

HEALTH AND STRESS

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STRESS AND ASTHMA: SOME CURIOUS CONNECTIONS

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The Greek word *asthma* is derived from the verb *àzein*, "to breathe hard" and is related to *àein*, "to blow", which became "air" in English. In Medieval Latin and early English it was *asma*, a pronunciation that is still retained even though the Greek spelling was later adopted in the 16th Century. Asthma has been defined as "a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role, particularly mast cells, eosinophils, T-lymphocytes, neutrophils and epithelial cells.

Extrinsic (also known as allergic) asthma is more common in children and young adults and can be triggered by pollens, animal dander, dust mites and cockroaches. Exposure to these and other environmental allergens stimulates the production of antigen-specific IgE (immunoglobulin E) antibodies that bind to mast cells in the bronchial walls. Excessive numbers of IgE antibodies are produced that react with the specific antigen following each subsequent exposure. This causes mast cells to release histamine, leukotrienes, prostaglandins and chemotactic factors that attract eosinophils, platelets, neutrophils, T-lymphocytes and other inflammatory agents into the airways. These cause swelling and bronchospasm within minutes that can last up to three hours.

The large number of eosinophils and T-lymphocytes that infiltrate the airways subsequently release a variety of various inflammatory chemicals that produce bronchial inflammation and epithelial cell damage. This causes more airway edema, the production of thick mucous and increased airway reactivity. This delayed response occurs about five to eight hours after exposure and can last for days if not treated successfully.

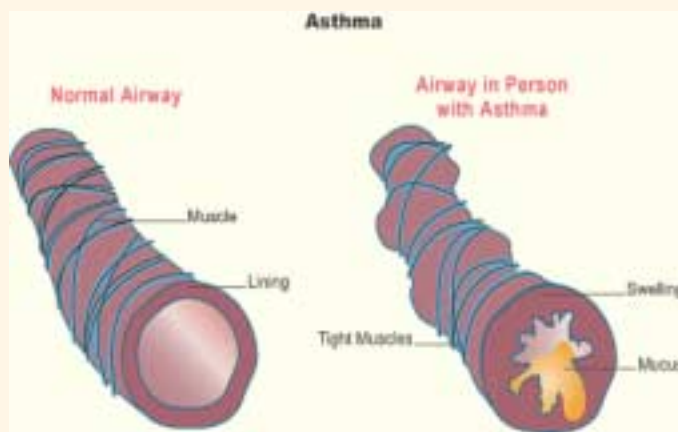
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Intrinsic asthma has no known allergic cause and tends to occur in middle-aged or older patients. Bronchial sensitivity is not IgE mediated and appears to be caused by respiratory infections, stress, exercise, chemical irritants, food additives, aspirin, non-steroidal anti-inflammatory drugs, and gastroesophageal reflux. The mechanisms involved

in this type of airway response are not clearly understood but its intensity may be related to the degree of underlying inflammation that exists at the time. Intrinsic and extrinsic asthma have similar signs and symptoms such as wheezing, cough and chest tightness but intrinsic asthma tends to be less responsive to treatment. **It's important to note that many asthmatics often display characteristics of both intrinsic and extrinsic groups and although treatment for both is usually similar, this may start to change.**

Although some chronic inflammation may be present there can be few symptoms until an asthma attack is precipitated by exposure to allergens, infections, smoke or other atmospheric pollutants. Even exercise can be a trigger in certain patients. The bronchi and bronchioles overreact to these environmental and physiologic stimuli and while such attacks are usually temporary and reversible, scarring and structural changes can result from repeated episodes. This helps to explain why the disease tends to be chronic since the narrowing and obstruction that is produced can significantly limit normal airflow and breathing becomes difficult.



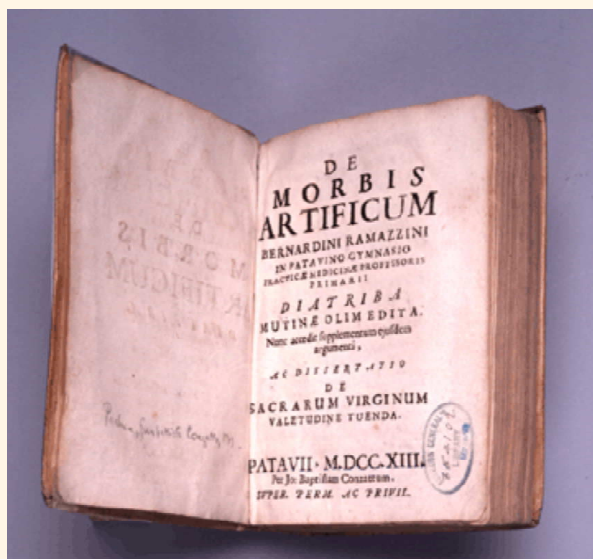
Typical findings in both types include inflammation of the bronchi and swelling of their inner lining along with increased secretion of mucous that plugs the smaller airway tubes causing constriction due to bronchospasm.

Some 30 million Americans have been diagnosed as having had asthma at some time in their lives and more than 20 million Americans are currently being treated for asthma. Women are affected more than men and compared to Caucasians, it is more common in African Americans and Hispanics, with Puerto Ricans having the highest incidence. **Over 6 million youngsters are afflicted, making asthma the most common chronic childhood disease. Despite improvements in diagnosis and treatment the prevalence of asthma, as well as mortality rates, continue to climb, especially in young children and those living in urban areas.** The explanation for this is not clear but may be related to increased exposure to respiratory pathogens, allergens and environmental pollutants.

A Brief History Of Asthma Down Through The Ages

As indicated, ancient Greek physicians used the word *asthma* to describe gasping or breathlessness. Most believed that like all illnesses, breathlessness resulted from internal imbalances that could be corrected by diet, plant and animal remedies, praying to the gods or lifestyle changes. Good health depended on an equilibrium between the four humors: blood, phlegm, black bile, and yellow bile. Most people were visualized as having a mild excess of one of these humors that determined not only their temperament but also their propensity to sickness and the kinds of disorders they might be likely to develop. This humoral theory of illness dominated Western Medicine well into the 1700's and we still characterize people as being sanguine, phlegmatic, bilious or melancholy (Gr. *mélas chole* or black bile). Asthmatics were generally regarded as phlegmatic because of their coughing, sneezing, and congestion although other humors could play a role in certain patients.

Chinese physicians believed that *xiao-chuan*, literally "wheezy breathing," like all disorders, was due to a disruption in the life force they called *Qi* (or *ch'i*) or an imbalance in its complementary components *yin* and *yang*. Health could be restored by utilizing acupuncture, moxibustion, certain herbs, dietary changes, massage and exercise. Traditional Chinese medicine was based on careful observation of the patient, sensitive reading of the pulses, and treatment directed to the whole person rather than focusing on a single system or organ. Moses Maimonides was a celebrated twelfth-century physician, philosopher, and rabbi. He declined an offer to serve as personal physician to King Richard the Lion-Hearted since he had been invited to practice in the court of Saladin, sultan of Egypt and Syria. Maimonides wrote the first treatise on asthma in 1190 and his recommendations included moderation in food, drink, sleep, and sexual activity; avoiding polluted city environments; and soup from a chicken, preferably a fat hen. (He also prescribed chicken soup for leprosy, migraine, constipation and melancholy due to "black bile" and other disorders, which may be why it is still referred to as "Jewish penicillin".)



In *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, farmers, and professors. Ramazzini outlined health hazards of the dusts, fumes, or gases that such workers inhaled. The bakers and horse riders he described would probably be diagnosed today as suffering from allergen-induced asthma. The diseases suffered by most of the other workers would now likely be classified as "pneumoconiosis," a group of dust-related chronic pulmonary diseases.

Doctors were unable to examine the interior of patients' bodies until 1761, when Leopold Auenbrugger, an Austrian physician, discovered a new technique for examining lungs by percussion, tapping a patient's chest to elicit differences in reverberating sounds that could detect the presence of fluid. About sixty years later, an asthmatic French doctor, René Laënnec, designed the first crude stethoscope, a tube made of 24 sheets of tightly rolled up paper. This avoided the embarrassment of having to place the ear directly on a female patient's chest to listen to heart and breath sounds. The sounds were also much clearer and further improvement was obtained when he created an instrument from some cedar he had turned into a tube on his home lathe that had two pieces. One end had a hole to place against the ear, and the other was hollowed out into a larger cone to listen to the lungs. There was a third piece that fit into this cone which had a hollow brass cylinder placed inside it to listen to heart sounds. He referred to this device as "Le Cylindre" and found that it enabled him to more accurately diagnose different chest diseases, including asthma and tuberculosis. The name was changed to "stethoscope," derived from the Greek words for "I see" and "the chest" when he published his famous 1819 treatise on auscultation. A decade later, improvements in microscopes similarly enhanced diagnostic skills by allowing doctors to examine a patient's lung tissue and secretions more accurately.

During the early 1800's, pharmacists and physicians ground their own medicines with mortar and pestle and asthma medications included ingredients like henbane, stramonium, belladonna and lobelia that were dissolved in alcohol, mixed with honey, or combined with other ingredients to make elixirs and pills more palatable.



However, after the Civil War, factories began producing large quantities and varieties of ready-made drugs, and the growing network of trains moved them rapidly all over the country. Drug manufacturers competed vigorously for customers through extensive, sophisticated, and eye-catching advertisements. Many people considered lobelia to be a panacea and a very specific remedy for asthma. In some parts of the country, the plant was referred to as the "asthma weed."

Towards the end of the century, asthma sufferers could buy mass-produced medications without a physician's prescription that replaced the made-to-order remedies for individual patients. They learned about these remedies through advertising campaigns in newspapers, leaflets and mail solicitations. Some of the most attractive and compelling ads were those making outlandish claims that were launched by drug companies competing for customers. Very large quantities of manufactured tablets, powders, and liquid preparations were shipped nationally as well as around the world. While many were advertised as secret formulas, their benefits were usually due to ingredients including alcohol and narcotics like cocaine and morphine that were common constituents.



Curiously enough, many physicians around the turn of the century, including Oliver Wendell Holmes and Sir William Osler, actually viewed asthma as a symptom of health since it was thought to indicate that a patient would recover rather than expire from shortness of breath due to a feverous infection. **Osler termed asthma "all in the mind" and "a slight ailment that promotes longevity".** Pipes and cigarettes were the main or only way to introduce medications directly into the lungs and patients smoked several different medicinal substances to treat their asthma, including nitrate powders, tobacco, cubeb, and plant-derived stramonium. By 1900, experimenters were developing other methods that used air or steam instead of smoke. Epinephrine, the first hormone to be identified, had just been isolated from the adrenals and was subsequently purified and prescribed to asthmatics as adrenaline. This was administered by injection to provide immediate relief and longer acting adrenaline in oil and aqueous suspensions like Sus-phrine® as well as rapid acting inhaled Primatene® Mist were developed. A self administered EpiPen® auto-injector is now available to relieve severe asthma attacks in certain patients.

Tuberculosis was far and away the most common lung disease but as its incidence started to decline, physicians, researchers and public health workers adapted the tools and techniques used for tuberculosis to treat asthma and other lung diseases. In addition, asthma was no longer considered a benign disease, especially after the publication of a 1922 paper

demonstrating 21 deaths due to asthmatic lung disease. Hospitals and institutions formerly devoted to tuberculosis also started to specialize in asthma and promoted their services. Doctors and others also recommended and advertised resorts and health spas that offered ventilation systems, mineral water springs for drinking and bathing and sun porches to give asthmatics the benefits of clean water, air and sunlight as had been done for tuberculosis. Many treatment centers were located in high altitudes with fresh mountain air such as Saranac in the Adirondacks or dry climates like Arizona that had fewer allergens and pollutants, and patients with severe disease often relocated permanently to these areas.

The problem was that, unlike the tubercle bacillus, there was no clear cause. Since varied opinions included allergies, environmental irritants, a primary lung disease and emotional distress, patients sought relief from experts in lung diseases, allergists, general practitioners, and psychiatrists. We now recognize that all these influences can contribute to asthma and current research is focusing on how they interact, together with the role of genetics, the immune system, psychosocial as well as physical environmental factors.

The Role Of Emotions, Personality, Stress And Heredity

The influence of emotions and stress on the frequency and severity of asthmatic attacks has been recognized since antiquity. In his 1190 treatise *On Asthma* written for his royal patient, Prince Al-Afdal, Maimonides noted,

"When in mental anguish, fear, mourning or distress his agitation affects his respiratory organs and he cannot exercise them at will. The weight of the accumulated gas residue within him keeps him from inhaling a sufficient volume of air. The cure of such conditions lies not in food recipes, neither in drugs alone, nor in medical advice. Psychological methods are a greater help."

While Ramazzini's 1713 *Diseases of Workers* focused on environmental influences he also acknowledged that emotional distress could aggravate complaints of wheezing and difficulty breathing. In an 1886 *American Journal of Science* article entitled *The production of so-called "rose cold"*, J.N. Mackenzile described **an asthmatic patient so sensitive to rose pollen that she consistently had symptoms whenever she saw a rose encased in glass.** Many other physicians in the late 19th and early 20th century viewed asthma as a nervous disorder because autopsies failed to show impressive or consistent abnormalities in the lungs. In addition, as the British physician J. B. Berkart pointed out in his 1914 *The Pathology and Treatment of the So-called Nervous Asthma*, sedatives, cocaine and morphine were often effective. Interest in the role of emotions accelerated with the growth of psychiatry and especially the advent and spread of psychosomatic medicine. The establishment of the journal *Psychosomatic Medicine* in 1939 provided a powerful impetus and platform for researchers and clinicians to share their findings and opinions. Following the 1950 publication of Hans Selye's *Stress*, the number of *Psychosomatic Medicine* articles on asthma almost tripled. As more effective asthmatic medications became available, it was also evident that perhaps 80 or 90% of patients did not need constant treatment because they learned that mild episodes of wheezing and tightness tended to be transient or quickly responded to a bronchodilator. This significantly reduced their stress because they now had a much greater sense of control. It also became obvious that relocating to places like Arizona often failed to provide benefits because asthma can have so many different triggers. Most patients who improved likely did so because they had been removed from their source of stress and similarly developed a greater sense of control over their illness as attacks diminished.

Unlike disorders ranging from hypertension to accident proneness, no distinct "asthmatic personality" was identified although separation from a parent or other "mother figure" emerged as an important antecedent. This was particularly apparent in children where some

asthmatic attacks seemed to have the significance of a suppressed cry. Franz Alexander, a psychosomatic pioneer, noted that attacks were often precipitated by a peculiar habit of sustained breath holding that, similar to a hunger strike, seemed to signify a protest against something. Prolonged breath holding could prompt an attack by putting extra pressure on the lungs and he also found this to be a frequent trait when he asked older patients about their childhood habits. The extra pressure put on the lungs by laughing, hyperventilating, strenuous physical activity or crying, all of which may be associated with stress, can also precipitate asthma. Children may consciously or unconsciously use crying to induce an attack when upset because it generates sympathy, concern and frequently allows them to receive special treatment. **Some specialists suspect that over-protective parents are one of the greatest dangers to the healthy development of asthmatic or other chronically ill children because they unwittingly encourage this type of behavior.**

Researchers, who tried to demonstrate that stress could precipitate or aggravate an asthmatic attack, and delineate the mechanisms involved, often came up with different results and conflicting conclusions. In one report, asthmatic students had greater airway inflammation and decreased lung function to an allergen inhalation challenge during final examination week compared with an identical challenge during a relatively stress-free period. Others found that pulmonary function tests paradoxically tended to show less airway obstruction in response to allergens during stressful sessions compared to non-stress control visits. This was quite consistent with the "flight or fight" response to acute stress that produces bronchodilation due to sympathetic nervous system stimulation rather than the bronchoconstriction seen in asthma. One explanation for this unexpected finding was the methodology used, which was based on the supposition that the pulmonary response to an allergen in sensitive patients would be potentiated by a stressful interview. However, this stressor was limited to a specific type of acute emotional arousal and all the patients had allergic asthma. Subsequent studies showed that these individuals were not as reactive to other chronic stressors compared to those with intrinsic asthma. Nevertheless, there was little doubt that stress could precipitate or aggravate an asthmatic attack, especially in children, since this had long been recognized based on anecdotal patient reports and clinical observations by skilled physicians. Researchers later found that increased reactivity was also largely determined by prior exposure to chronic stress. One study showed that severe negative life change events significantly increased the risk of children's asthma attacks over subsequent weeks. This was further magnified when there was a history of multiple chronic stressors such as disruptive family relationships or separation from a parent. A very recent report revealed that a stressful home life diminishes the expression of certain proteins on the surface of cells that regulate airway responses and inflammation. Asthmatic children and healthy controls were followed for six months during which levels of corticosteroid and beta-2-adrenergic receptors were measured. Younger asthmatics with abusive family relationships, or an unstable home environment, expressed less of these than those not exposed to such chronic stress. In those who had experienced a major life event in the previous 3 months in addition to chronic stress, glucocorticoid receptor decreased 5.5-fold and beta-2-adrenergic receptor decreased 9.5-fold. Such significant reductions could readily cause more inflammation and bronchospasm after exposure to allergens as well as diminish sensitivity to various asthma medications.

Superimposed on all of this is the powerful role of genetic influences. Children with one asthmatic parent have a 20% likelihood of developing asthma and this jumps to almost 50% if both parents are affected. Three genes were initially identified that had separate effects, such as control over the tendency of airways to become narrowed, susceptibility to allergens and, most importantly, the sensitivity and nature of autonomic responses to stress. Risk factors for asthma include childhood stress, high IgE levels, viral infections in kids that cause wheezing, exposure to highly allergenic substances like dust mites, animal dander, mold and cockroaches in sensitive individuals, and especially genetic risk based on how many close relatives had asthma. **If there is no genetic tendency all these other risk factors may**

have very little or no effect. The significance of this is supported by a study showing that identical twins, who share all their genetic make-up, had much more similar rates and patterns of asthma than non-identical twins who share only half. Specific genes accounted for almost 70% of asthma prevalence and influences like allergens and other environmental triggers that made up the remaining 30% can also be determined by genes. Asthma can start at any age and while older people often recall having had an earlier episode, an inherited tendency may not kick in until age 65 or later. To complicate things further, other genes have now been discovered that can predict how well patients will respond to certain medications as well as the likelihood of adverse side effects.

There are dozens of drugs that are used depending on whether asthma is

1. Mild and intermittent – patients have no symptoms between attacks. Symptoms are mild and occur less than once a week, with nighttime symptoms occurring less than twice a month.
2. Mild but persistent - patients have symptoms more than once a week but less than once a day, and nighttime symptoms occur more than twice a month.
3. Moderate and persistent - patients have daily symptoms with intermittent exacerbations that can last for several days at a time. Nighttime symptoms occur more than once per week and there may be interference with daily activities and frequent absences from school or work.
4. Severe and persistent asthma - patients have continuous daytime and frequent nighttime symptoms. Daily activities tend to be significantly limited and there are frequent emergency room visits that often lead to hospitalization

Popular asthma medications fall under the following general categories:

- Beta-agonists (Proventil, Volmax, Ventolin, Xopenex, Alupent, Maxair, Brethine) are used to provide rapid relief from symptoms due to bronchoconstriction by relaxing airway musculature. These inhaled drugs, often referred to as "rescue medications", are most effective when used on an as-needed basis and have fewer side effects than oral forms. Long-acting beta-agonists (Serevent and Foradil) provide long-acting relief (up to 12 hours) and are especially effective for nighttime symptoms. However, when used alone they can increase bronchial sensitivity and therefore should always be used in conjunction with an inhaled corticosteroid. These so-called "long-term controllers" should not be used for quick symptom relief.
- Anticholinergic agents like Atrovent, which blocks specific nerve impulses that trigger airway muscle contraction and reduce mucus hypersecretion are also used as bronchodilators and are especially effective when combined with a short-acting beta-agonist.
- Theophylline (Slo-bid, Theo-Dur, Uniphyll) is an oral bronchodilator mainly reserved for patients with severe, persistent asthma that has not responded well to beta-agonists. It promotes bronchial smooth muscle relaxation, decreases mucous formation but requires careful monitoring because it is a central respiratory stimulant and can have significant and sometimes serious side effects.
- Inhaled corticosteroids (Beclovent, Vanceril, Qvar, Pulmicort Respules, Aerobid, Flovent, Flonase, Azmacort) are the cornerstone of treatment for all asthma cases above the "mild and intermittent" severity level. They are particularly effective in reducing the primary problem of bronchial inflammation by preventing the activation and migration of inflammatory cells into the airways. When taken regularly, they can significantly reduce the frequency and severity of attacks and also improve pulmonary function. Because they are delivered directly to the airways with minimal systemic absorption, they have far fewer adverse side effects than long-term use of oral or injectable corticosteroids. There are also combination therapies such as Advair (which combines a long-acting

bronchodilator, Serevent with an inhaled corticosteroid like Flonase) that can be more effective than either alone in controlling asthma symptoms.

- Systemic corticosteroids are used most often for very short periods of five to seven days to treat asthma exacerbations when bronchodilators have failed. They are usually given in a large dose the first day and tapered down over the next five to seven days depending on the response. Chronic, long-term use is not advisable because of the potential for serious side effects. When prolonged use is necessary because other medications are not effective, close monitoring is required. Generic prednisone is frequently used because it is much less expensive than numerous brand name products like Prelone, Pediapred and Medrol.
- Mast cell stabilizers (Intal, Nasalcrom) are anti-inflammatory drugs that act by blocking the release of histamine and leukotrienes from mast cells in the airways. They are often effective in patients with mild but persistent asthma, especially young children, and have few side effects.
- Leukotriene modifiers (Singulair, Accolate, Zflo) are the newest class of anti-inflammatory asthma drugs. Leukotrienes are chemicals produced by inflammatory cells within the airways that cause airway walls to contract and increase the leakage of fluid from blood vessels into the lungs. Leukotriene modifiers work by blocking these effects or inhibiting leukotriene formation. They are used for long-term management and may be most effective when used in conjunction with corticosteroids.
- Anti-IgE monoclonal antibody (Xolair) is another new medication approved for patients 12 or older with a clear allergic component who are not well controlled with inhaled corticosteroids. It inhibits the allergic reaction that causes airway constriction in an entirely new way that reduces and sometimes eliminates the need for corticosteroids.
- Intravenous immunoglobulin (IVIG) has also been shown to benefit asthmatics resistant to corticosteroids and is particularly effective in patients with poor immune system function. It contains antibodies obtained from pooled plasma specimens that can lower blood levels of IgE and also increase resistance to respiratory infections.

All of these medications have side effects, some of which are serious and have only surfaced after their widespread use. In 2003, the FDA added a Black Box warning for Serevent and Advair products because of a report showing they were associated with an increased number of deaths. An additional Public Health Advisory was issued in 2005 emphasizing this and warning that, although these and other long-acting beta-agonists like Foradil could decrease the frequency of asthma attacks, they might also make them much more severe and should never be the first medication tried. On August 11, 2006, the FDA warned three firms to stop manufacturing and distributing thousands of doses of compounded unapproved inhalation drugs. Compounding is usually done when pharmacies prepare medications that are not available for patients because they are allergic to some ingredient in an approved product. This type of compounding follows a physician's prescription indicating that the patient has a special medical need that cannot be met by approved drugs. The FDA does not object to or monitor such occasional practices. However, in this instance, inhalation drugs were distributed to patients throughout the country and neither patients nor their doctors were aware they had been taking compounded rather than FDA approved products. As the warning letter stated, "Compounded inhalation drugs are not reviewed by the FDA for safety and effectiveness, often are not produced according to good drug manufacturing practice, and typically are not sterile. This may expose patients to unnecessary risk". Asthma death rates have steadily increased over the past fifteen years in sharp contrast to the previous decade when they had been declining. Authorities are correctly concerned since this subsequent increase in asthma mortality rates occurred during the period when most of these drugs started to become widely available.

Pharmacogenomics, the study of the relationship between genes and patterns of genetic variability and differences in the response to drugs has the potential to reverse this disturbing trend. **In the not too distant future, physicians will be able to order a pharmacogenic profile and find out within a few days whether specific medications alone or in combination are apt to be effective and relatively free of side effects for any asthmatic patient.** One study currently underway is comparing information from 2,000 managed care asthmatics to determine the effect of common genetic variation patterns with pharmaceutical claims of efficacy and side effects based on detailed data obtained from careful clinical records.

Genes and genotypes have already been identified that can predict responsiveness to as well as side effects from corticosteroids, leukotriene modifiers, rapid acting beta-agonists like Ventolin and Proventil, sensitivity to aspirin, other analgesics and beta blockers. Asthma patients with increased amounts of the macrophage migration inhibitory factor gene (MIF) are more likely to have severe disease. Links have also been found to phenotypes such as abdominal obesity. Obese people are more prone to develop asthma but a recent study also showed they have better results with Singulair, a leukotriene modifier than an inhaled corticosteroid like Beclovent and that it is just the opposite in lean individuals. Abdominal fat is especially associated with the release of inflammatory chemicals like eotaxin, which causes bronchial constriction. A recent study found that obese patients' eotaxin levels were significantly reduced with weight loss and may help explain why losing weight can also reduce asthmatic attacks.

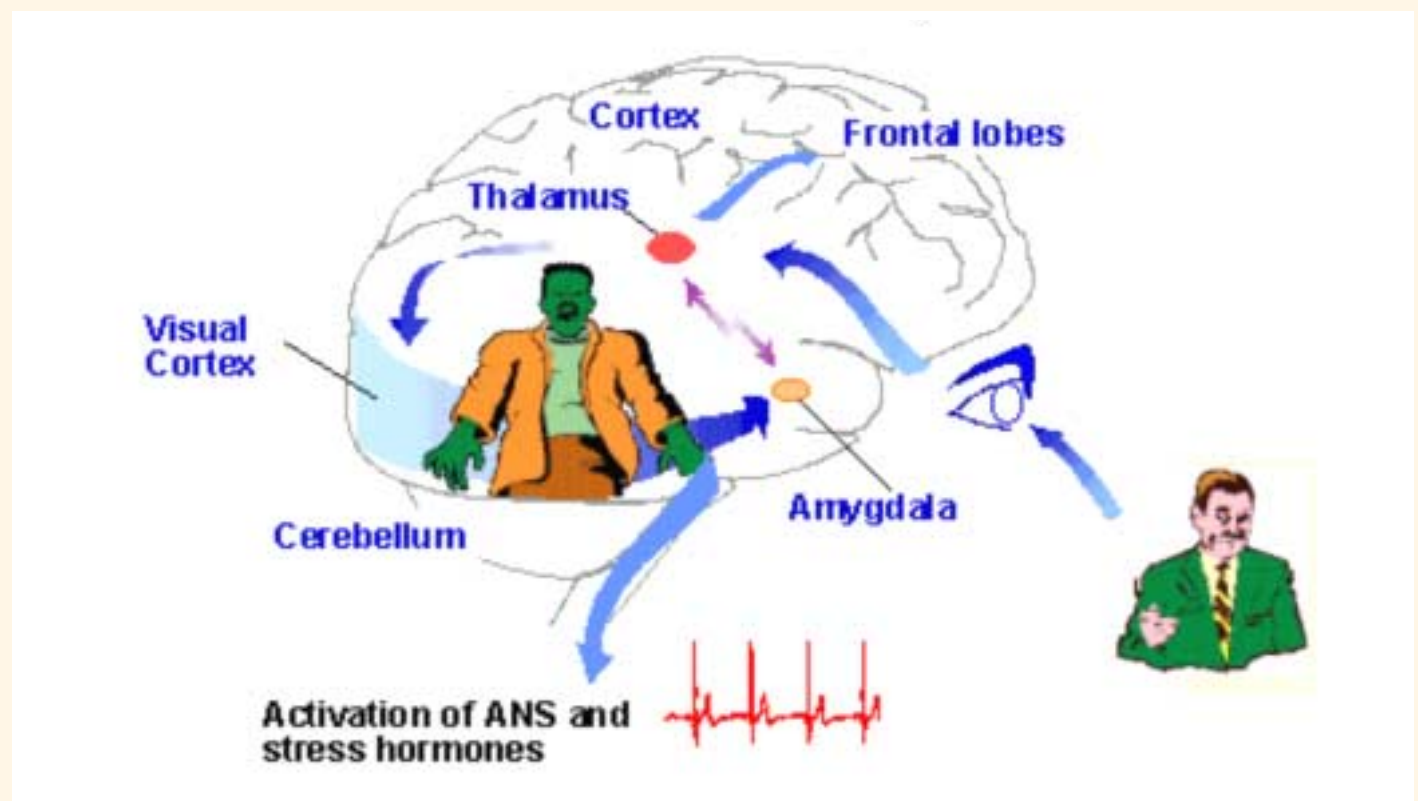
Asthma tends to be more common and possibly more severe in women, suggesting that there are hormonal influences. A very large survey showed that postmenopausal women on estrogen replacement therapy had more than double the risk of asthma compared to those who never took hormones. Women with asthma who are carrying a female fetus are also more likely to experience worse asthma symptoms than those with a male fetus. Another report suggests that asthma can be a risk factor for obesity in girls. Levels of leptin, a hormone produced by fat tissue, are higher in girls than boys and increased leptin has been found to be associated with asthma, particularly in children. Whether endocrine interventions might provide benefits remains to be seen.

Prevention, Stress Reduction, Breathing And Heart Rate Variability

The first consideration in treating asthma should be to prevent it by removing, avoiding or managing known risk factors like pollens, animal dander, dust mites, cockroaches smoke and other environmental pollutants, gastroesophageal reflux and obesity. In some sensitive patients, exercise, aspirin, and non-steroidal anti-inflammatory drugs like Motrin and Aleve should be avoided. While Tylenol is often recommended as a substitute that is less likely to cause stomach irritation and bleeding, a recent study showed that **people who took Tylenol or other acetaminophen products daily were over twice as likely to have asthma** and frequent use was also associated with more severe asthma. These drugs decrease the antioxidant glutathione, high levels of which are found in the lining of the airways and the nose that protect the lungs from the damaging effects of pollutants and free radicals. Other little known risk factors include working in a supermarket bakery or an automobile paint shop. In one study, 9% of bakers, 4% of bakery managers and 3% of bakery assistants had asthma due to sensitivity to flour and various common bakery additives. Automobile paint workers are exposed to chemicals in paints and solvents that may cause or aggravate asthma, particularly isocyanates. These highly reactive chemicals found in paints are known to trigger asthma and respiratory symptoms that can affect up to 10% of workers who are exposed to them. Urban air pollution is hard to avoid but even being near traffic can cause problems. One study found that children who lived within 80-85 yards of a major road were almost 50% more likely to have asthma compared to controls living 330 or more yards away.

The harmful effects of cigarette smoke cannot be overemphasized. A child whose grandmother smoked while pregnant may have double the risk of developing childhood asthma, according to a recent report. Children with mothers who smoked during pregnancy were 1.5 times more likely to develop asthma early in life, and those children with grandmothers who smoked were 2.1 times more likely. **Even if a child's mother did not smoke but the grandmother did, the risk for asthma was 1.8 times greater and if both smoked while pregnant, risk was 2.6 times greater.** Researchers suspect that tobacco affects the fetus's DNA and damages the immune system, resulting in increased susceptibility to asthma that is passed down but may skip a generation.

All of the above demonstrate the important role of genetic factors in asthma that are beginning to be uncovered. Unfortunately, there's not very much we can do about what we inherit. However, that's not true for stress, which can come in all shapes and sizes and have myriad effects. These include causing people to smoke, deep abdominal fat deposits that promote inflammation, increased reactivity to asthma triggers, and a host of complex cortical as well as involuntary influences that regulate crucial autonomic nervous system as well as immune and endocrine responses.



The above diagram adapted from the Institute of HeartMath shows some of the brain structures that modulate stress responses. We learn how to ride a bike or ski by repetition, which creates neural circuits to retain muscle memory for these and other physical activities. Similarly, exposures to stressful stimuli are stored in neural pathways concentrated in the amygdala and related structures as part of our emotional memory. These influence how we perceive subsequent stimuli that immediately generate various thoughts and feelings that elicit autonomic nervous system and neuroendocrine responses. The amygdala plays a key role in coordinating these activities by instantaneously assessing the potential threat from incoming sensory information and relaying instructions to the hypothalamus and autonomic nervous system before higher cortical centers receive this information. In the illustration

above, an individual who sees a person that reminds them of someone they had a bad experience with can result in faulty responses based on past situations rather than any present danger. The frontal cortex subsequently determines whether these responses are appropriate and other areas of the brain not depicted also play a role. In one experiment, patients with mild allergic disease were shown and heard asthma related words like "wheeze", emotional but non-asthma related words such as "loneliness" and "curtains", a neutral word. At the same time, they inhaled ragweed, dust-mite extract and other known asthma triggers and their brain responses were monitored with functional magnetic resonance imaging. Only the anterior cingulate cortex and insula regions showed increased activity when the asthma-related words were heard and these correlated with the severity of reactions to inhaled allergens. As one of the authors noted, "Our research shows that **69% of people with asthma say stress triggers their symptoms**, and this study shows an actual link between the parts of the brain processing emotion and physiological asthma symptoms."

There are numerous stress reduction techniques but meditation can be particularly effective in asthma. While meditation promotes a sense of relaxation that reduces many stress related symptoms, asthma benefits appear to be based on its effects on breathing. Traditional Oriental meditative techniques as well as Indian Ayurvedic practices have demonstrated the stress reduction benefits of slow and relaxed breathing for millennia. Many asthmatics have also learned that deep abdominal breathing with a prolonged period of expiration reduces attacks as well as medication requirements. This type of retention respiration is accomplished by slowly inhaling to a count of three, holding for three, and exhaling for six and doing this 9 or less times a minute instead of the usual 15-19 at rest. We now know that these benefits are due to improvements in heart rate variability (HRV) the most sensitive and accurate way to measure stress. As explained in a prior Newsletter, HRV really refers to the imperceptible variation in intervals between consecutive heartbeats during respiration rather than actual changes in heart rate that can easily be measured. It has only been possible to measure HRV accurately and rapidly by advances in computer analysis developed over the last two decades that evaluate data from hours or a day of constant ECG monitoring.

These have now confirmed that HRV is diminished in asthma and the effects of emotions have been vividly demonstrated in studies showing that public speaking, solving mathematical problems or making complex decisions under time pressures and other stressful tasks lower HRV. Even thinking about something very stressful diminishes HRV whereas engendering feelings of deep appreciation and love have an opposite effect. Low HRV has been demonstrated in patients with infections, especially those associated with impaired immune system function that is often due to stress and others who are depressed, hostile as well as anxious, particularly in those suffering from panic or posttraumatic stress disorder and certain phobias. Low HRV is seen in obesity and insulin resistance, coronary heart disease and hypertension and other components of metabolic syndrome that can be stress related. Several prospective studies have shown that low HRV independently predicts mortality within the next two years following a heart attack, especially from lethal arrhythmias that are often stress induced. HRV also seems to be a marker for the cumulative wear and tear stress that occurs with aging. Although resting heart rate does not change significantly with advancing years there is a progressive decline in HRV. Conversely, regular physical activity, which can slow down the aging process as well as reduce stress, raises HRV. In recent years, further refinements have led to at least two dozen different arithmetic manipulations to measure specific HRV characteristics in consecutive cardiac cycles. In addition to various time measurements, spectral analysis has revealed three major power components that have high, low, and very low frequency oscillations that are associated with different sympathetic and parasympathetic relationships. It is not inconceivable that some day an even more sophisticated analysis will permit diagnosing one of these disorders or the likelihood that it will occur.

More importantly, a 2004 landmark HRV biofeedback study demonstrated that asthmatic patients could learn to increase their heart rate variability resulting in a significant reduction in asthma symptoms and the need for medications and improvement in pulmonary function that were not entirely explained by changes in breathing patterns. Since then, relatively inexpensive hand held devices like emWave - www.emwave.com - and StressStopper - www.stressstopper.com - promise to provide similar results using real time HRV biofeedback. RespeRate - www.resperate.com - is the only biofeedback device approved by the FDA as an aid in treating hypertension and is approved in other countries for relaxation to relieve stress related symptoms. It uses a chest sensor along with timed music to teach patients to lower respiration to a relaxed 10 or fewer breaths per minute that has also benefited asthmatics.

Breakthroughs in diagnosis also promise to improve asthma therapy. Bronchospasm is responsible for most asthma symptoms but its location is not always clear, can vary in different patients, and the site of narrowing could determine which medications might be most effective. Models can predict where closure and constriction are most likely to occur but airways have never been visualized during an asthma attack. This problem may now be solved with a new MRI technique using hyperpolarized helium. One inhalation illuminates airways down to even the tiny seventh-generation breathing tubes. Symptoms can be correlated with data obtained from imaging procedures that may provide useful information about where different drugs work best. Since most existing MRI machines can be easily adapted to helium imaging, this non-invasive and safe procedure should soon be available for many patients. Stay tuned for other developments in asthma diagnosis and therapy and especially progress in heart rate variability discoveries.

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