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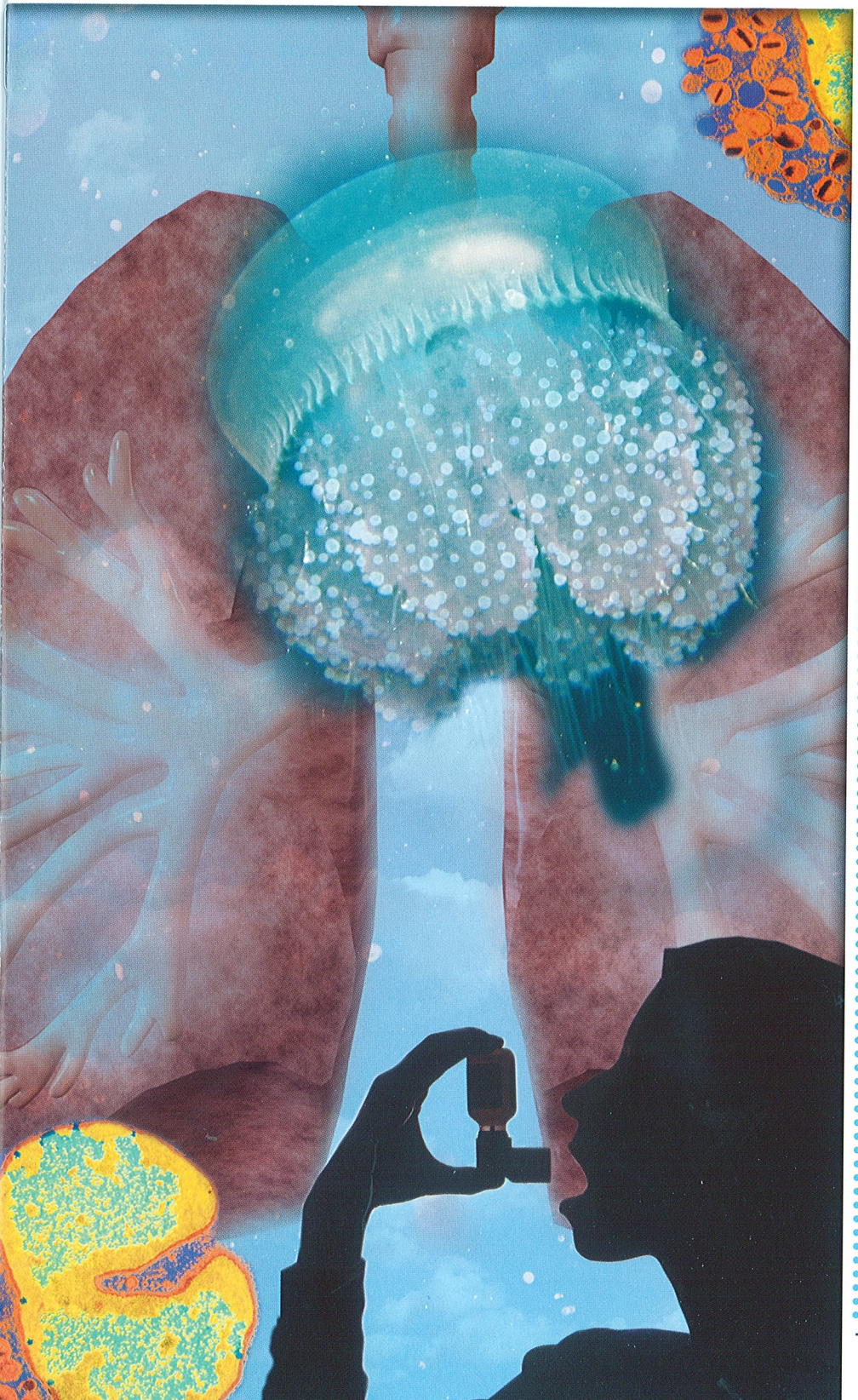

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Breathtaking Discoveries: How Basic Research Led to Treatments for Asthma

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COVER: Fundamental research on the underlying causes of asthma has resulted in a greater understanding of this complex condition and the development of improved and diverse treatment options. Clues revealed by scientists studying lung physiology, cells of the immune system and even jellyfish toxins have led to asthma therapies that are allowing millions of asthmatics to breathe more easily. Graphic Collage: *Creative Media Group, Corporate Press,* Figures courtesy of Getty Images, NIBSC / Science Photo Library, and the National Oceanic and Atmospheric Administration.

Breathtaking Discoveries: Asthmatics Breathe Easier Through Basic Research

MARGIE PATLAK

There may be nothing more frightening than not being able to breathe. Imagine being out enjoying a pleasant bike ride through grassy fields dotted with flowers when you realize that you can't seem to "catch your breath." You stop biking, but this doesn't help. After five minutes, you find yourself hunched over and noisily panting in an effort to gain more life-sustaining air, but still it feels as if someone is sitting on your chest and preventing the air from flowing in and out of your lungs (Figure 1). Soon your heart starts to pound and your pulse races as anxiety builds. Fortunately, after taking a few puffs from an asthma inhaler you had stashed in your backpack, you eventually start breathing sufficiently, but the whole experience leaves you shaken and exhausted.

Welcome to the World of Asthma

Welcome to the world of asthma, a chronic condition that can be spiked with attacks of difficulty breathing, as described above. Often these asthma attacks are triggered by inhaling mold or other allergens, cigarette smoke, pollutants, or other irritants. Viral infections, exercise and certain medicines, such as aspirin or beta blocker heart drugs, can prompt asthma attacks, as well. Asthma can also cause less pronounced but more frequent symptoms, such as wheezing during the night and a chronic cough.

Asthma afflicts more than 20 million Americans, with about one out of every ten people in this country developing the condition during their lifetimes. Each year, this costly syndrome causes close to 2 million visits to the emergency room, 13 billion dollars in health care costs, and about 4,000 deaths, according to the National Center for Health Statistics. Disturbingly, the number of people with asthma in this country has been rapidly increasing since the early 1980's, causing its prevalence to triple in the past 20 years, and leading experts to claim we are in the midst of an asthma epidemic (See "Hygiene Hypothesis" sidebar).

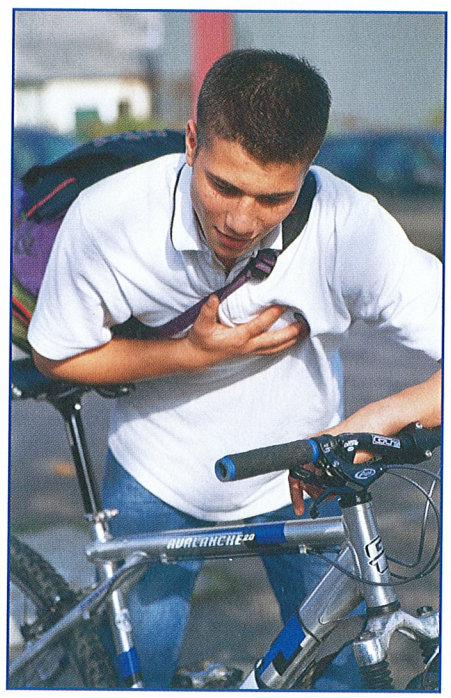


Figure 1, Asthmatics Struggle to Breathe: Symptoms of asthma include breathlessness, wheezing, and coughing and may be triggered by exercise. Research advances in the understanding of how asthma works have led to a greater variety of treatments. *Photo by Mark Clarke/ Science Photo Library.*

There is no cure for asthma, but fortunately, there are a number of effective treatments for the condition, thanks to decades of research on seemingly unrelated topics, including neurobiology, allergies, and basic immunology. Science has shown that asthma is not actually a single disease, but rather a collection of different overlapping syndromes, each with their own unique pathological pathways leading to the same set of asthma symptoms. This breakthrough in the understanding of asthma, along with discoveries deciphering the major players that cause asthma, has culminated in multiple effective asthma drugs and several others on the horizon. Such treatments have allowed millions of asthma sufferers to again take easy breathing for granted. None of these drugs would have been possible if it weren't for dozens of curious scientists who collectively helped figure out what causes asthma, thus showing the way to effective targeted therapies.

Why is asthma on the rise?: The Hygiene Hypothesis

Basic research on the role that early infections play on the developing immune system may help explain why the incidence of asthma is on the rise, most notably in Westernized, affluent countries. The marked increase in asthma prevalence has puzzled the medical community because it suggests that some changing environmental factor(s) must be causing an increase in asthma. But what could those environmental factors be?

The first clues came from studies of populations that showed that the rate of asthma increases as people move from more rural to urban environments, and that children growing up on farms are less likely to develop asthma than those in urban settings. Then, in 1989, British epidemiologist David Strachan, who was puzzled by why hay fever was on the rise in industrialized nations, began to look for any environmental factors linked to the development of hay fever in a large British population. Of the 16 possible factors he explored, the one that showed the most striking links to protection from developing hay fever was being part of a large family, especially having a number of older siblings.

Those of us with older siblings might see them acting as role models or the source of ceaseless teasing, but to a medical researcher like Strachan, older siblings are primarily known for passing on their infections to their younger brothers and sisters. Perhaps allergies were becoming more prevalent, he proposed, because of a decline in family size combined with higher standards of personal cleanliness. This increase in hygienic environments, according to Strachan, has limited the number of infections people experience in early childhood when their immune systems are developing. A lack of such infections early in development could skew the immune response so it became more reactive to allergens than to pathogens, he said, thus giving birth to the "hygiene hypothesis."

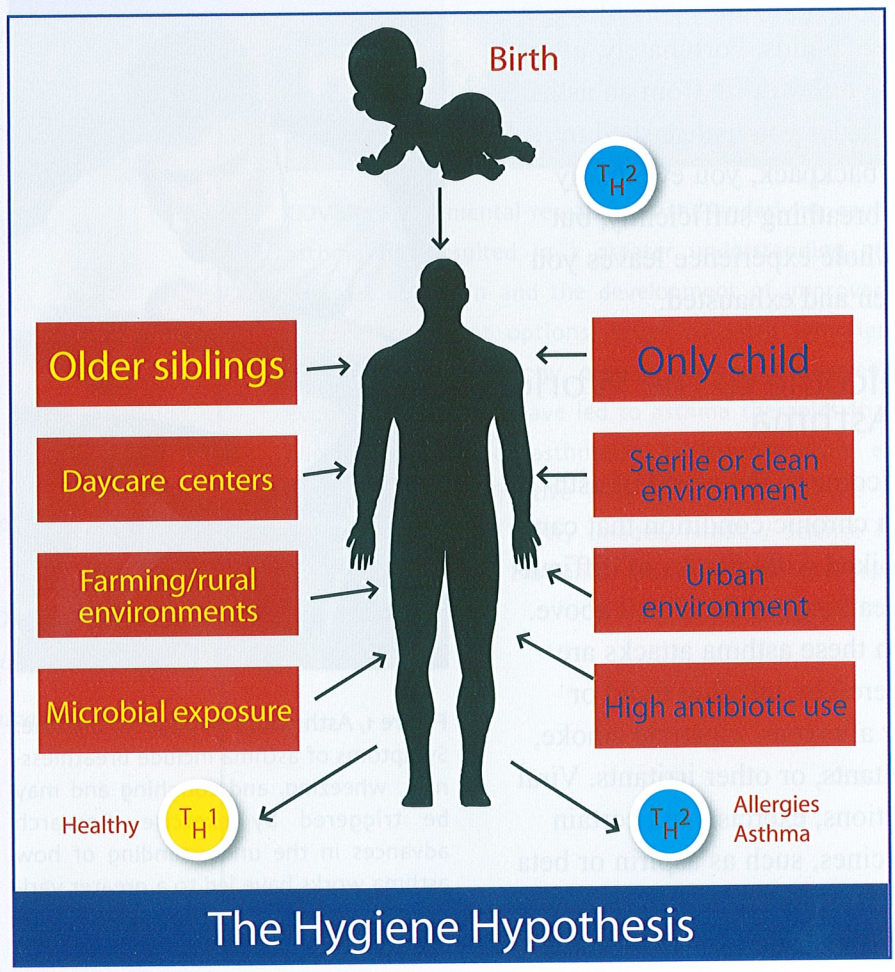
Although Strachan's hygiene hypothesis seems contrary to the notion that respiratory infections exacerbate asthma, basic laboratory and animal studies offer support to the notion that the immune system is influenced by what it encounters early on in its development. Studies in mice in the 1980's revealed that there are two main branches to an immune response in these animals. One branch, called Th1, contains a subset of white blood cells and interferons, interleukins, and other cellular hormones that are used to fight off viruses and other microbes that make their way into cells of the body. The other branch, called Th2, contains a subset of white blood cells and cellular hormones that typify an allergic or asthmatic response or a response to parasitic invaders.

Further research in animals and human tissues has shown that early in development, activation of one branch of the immune system seems to suppress the activity of the other branch. When these basic research findings are examined in conjunction with Strachan and others' findings on the link between allergy and family size or hygiene, it seems to support the hygiene hypothesis. In short, this states that smaller family size, a more hygienic home environment, and the use of vaccines and antibiotics in Westernized nations have prevented infants from developing infections that would have shifted their immune systems to be more primed to fight microbes (Th1). So instead they overreact to allergens and thus are more likely to develop allergies and asthma (Th2).

More recent studies provide both supporting and conflicting data for the hygiene hypothesis. For example, there's no evidence that vaccines commonly used today increase the risk of allergy or asthma. Several researchers have more recently found that neither the number of personal infections nor sibling infections during early childhood seemed to influence the development of allergies and asthma. But other studies reveal that some types of infections seem to be more likely to prevent the development of allergies or asthma than others. These infections include tuberculosis, and gastrointestinal infections such as hepatitis A.

The hygiene hypothesis has opened up a whole new set of possible prevention measures for allergies and asthma that are currently being tested, including drugs or vaccines designed to boost the Th1 response, and oral solutions of *Lactobacillus* and other "good bacteria" that do not cause any harmful infections but are likely to foster an immune response that could keep an allergic response at bay. But there are still skeptics of the hygiene hypothesis who point out that the Th1/Th2 dichotomy has not been definitively shown in humans, and that cellular hormones from both the Th1 and Th2 branches are overproduced in people with asthma.

Clearly, the question of why asthma is on the rise will continue to keep research scientists busy.



The Hygiene Hypothesis

From Divine Origins to Twitchy Airways

The drama of an asthma attack led the condition to be one of the first medical ailments described in written history. The ancient Egyptians recorded various remedies for asthma (including animal dung!) on their papyri scrolls (Figure 2), and Homer noted in the *Iliad* that one warrior died on the battlefield not from his wounds but from his wheezing. The causes of asthma, however, remained a mystery for millennia. In ancient Greece, the sudden attacks of gasping for breath were thought to have divine origins, such as possession by an avenging or malevolent deity. In 1662, the Belgian physician and asthma sufferer Jean van Helmont suggested that asthma was caused by the lungs being contracted or drawn together, but offered no suggestions for the cause of the contraction. It was not until the 20th century that researchers began applying rigorous science to solving the puzzle of what causes asthma.

For many diseases, uncovering their causes hinges on discovering telltale flawed organs, tissues, or cells in afflicted individuals, and then working backwards to discover what caused those flaws. But this approach didn't seem to work for asthma. When pathologists first performed autopsies of people who died from this condition, their lung tissue looked surprisingly good. Each lung has a branched windpipe that itself branches into progressively smaller airways, collectively called bronchi, which culminate in tiny air sacs, known as alveoli. Autopsies revealed that the lungs of people who had died from asthma had mucus plugging some of their small airways, an excess of the types of cells that typically respond to injury or infection, and some excess growth of muscle tissue and fluid accumulation that was narrowing some of their air passages (Figure 3). But there was no obvious smoking gun—none of the rampant destruction of alveoli seen in emphysema, for example, or other irreversible changes.

This led English physician and asthma sufferer Henry Hyde Salter to propose, in 1868, that maybe people with asthma have "twitchy" airways. Their "perverted nervous action," he said,

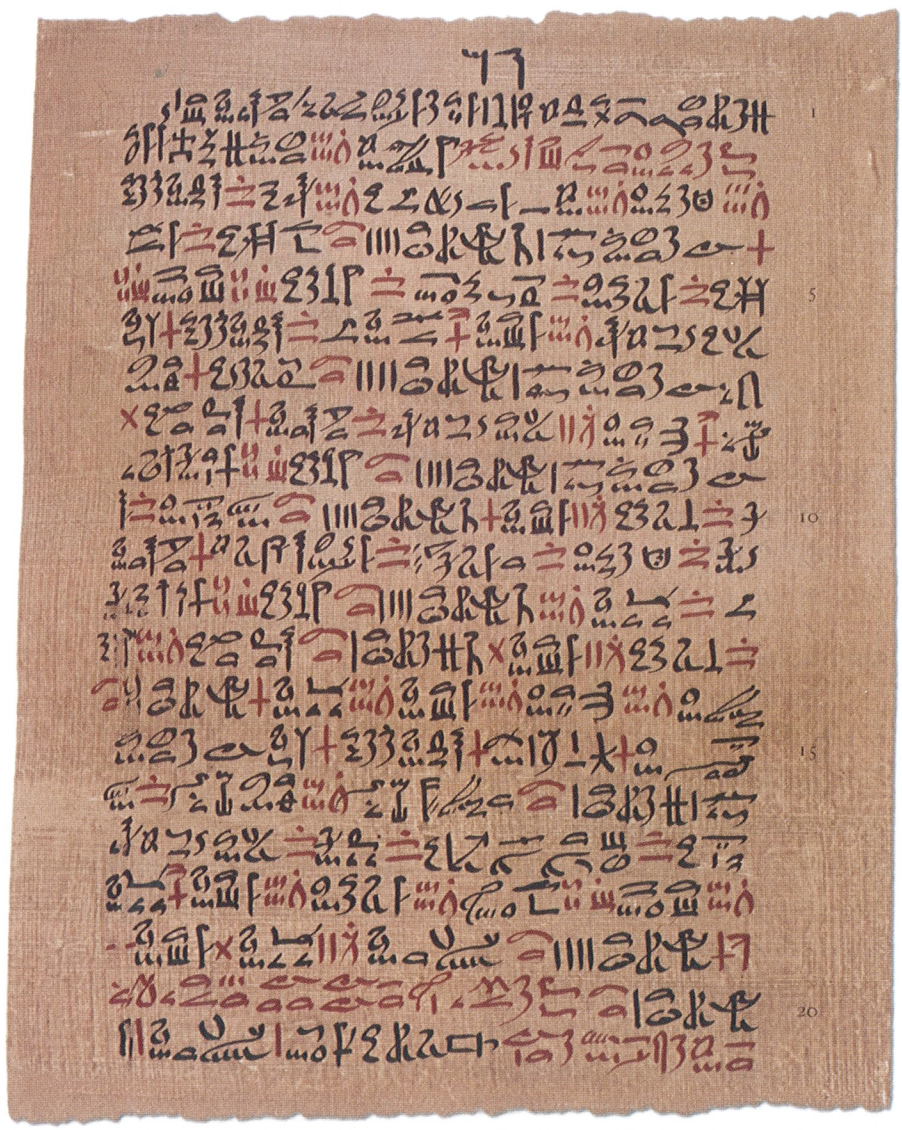


Figure 2, Ebers papyrus (c. 1600 BCE): The Ancient Egyptians discussed treatments for asthma, including dung and herbs heated on a hot brick, in the Ebers papyrus, the most voluminous medical record of Ancient Egypt currently known. *Image courtesy of the National Library of Medicine, National Institutes of Health.*

Why Asthma Makes it Hard to Breathe

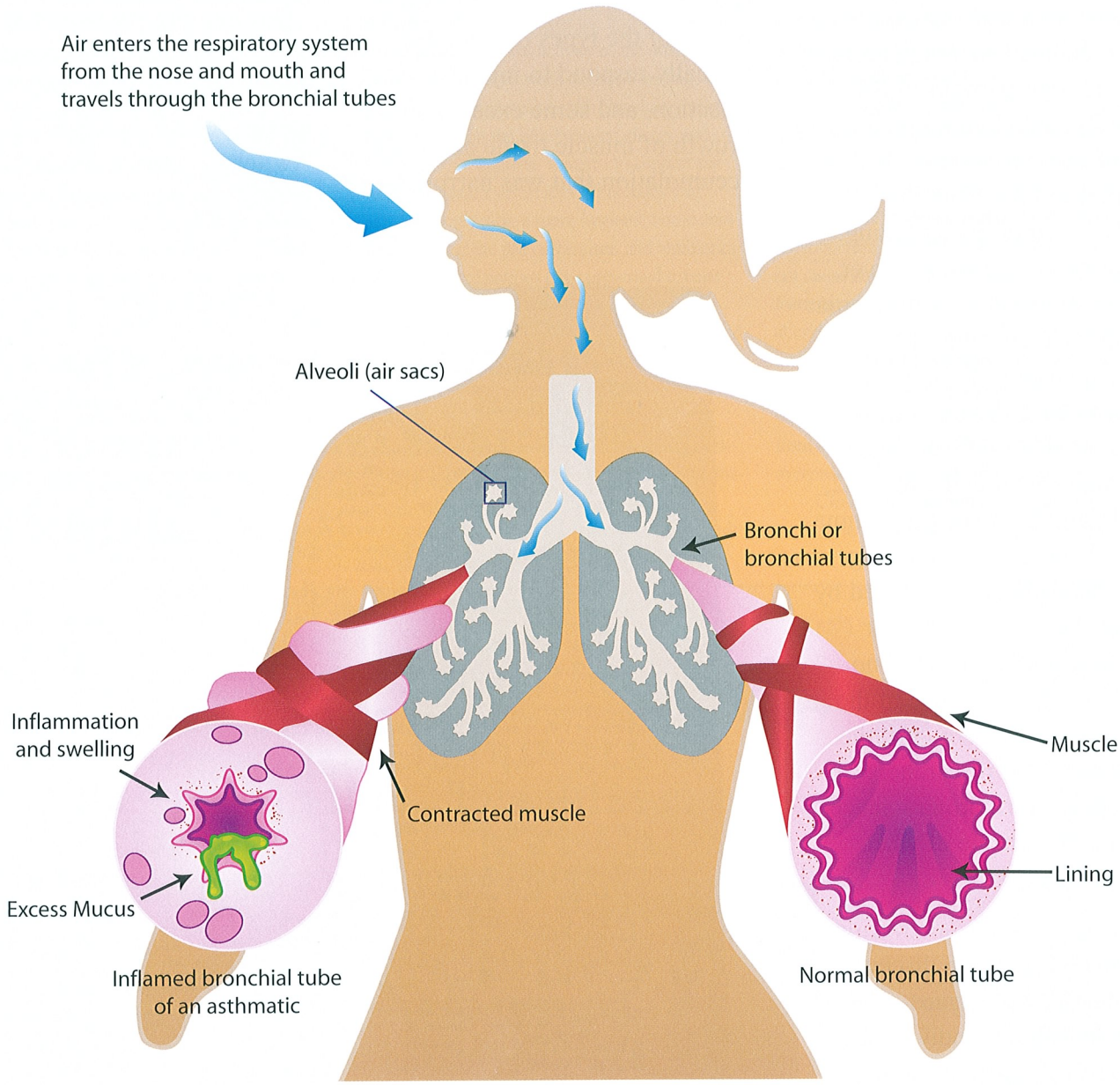


Figure 3, Why Asthma Makes it Hard to Breathe: When you inhale, oxygen travels into your lungs through passages called bronchi or bronchial tubes. During an asthmatic episode, the airways become temporarily obstructed, making it difficult for oxygen to enter the lungs. This obstruction is caused by inflammation and swelling of the bronchial tubes, contraction of the smooth muscle surrounding the bronchial tubes, and a buildup of excess mucus inside the tubes. Although scientists and physicians have long known these symptoms cause the shortness of breath associated with asthma, basic research has unraveled the physiological events that underlie the symptoms themselves, identifying new targets for therapies. *Figure designed by Corporate Press.*

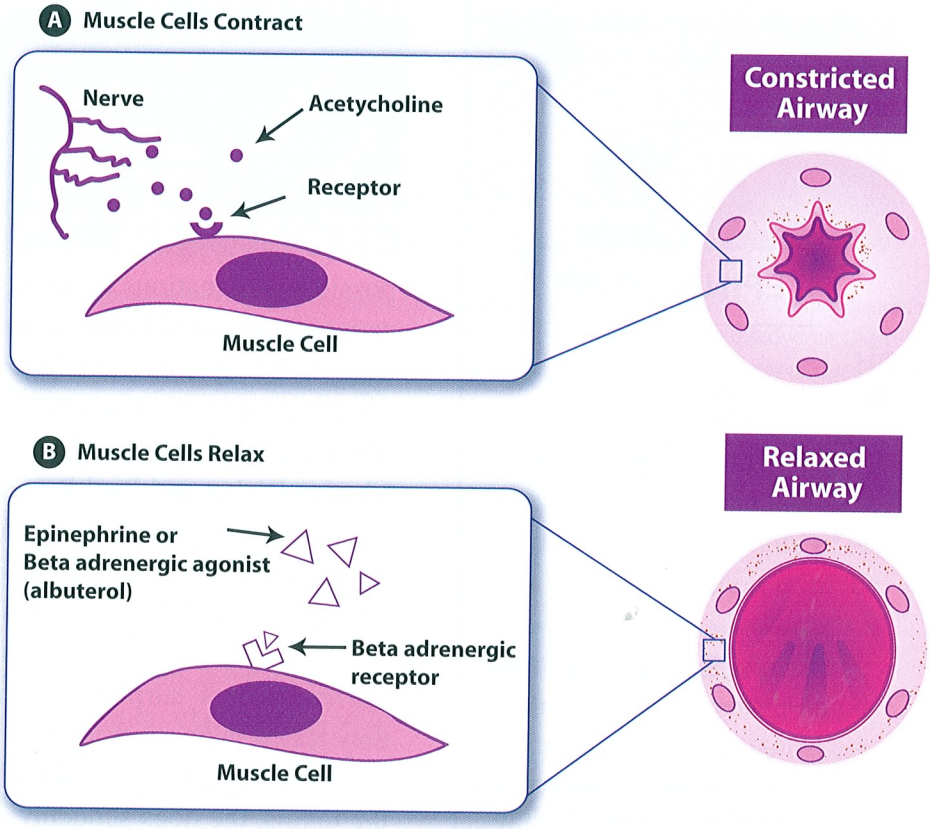


Figure 4, Nervous theory of asthma: When acetylcholine, a substance produced by nerves in the lungs during asthma, binds to its receptor on the smooth muscle surrounding the bronchi (airways), it causes the muscle to contract, obstructing passage of air (A). Epinephrine, another chemical produced by the nerves in the lungs, has the opposite effect; when epinephrine latches onto specific binding sites known as beta adrenergic receptors, it causes the muscle to relax (B). Drugs such as albuterol are beta adrenergic agonists (mimics the effect of epinephrine). During an asthmatic episode, they bind to the beta adrenergic receptor and cause the muscle to relax. *Figure designed by Corporate Press.*

caused their airways to excessively constrict in response to environmental irritants. But this hypothesis was largely ignored until the beginning of the 20th century, when basic researchers made headway in uncovering the push-pull dance of chemicals that the nervous system employs to cause airways to expand or contract. After years of experimenting on animals and isolated human tissues, these scientists discovered that certain compounds, such as acetylcholine, are released by nerves in the lungs. These chemicals put the squeeze on bronchi by triggering the muscles surrounding the airways to contract. But when other compounds traveling in the bloodstream, such as epinephrine (also known as adrenaline), latch onto special *beta adrenergic* receptors in lung muscle cells they do the opposite—they prompt the muscle cells to relax, thereby expanding the size of the airways (Figure 4). (Receptors are molecular structures embedded in cells that bind to specific compounds. When beta adrenergic receptors in lung muscle cells bind to epinephrine, they trigger the molecular effects of this hormone on these cells.)

Researchers wondered whether asthma patients had a faulty nervous system in which the delicate balance between airway muscle contraction and relaxation was tipped such that more contraction happens than relaxation. This "nervous theory" was supported by studies that showed people with asthma experienced more bronchial constriction at a lower dose of inhaled acetylcholine than individuals without the condition. And difficulties breathing would often quickly vanish when people experiencing asthma attacks were given epinephrine shots, which first became available in the 1920's.

The nervous theory of asthma led to the development of metered-dose inhalers of epinephrine agonists (mimics). These act on the beta-adrenergic receptors in the lung to induce a widening of the airways. In the 1960's and 1970's, people widely used these inhalers, comprised of isoproterenol (chemically similar to epinephrine), to relieve and prevent their asthma attacks. However, instead of the death rate from asthma being reduced, it went up. Further investigation revealed that many of the asthma deaths stemmed from people

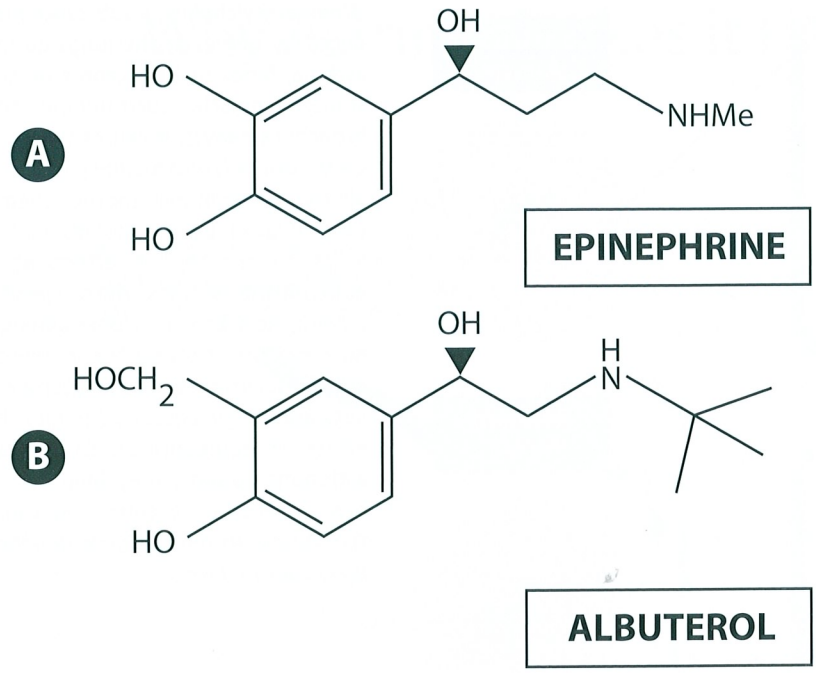


Figure 5, Albuterol and epinephrine: Albuterol (B) has a similar chemical structure to epinephrine (A) and thus mimics epinephrine's effects. In asthma, albuterol binds to the beta adrenergic receptors in the lungs causing relaxation of contracted muscles and relief from constricted airways, also known as bronchiodilation. The chemical differences between albuterol and epinephrine, as seen in this figure, allow albuterol to act specifically in the lungs and have a slightly longer lasting effect. This is an improvement over epinephrine, which affects many organs and is rapidly metabolized by the body. *Figure designed by Corporate Press.*

using high-dose inhalers that made them susceptible to dangerous irregular heartbeats. This was because the compounds in the inhalers did not act on beta adrenergic receptors in just the lungs, but also affected these receptors in the heart. Safer, more selective inhalers, such as albuterol, which only act in the lung, became available in 1980 and offered people with asthma quick relief from asthma attacks (Figure 5). Then in the 1990's, long-acting inhalers such as salmeterol and formoterol, which also mimic epinephrine, hit the market, relieving symptoms for as long as 12 hours. For the first time people with night-time asthma symptoms could finally sleep well.

But these long-acting inhalers, which go by the acronym LABAs (long-acting beta adrenergic agonists), have been dogged by findings that their use may be linked to an increased risk of dying from asthma, suggesting that simply treating the nerve-related aspects of asthma may not be sufficient. In addition, some people with asthma do not get adequate relief of asthma symptoms and/or asthma attacks when they use epinephrine-mimicking inhalers. This led researchers to reexamine the notion that an imbalance in the nervous system was the sole cause of asthma.

Immune Defenses Gone Awry: Allergies, Antibodies, and the "Slow Reacting Substance"

Fortunately, basic research on the immune system offered other possible explanations for what causes asthma and better ways to treat it. This line of basic research got its start in 1902, when French physiologists Charles Richet and Paul Portier tried to induce protection from a jellyfish toxin in dogs by vaccinating them with tiny amounts of the toxin (Figure 6). But much to the researchers' surprise, when they tested their vaccination strategy by again giving the animals the toxins, the dogs suddenly developed breathing difficulties and died within a half-hour.

They called this dramatic reaction *anaphylaxis* (Greek for "against protection") and Richet correctly speculated that the toxin must have prompted the dogs to produce a substance that caused an overreaction to the same toxin the next time it was given to them. (Richet later won a Nobel Prize for his findings, but it took 60 more years of research before scientists identified the mysterious substance causing the overreaction—an antibody called immunoglobulin E.) More pertinent to asthma, Rockefeller University researchers following Richet and Portier's lead discovered, in 1910, that guinea pigs undergoing anaphylaxis had constricted airways and fluid-filled lung tissue strikingly similar to what is

Figure 6, Anaphylaxis: French physiologists Charles Richet and Paul Jones Portier were honored on a stamp issued by Monaco for describing the process of anaphylaxis, an acute hypersensitive reaction to an allergen. They discovered this reaction while trying to develop protections against jellyfish toxins using dogs as experimental models. Subsequent basic research discoveries made the connection between allergic response, such as anaphylaxis, and asthma.

seen in patients during an asthma attack (Figure 7).

The next person to jumpstart the field was the German bacteriologist Carl Prausnitz who was exploring why his colleague, Heinze Kustner, experienced itching, skin swelling, coughing, sneezing and vomiting whenever he ate fish. Prausnitz suspected that some compound lurking in the blood of Kustner caused all these unpleasant allergy symptoms when the compound bumped into fish proteins. To test his theory, Prausnitz, who was not himself allergic to fish, took a blood sample from Kustner and injected it into marked sites on his own arm. Then he injected small amounts of fish extract into the marked sites as well as into other areas of his skin. All the marked sites erupted into red and itchy hives, but the other areas did not react. He published his findings about what he called "reagin," a compound found in the blood that transmitted an allergic reaction.

Prausnitz's findings triggered dozens of researchers to join the hunt to discover the identity of reagin by trying to isolate it from the blood. Because this substance was generated in such tiny amounts and was so similar to other blood components, reagin remained elusive until the late 1960's when more refined chemical separation and identification techniques became available. Also aiding the search was the discovery that certain cancer cells produced large quantities of the allergy-promoting substance, which allowed for more rapid isolation.

In 1967, two groups of independently working scientists, Drs. Kimishige and Teruko Ishizaka of the Children's Asthma Research Institute and Hospital in Denver, and Drs. S. G. O. Johansson and Hans Bennich of the University Hospital in Uppsala in Sweden, simultaneously identified reagin, which was renamed immunoglobulin E or IgE, a type of antibody produced by the immune system.

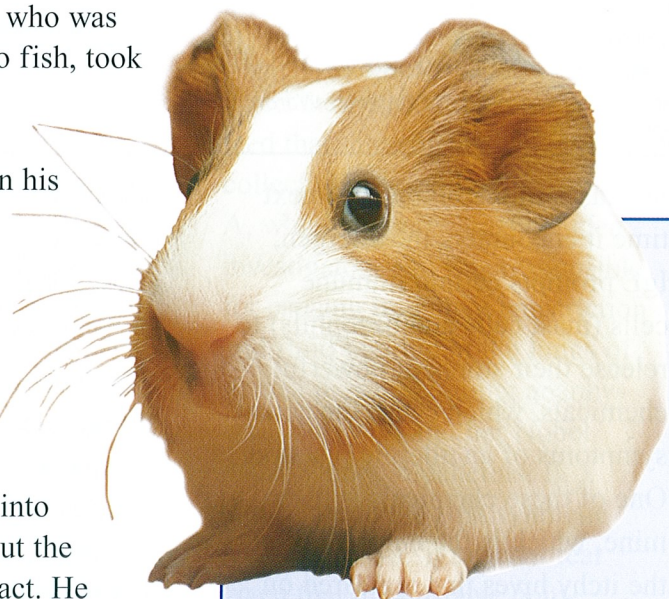


Figure 7, Animal models play a role in asthma research: A number of animal models have played an invaluable part in key discoveries related to asthma. Experiments involving species as diverse as jellyfish, guinea pigs, and dogs have all shed light on the allergic response that is now known to play a role in asthma. *Image courtesy of the National Oceanic and Atmospheric Administration and Getty Images.*

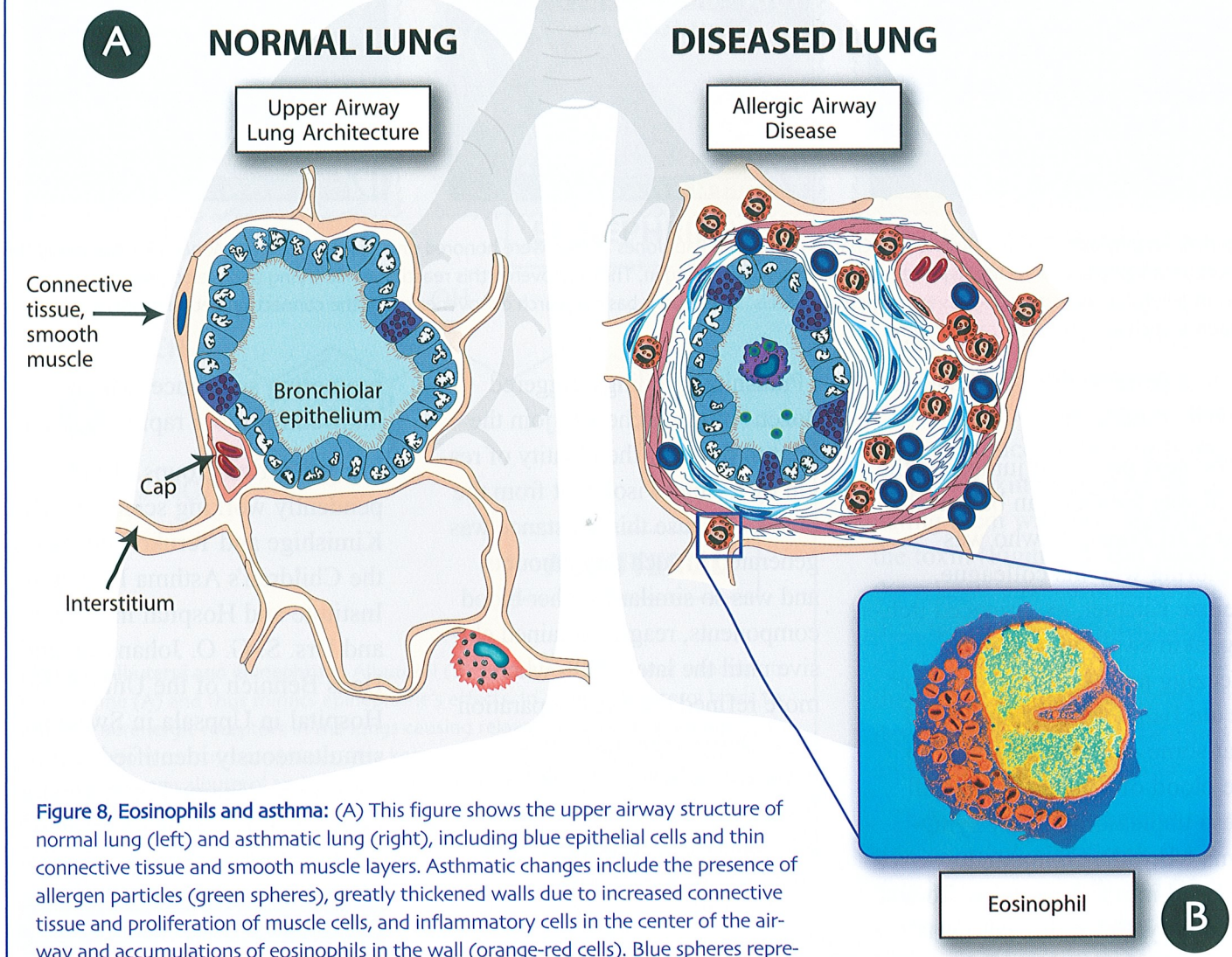


Figure 8, Eosinophils and asthma: (A) This figure shows the upper airway structure of normal lung (left) and asthmatic lung (right), including blue epithelial cells and thin connective tissue and smooth muscle layers. Asthmatic changes include the presence of allergen particles (green spheres), greatly thickened walls due to increased connective tissue and proliferation of muscle cells, and inflammatory cells in the center of the airway and accumulations of eosinophils in the wall (orange-red cells). Blue spheres represent lymphocytes. (B) A colored image from a transmission electron microscope (TEM) shows an eosinophil magnified more than 3000x. *Figure A courtesy of Dr. Peter Ward and Robin Kunkel; Figure B is credited to NIBSC / Science Photo Library.*

Further basic research on IgE revealed that this compound, unlike other previously identified antibodies, does not seem to play a major role in fighting infections, with the exception of certain parasitic invaders. Instead, IgE is an antibody that reacts to seemingly harmless proteins called allergens that the body encounters. When allergic individuals are first exposed to an allergen, the level of IgE, the kingpin of allergic reactions, increases in the blood. The next time it encounters the allergen, IgE prompts certain immune cells (mast cells and basophils) to release their stores of powerful chemicals, which cause the actual symptoms of an allergic reaction. One of these chemicals is histamine, which is the culprit behind the itchy hives that appeared on Prausnitz's arm when he injected it with the serum from his allergic friend. The chemicals released by mast cells and basophils also draw more cellular players into the fray, including a grainy white blood cell known as an eosinophil.

The growing understanding of allergies led to the hypothesis that asthma was a kind of allergic reaction to allergens in the environment. This made sense given that many people with asthma (especially children) also have allergies, and their asthma worsens when they are exposed to what they are allergic. The allergy

hypothesis of asthma was also supported by an intriguing finding—the presence of large numbers of eosinophils in the sputum, blood, and lungs of patients with asthma. These speckled, immune cells come out in force wherever an allergic reaction is underway (Figure 8). This discovery led some scientists to propose that if you stopped the action of eosinophils, maybe you could stop an allergic/asthmatic reaction. There was only one problem—no one knew what these cells did exactly, so it was hard to figure out how to put a monkey wrench in their operations.

The first hints of how eosinophils might be connected to asthma came to light by 1940, when Australian scientists Charles Kellaway and Everton Trethewie detected a substance in the fluid of guinea pig lungs induced to have an anaphylactic allergic reaction. Unlike histamine, whose effects in the body are immediate and only last for a short time, this substance appeared to be slow to act and/or long lasting, causing its effects to persist. Called the "slow reacting substance of anaphylaxis" or SRS-A, this compound was presumably released by eosinophils, but it proved difficult to separate and identify. Pursuit of the substance was essentially put on the back burner until thirty years later when scientists, including Nobel Prize winning chemist Bengt Samuelsson, came upon a set of compounds that seemed to be promising candidates for SRS-A, while painstakingly investigating a trail of seemingly far removed basic research.

Samuelsson was involved in figuring out the body's recipe for making the compounds that foster inflammation, the localized protective reaction of tissue to irritation, injury, or infection that is characterized by pain, redness, and swelling. Because it had already been discovered that aspirin and steroid drugs affected inflammation in different ways, he speculated that the differences indicated a missing ingredient in that recipe. To try to tease out that missing element, Samuelsson incubated white blood cells (called leukocytes) with a compound that the body uses to form inflammation-inducing prostaglandins (a kind of hormone). Doing this caused the leukocytes to produce a unique set of chemicals, which Samuelsson called *leukotrienes* after their cellular origin.

When he and his colleagues analyzed their structures, they realized that three of the leukotrienes collectively comprised the SRS-A, which had previously eluded investigators and was responsible for causing bronchial constriction and fluid buildup in the lungs of guinea pigs undergoing anaphylaxis. In 1977, another Nobel Prize winner, biochemist E. J. Corey, made the first synthetic leukotrienes, a significant feat given that the unstable compounds occur naturally only in vanishingly small amounts. Yet these compounds were shown to be remarkably powerful—a mere billionth of a gram can constrict airways in the lungs, trigger the leaking of fluid from blood vessels leading to fluid buildup in the lungs, and stimulate nerves to release bronchi-constricting acetylcholine, all symptoms associated with asthma. Moreover, leukotrienes are made by such notable white blood cells as the granular (speckled) eosinophil cells that signal allergic reactions. Studies showed that leukotrienes can also act on the muscle cells of the airways. Clearly, another potential target for asthma therapy had been discovered.

Corey gave his recipe for leukotrienes to various drug companies who used it to develop drugs, such as zafirlukast (Accolate®) and montelucast (Singulair®), which prevent the formation or actions of leukotrienes. These drugs first surfaced on the market in the 1990's, and have been shown to significantly relieve asthma symptoms and prevent asthma attacks of many people with mild to moderate asthma. Studies reveal that compared to a dummy pill called a placebo, regular treatment with anti-leukotriene drugs double the number of days patients go without experiencing an asthma attack. Anti-leukotriene drugs are especially effective for patients whose asthma is provoked by exercise or aspirin, or whose asthma is seasonal because of allergies. While leukotrienes are not effective in every patient, as discussed below, they are considered to be an important breakthrough therapy (Figure 9).

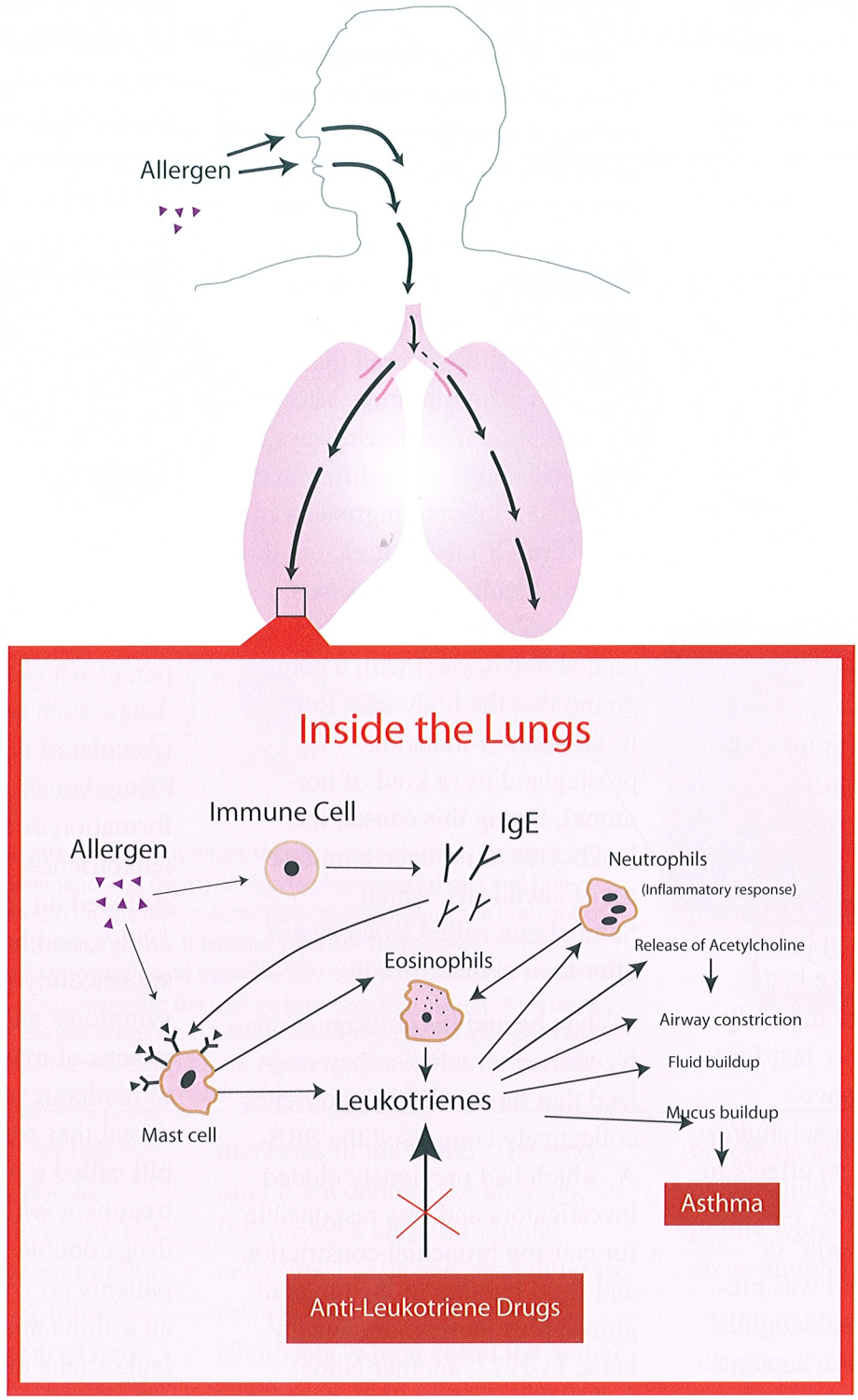


Figure 9, How anti-leukotriene drugs work: Inhalation of an allergen can trigger an asthma attack by setting off a cascade of events leading to airway constriction and mucus and fluid buildup. Allergens are recognized by immune cells which release immunoglobulin E (IgE) which in turn interacts with another kind of immune cell known as a mast cell. When the IgE bound mast cell recognizes the presence of the allergen, it releases chemical signals called leukotrienes, as well as signaling eosinophils, which release more leukotrienes. Leukotrienes trigger a number of responses associated with asthma, including airway constriction (both directly and through release of acetylcholine) and fluid and mucus buildup. A type of white blood cell known as a neutrophil, which plays a role in inflammation, also responds to leukotrienes, as well as signaling for the presence of more eosinophils. Anti-leukotriene drugs prevent the synthesis or inhibit the action of leukotrienes, thus preventing this complicated series of events from leading to asthmatic symptoms. *Figure designed by Corporate Press.*

Around the time that the first anti-leukotrienes entered the market, and after many previously frustrating attempts, scientists finally concocted a drug that latches onto IgE, thereby blocking its actions. In 2003, this drug, called omalizumab (Xolair®), debuted with much hope for allergy and asthma sufferers. But omalizumab proved to be highly effective only in about one-third of people with asthma. That neither anti-IgE nor anti-leukotriene drugs are effective in all people with asthma—yet highly effective in some—suggested that not all asthma can be attributed to an allergic reaction. Although allergy alone does not fully explain why some people have asthma, the allergic response seems to play an important role in helping drive another process that researchers recently discovered underlies many asthmatic symptoms: inflammation. This breakthrough discovery, in which leukotrienes are again a key player, has led to a whole new paradigm in asthma treatment that has proven highly effective for the vast majority of asthma patients.

An Inflammatory Clue

By the 1980's, a century's worth of basic research on the immune system had identified the major cellular players in the inflammation experienced in response to infection, injury, or to an irritant. Research has revealed that the hallmark swelling and redness of inflammation ensuing after bodily insults is due to the influx of white blood cell warriors (leukocytes), which chemically attack or gobble up any offending material, as well as call up more cellular recruits by releasing powerful chemical signals. The cellular hallmarks of inflammation are the leukocytes, eosinophils, and neutrophils—microbe-ingesting cells (phagocytes) that account for the whitish appearance of pus. Leukotrienes act as chemical magnets for eosinophils and neutrophils, drawing them to an injury site or area of the body being invaded by microbes or irritants, studies revealed. Once they are activated by leukotrienes and other mediators, eosinophils and neutrophils orchestrate the inflammatory response. Could inflammation play a role in asthma?

The development of fiberoptic bronchoscopes in the 1970's helped immensely to answer this question. Doctors could easily thread these thin tubes lit by fiber optics down into people's bronchi allowing researchers to sample lung tissue and fluid. Such samplings revealed that the full spectrum of people with asthma—from mild to severe, including those with or without allergies—have significant signs of inflammation in their bronchi, including all the telltale cells of an inflammation response. In addition, the degree of inflammation was closely tied to the severity of their asthma and increased during asthma attacks. Even many asthma patients not experiencing obvious asthma symptoms were found to have signs of inflammation in their airways, suggesting that it was the ever-present underlying inflammation that made their airways overly sensitive to environmental triggers. Thanks to science, another piece of the asthma puzzle had just clicked into place.

Further support for inflammation underlying asthma came from animal studies that revealed that when production of neutrophils, eosinophils and other key players in an inflammatory response was stopped by bone marrow treatments, the animals no longer experienced asthma-like symptoms in response to an environmental trigger that normally would constrict their airways. More revealing still was the finding that asthma patients who continuously took inflammation-suppressing drugs, called corticosteroids, experienced a significant reduction in their asthma symptoms. Discontinuation of the corticosteroids often led to a worsening of airway inflammation and a resurgence of asthma symptoms.

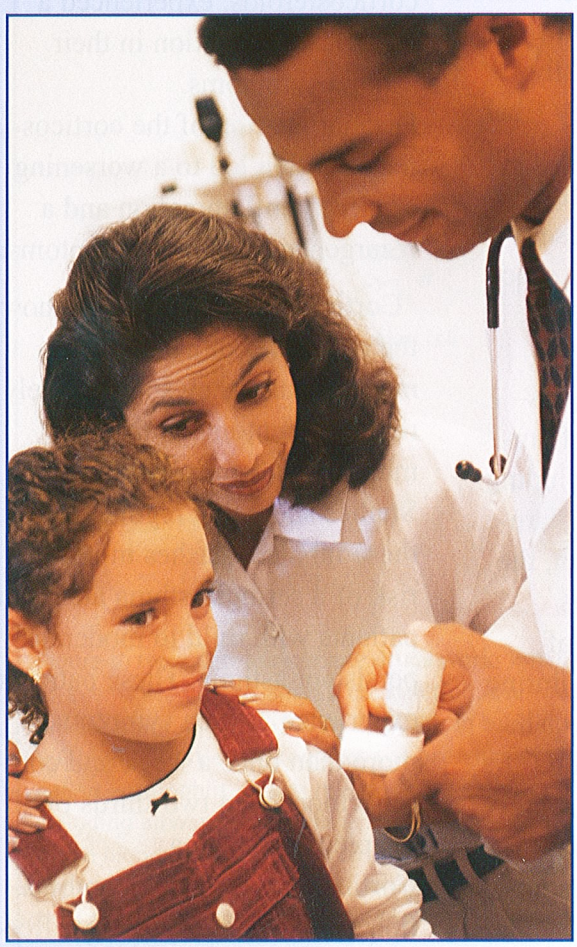
Corticosteroid inhalers are now the mainstays of asthma treatment because they so effectively relieve symptoms in the vast majority of asthma patients. Studies show that regular use of these inhalers slashes in half the risk of a serious asthma attack in patients with mild to moderate persistent asthma. These patients experience asthma symptoms more than once a week and comprise more than two-thirds of all people with asthma. Corticosteroid-LABA combination inhalers are especially effec-

Asthma Made Easier—Samantha's Story

When Risa R. thinks of her daughter's childhood asthma, she is haunted by an image of Samantha's small and scrawny shoulders heaving with every breath—it was so hard for her to breathe that she enlisted her whole body in the effort. Normally a bouncy girl with lots of energy to hoola hoop and chase her sister, when the asthma attacks happened Samantha was transformed into a child desperate for air. At first her breaths would become shallow and accompanied by a high-pitch whistle and coughing. Then the shoulder heaving would start. Particularly frightening were the times when Samantha would become so short of air that her lips would turn blue.

Fortunately for both Samantha and her mother, a number of effective asthma drugs came to the rescue during Samantha's childhood. These drugs stem from several breakthroughs in understanding the many causes of asthma that basic research revealed. Samantha was first diagnosed with asthma at the age of 4, when she wheezed and coughed her way through many a night. Samantha also showed signs of allergies—she often had itchy eyes and nose and congestion. So her doctor gave her an antihistamine to help her congestion and post-nasal drip, and a bronchodilator inhaler that she could take every four hours to help with her wheezing at night. But, like clockwork, Samantha was up as soon as the inhaler wore off and there rarely was a night of uninterrupted sleep.

At about that time, researchers were discovering the important role that inflammation played in asthma. This inflammation and accompanying asthma symptoms was relieved by taking regular treatments of a corticosteroid inhaler, studies showed. So Samantha started taking a corticosteroid inhaler twice a day and quickly showed signs of improving—whole nights would go by without her wheezing and coughing when her inhaler wore off.



But Samantha still continued to have those frightening evening asthma attacks every few months—especially during the spring when the pollen to which she was allergic was prevalent. Taking an antihistamine regularly during the pollen season didn't prevent her asthma attacks, nor did any of her asthma medicines until a new drug came on the market. This drug, called a leukotriene inhibitor, targets the allergic trigger of an asthma attack and is especially effective in asthma patients with allergies. Adding the new drug seemed to do the trick—Samantha's allergy attacks became rare and both she, (and her mother), breathed easier at night.

tive at relieving moderate, persistent asthma. The addition of the corticosteroid to a LABA not only dramatically reduces the number of asthma attacks experienced, but it significantly reduces (although doesn't completely eliminate) the heightened risk of dying from asthma that is linked to using LABAs.

Recognizing that inflammation plays a major role in asthma caused a revolutionary shift in the focus of asthma treatment from treating not just asthma attacks but to treating the chronic inflammation that underlies asthma, thereby preventing such attacks. And for the first time doctors had an asthma drug that worked for their asthma patients whose asthma was not tied to allergies or some other contributing factor.

One Name, Many Diseases: Targeted Asthma Therapy

There are still many unanswered questions about asthma, such as what exactly causes exercise-induced asthma, why some people have more severe cases of asthma, and why children often outgrow the condition. But more than a century's worth of research has led to a much better understanding of asthma's underlying causes and how best to treat it and prevent asthma attacks. We now know that all people with asthma have super-sensitive airways that often reversibly constrict in response to environmental triggers, and that inflammation underlies that hypersensitivity.

But just as many different factors—like diet, smoking, or lack of exercise—can separately or together cause heart disease, there are many factors, including allergy, various respiratory infections, and exposure to pollutants, that can separately or together cause asthma or asthma attacks. As described in this article, basic research has revealed that asthma appears not to be a single disease, but rather a collection of several overlapping syndromes, each with their own unique pathway to the same set of symptoms. Consequently, a treatment that is highly effective for one type of asthma may not work for another. This explains why some treatments, such as anti-IgE drugs, can dramatically prevent asthma attacks in some patients but not in others.

Recognizing this, many physicians are starting to base their treatment decisions on what appears to be driving their patients' asthma (see Sidebar "Asthma: Common Name, Complex Condition"). For example, asthma patients who also have allergies are more likely to respond to anti-IgE or anti-leukotriene drugs. Such a targeted approach will be aided by a major new focus of asthma research, which aims to find genetic or other biomarkers that can indicate which treatments are best suited for individual asthma patients. Some of these biomarkers, such as the presence of heightened numbers of eosinophil cells in sputum, reflect the underlying cause of asthma (allergy). Heightened numbers of neutrophils in the sputum, in contrast, is likely to indicate an asthma that is driven by viral infections or other non-allergy causes.

Two studies have found that when physicians based their asthma treatment on how effectively it lowered levels of eosinophil cells in the sputum of their patients, the treatment resulted in far fewer asthma attacks and asthma symptoms compared to physicians who took a more traditional approach that considered lung function and symptom frequency in their treatment decisions. Other studies are turning up genetic markers for response to specific asthma treatments. One genetic marker, for example, seems to predict response to certain anti-leukotriene drugs, although more work needs to be done to validate these findings. Research on genetic changes

Asthma: Common Name, Complex Condition

Doctors categorize different types of asthma based on what triggers or worsens asthma symptoms:

Allergic asthma: The most common type of asthma, particularly among children. People with this type of asthma test positive for allergy skin testing or blood tests and often have allergic symptoms, such as a sneezy, runny nose, and itchy eyes and nose, as well as a family history of asthma or allergies. Common asthma triggers in people with allergic asthma include pollen, animal dander, house dust mites or mold. Studies suggest people with allergic asthma are more likely to have an excess number of eosinophil cells in their sputum, and are more likely to respond to anti-IgE or anti-leukotriene drugs. Corticosteroids are also helpful in treating people with allergic asthma.

Occupational / Environmental asthma: First surfaces in adults and is triggered by exposure to compounds encountered in the workplace or the environment, and can disappear if patients stop being exposed to the offending chemical. These compounds include irritant chemicals used to make plastics and pharmaceuticals as well as various animal secretions or food components encountered by bakers, farmers, and grain handlers. Environmental pollutants and certain chemicals encountered in the home or office, including cigarette smoke and insecticides, can also trigger or worsen asthma. Some people with occupational/environmental asthma can have an allergic disposition, but a subtype can also develop in people without allergies.

Aspirin-induced asthma: First develops in adulthood in response to aspirin and other non-steroidal anti-inflammatory drugs, along with severe chronic sinusitis. People with aspirin-induced asthma tend not to have allergies and respond poorly to corticosteroids. Many of these patients have heightened levels of leukotrienes in their urine and/or airways and respond well to anti-leukotriene treatments.

Exercise-induced asthma: Thought to be caused by the loss of heat, water, or both from the lung during exercise because of the rapid breathing in of air that is cooler and dryer than that in the lungs, although the exact pathological pathway is unknown. This type of asthma usually occurs during or minutes after vigorous activity, reaches its peak 5 to 10 minutes after stopping the activity, and usually resolves in another 20 to 30 minutes. Asthma attacks can usually be prevented by taking a bronchodilator inhaler prior to exercising. Anti-leukotrienes drugs also tend to be effective in people with exercise-induced asthma.

Menses-related asthma: With this type of asthma, asthma attacks or symptoms are more likely to occur during certain periods in the menstrual cycle and are apparently due to the influence of sex hormones. Some studies suggest there is an increase in inflammation before menstruation in susceptible women. Menses-related asthma probably only occurs in a small proportion of women with asthma, but it can be severe.

"Why does a cold make my asthma worse?" Infectious Influences From Interferons to Interleukins

Recent studies confirm what most asthma sufferers already know—about three-quarters of asthma attacks occur in people experiencing viral respiratory infections, and the severity of the viral infection is closely tied to the severity of the asthma attack. Why do such viral infections prompt wheezing attacks in people with asthma but not in other individuals?

A number of basic research studies done in the lab or in animals suggest several answers to that question. These studies found that respiratory viruses are not just coincidental bystanders, but worsen asthma by calling into play the cells and cellular hormones that promote inflammation, production of mucus, and fluid buildup. Viruses may also directly trigger bronchoconstriction. All these effects might individually or collectively trigger a wheezing attack in people with asthma whose airways are already primed for such an attack

But there is more to this story: the deeper basic researchers dig, the more fine-tuned differences they find between the reactions of people with asthma to viral infections versus those of people without the condition. Thanks to the abundant basic research done on the body's response to viral attacks, we now know many of the weapons in the immune system's arsenal. These weapons include several proteins called interferons, which stem the reproduction of viral invaders, and more than a dozen cellular hormones known as interleukins. These compounds recruit more cellular fighters to an infection site. The body needs to make a precise balance of the various interferons and interleukins in order to wage a winning battle against an invading microbe. But people with asthma seem to launch faulty attacks because they do not follow these precise weaponry specifications. These differences help explain why a person without asthma can have just a three-day cold, whereas a person with asthma infected by the same cold virus can be laid up in bed for more than a week and may have to make a trip to the emergency room because of an asthma attack.

Preliminary findings also suggest that certain infections occurring during infancy or early childhood, when the lungs are developing at a rapid pace, can make children more susceptible to developing asthma. Studies in mice show that respiratory viruses can use a hit-and-run strategy that permanently alters the animal's susceptibility to asthma. Mice infected with a virus similar to those that that cause most serious lower respiratory tract illness in young children developed such signs of asthma as heightened airway contraction to certain inhaled substances, and excess growth of mucus-producing cells in the airways. These features persisted long after the animals rid the virus from their bodies. These findings in animals are paralleled by the finding that severe lower respiratory tract viral infections in infants increase their risk of developing asthma by age 13. It's not exactly clear how viral or other respiratory infections might make infants more susceptible to developing asthma, but basic research findings hint that certain respiratory infections early in life can forever alter the development of lung tissue so that asthma is more likely to develop.

The growing appreciation for the role of infections in asthma is suggesting new treatments to help prevent asthma or asthma attacks. These experimental treatments include those aimed at preventing the common cold, which is caused by a respiratory virus, and interferon therapy to boost immune defenses. Researchers are also exploring treatments that block the excess production of certain interleukins in asthma patients. More research is needed, however, to determine the validity of these new treatments.

linked to asthma is also uncovering novel targets that are the basis of current investigations to find new therapies.

This new, more targeted treatment approach for asthma would never have been possible if it weren't for the work of dozens of curious scientists pursuing the answers to such basic questions as: what causes airways to contract?; what causes allergic reactions?; and how do viral infections affect the lungs? (See "Infectious Influences" side bar.) These researchers collectively revealed the multi-faceted nature of asthma. This breakthrough combined with the discoveries of the roles that airway constriction, leukotrienes, IgE, and inflammation play in asthma, has led to targeted and/or combination therapies that effectively treat the condition in 85 percent of all patients. (See "Asthma Made Easier—Samantha's Story" side bar.) Asthma was originally thought to be a supernatural manifestation of a malevolent deity, but basic researchers revealed that the devil is actually in the details, and by uncovering and tackling those pathological details one by one, you can eventually help asthmatics to breathe easier.

Biographies

Margie Patlak writes about biomedical research and health from the Philadelphia region. She has written for *Discover, Glamour, Physician's Weekly, Consumer Reports on Health, The Washington Post, Los Angeles Times, Dallas Morning News* and numerous other publications. She also writes frequently for the National Institutes of Health and the National Academy of Sciences. This is her sixth article in the *Breakthroughs in Bioscience* series.

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