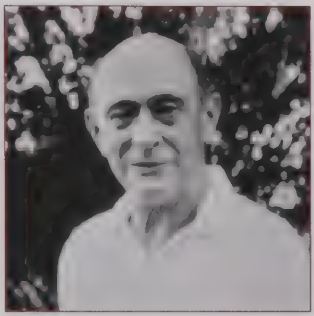
Courtesy Prints and Photographs Division, Library of Congress

Theodore (Teddy) Roosevelt (1858–1919)

Twenty-sixth president of the United States of America

Severe asthma made Theodore Roosevelt a sickly infant and a virtually homebound child. His parents tried all available remedies and traveled worldwide to find him a salutary climate. But it was vigorous exercise that helped turn him into a healthy, productive adult.

Courtesy Prints and Photographs Division, Library of Congress

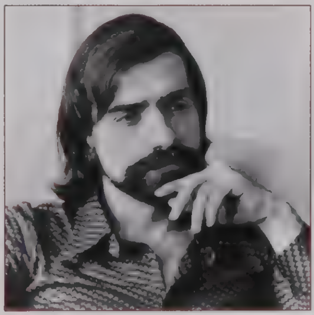


Arnold Schönberg (1874–1951)

Austrian composer

Undaunted by chronic asthma, acclaimed Viennese composer Arnold Schönberg revolutionized music by composing in a 12-tone scale. Schönberg's healthiest, most productive years were spent in Los Angeles, far from the Nazi terror in Europe and the harsh winters that compounded his asthma.

Courtesy Arnold Schönberg Center, Vienna



Martin Scorsese (b. 1942)

American film director

Martin Scorsese dropped out of seminary to study film. An asthmatic youngster, he watched movies on television and became an insatiable fan. Scorsese recently received the American Film Institute's Life Achievement Award.

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William Tecumseh Sherman (1820–1891)

American general in the Civil War's Union Army

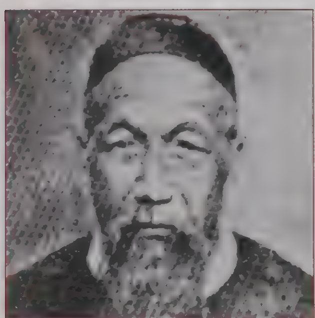
Asthma was William Tecumseh Sherman's lifelong enemy. Ironically, although he led an infamously destructive march through Georgia, it was the South's temperate climate that brought him relief from his symptoms.

Courtesy Prints and Photographs Division, Library of Congress

Howard Thurman (1900–1981)
American clergyman, educator, and author

Howard Thurman struggled against poverty and racism in the South as a child and against asthma in later years. He became a world-renowned spiritual and intellectual leader, pursuing a dream of unity—one community that would cross all lines of race, religion, and national origin.

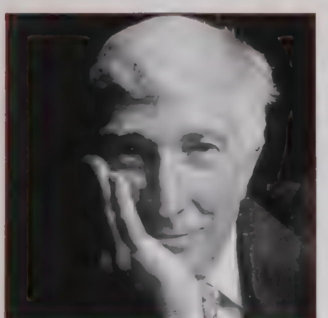
Courtesy the Howard Thurman Educational Trust



Tseng Kuo-Fan (1811–1872)
Chinese statesman, general, and scholar

Tseng Kuo-Fan's asthma caused incessant coughing and an inability to work. Diagnosing a yin deficiency, his physician gave him "an excellent prescription, but I really detest medicine and therefore did not take it," Tseng wrote.

Courtesy Prints and Photographs Division, Library of Congress



John Updike (b. 1932)
American writer

John Updike, prolific writer of novels, poetry, short stories, and essays, thought he was dying during his first attack of breathlessness in his twenties. The diagnosis was bronchial asthma, aggravated by his cats.

Courtesy Frank Capri/Archive Photos

Amy Van Dyken (b. 1973)
American swimming champion

Amy Van Dyken's doctor suggested she start swimming to relieve her severe asthma. Diligent training and asthma medications helped her become the first American woman to win four gold medals in one Olympic Games.

Courtesy Reuters/Gary Hershorn/Archive Photos

Benjamin Ward (b. 1926)
American police commissioner and criminal justice specialist

Brooklyn-born Benjamin Ward joined the New York City Police Department, the nation's largest, in 1951, becoming the city's first black police commissioner in 1984. He resigned after six years. "I am yielding," he wrote, "to the chronic asthma that has sapped my strength."

Courtesy Benjamin Ward

Harold D. West (1904–1974)
American medical educator, administrator, scientist, and humanitarian

As president of Meharry Medical College, Harold D. West fostered remarkable expansion of academic offerings, facilities, and endowments. West was plagued and often hospitalized by severe asthma, which hastened his death.

Courtesy Meharry Medical College

Edith Wharton (1862–1937)
American novelist and short story writer

Edith Wharton suffered from occasional bouts of asthma throughout her literary career. Wharton wrote short stories, travel books, and many successful novels, including *Age of Innocence,* which earned her a Pulitzer Prize in 1921.

Courtesy Archive Photo

Woodrow Wilson (1856–1924)
Twenty-eighth president of the United States of America

Exhausted by eighteen-hour work days at the Versailles Peace Conference, weakened by severe asthma, and impaired by arteriosclerosis, Woodrow Wilson was virtually incapacitated. Yet even after he was paralyzed by a stroke, his health problems were kept secret from the American public.

Courtesy Prints and Photographs Division, Library of Congress

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