THE STANDARD

Volume 1, No.2 May/June 1998

A CONCISE UPDATE OF IMPORTANT ISSUES CONCERNING NATURAL HEALTH INGREDIENTS

ALLERGIES: THE NATURAL APPROACH

Goldenrod - Solidago canadensis

"A sight that brings sore eyes to allergy sufferers"

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Perhaps one of the most common, recurrent ailments suffered by Americans is allergies. The symptoms of allergic rhinitis (red, itchy eyes and nose, sneezing, sinus headache and congestion) can be both seasonal, in the case of "hay fever" or perennial. Regardless of the particular allergen, the discomfort is experienced by nearly 20% of Americans (1). While rarely life-threatening, allergic rhinitis leads to periods of general misery, sleep loss, and lack of productivity in industry as well as education. We will look here at some of the common causes, treatments, and natural ingredients that help alleviate the many symptoms associated with allergic rhinitis.

What triggers an allergic response?

An allergic reaction can be best thought of as a cascading set of inflammatory reactions, started by the immune system, in response to environmental antigens which are usually considered harmless. In essence, an allergic response is an overcompensation of the immune system against relatively harmless airborne substances. Once an allergen is inhaled it is processed by the immune cells and stimulates a B-cell mediated IgE response. IgE is one of 5 types of immunoglobulin (antibody) produced by B-cells; IgA, IgD, IgM, and IgG are the others. Each type of antibody can bind to antigens or allergens, but differ in the type of responses they produce once they are bound to antigen. The typical allergic response is mediated by IgE antibodies when they bind the allergen with one end, and the IgE receptor of the mast cells or basophils with the other end. This cross-linking on the surface of the mast cell triggers a multi-step process leading to degranulation of the mast cell and release of histamine and other inflammatory mediators. Once the cascade starts, a whole host of secondary responses are triggered.

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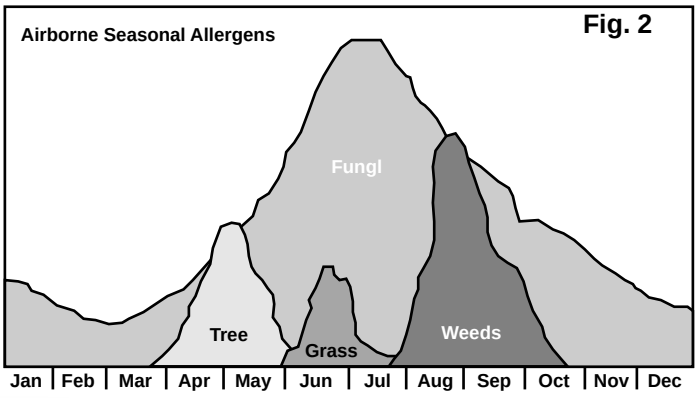
Two phases of responses are triggered by an IgE/allergen cross-linking event. The first is the release of preformed mediators such as histamine, interleukins, serotonin and Hageman factor from mast cells and basophils. These chemical mediators are found in preformed vesicles, released by a calcium dependent process induced by the cross-linking of two or more IgE receptors. This calcium dependent process may be the most important trigger, as well as a major key in preventing the cascading allergic response. Once these chemicals are released, they are responsible for allergic (inflammatory) processes like vasodilatation, increased vascular permeability, and increased chemotaxis of other inflammatory cells.

The second phase of the response begins at the same time, as the cell begins to synthesize lipid-derived mediators. These mediators are derived by the conversion of phospholipids into arachadonic acid via phospholipase A; followed by the subsequent conversion of arachodonic acid into leukotrienes, platelet activating factor (PAF) and prostaglandins (2,5). This is the identical process involved in a majority of acute and chronic inflammatory processes. Most of the symptoms associated with allergic rhinitis are a direct result of both the preformed and lipid derived mediators on the lining of the upper respiratory tract, and not a property of the allergen itself. Why some people react to some allergens and other people do not has a lot to do with genetics, geography and exposure levels.



The Allergens: Allergens can be classified as perennial or seasonal. Perennial allergens would include those things such as internal mold spores, dust and dust mites, animal dander, and specific chemicals (cleaning agents, certain powders). If a patient has allergic rhinitis symptoms lasting more than 2 hours per day for more than 9 months, this would be classified as a perennial allergic rhinitis. The allergen is most likely something in their home or workplace.

Seasonal allergies follow a predictable pattern based on the growing season. Figure 2 shows the typical pattern in the Midwestern United States. The first allergen of the season begins when trees begin to release pollen. Trees with little or no visible flowers have a higher pollen count since they rely on the wind rather than insects for pollination. The summer months are typically the time for grass pollen allergies. These can come from commercial crops such as corn pollen, and are often less of a problem in urban areas where grass pollinates less frequently (if mowed often enough). The fall is the most intense allergy season in the central U.S. due to the large amount of weed pollen that becomes airborne. Ragweed and goldenrod are among the most common offenders. Interestingly, the common term “hayfever” is actually a misnomer since neither hay (alfalfa) nor fevers are typically associated with allergies. Finally, there is the issue of fungal spores. As one can notice from figure 2, fungal spores are high at all times except during times of snow cover (typically late Nov through Feb). Fungal spores can be kicked up any time a person is walking through grass or leaves, cutting or stacking wood, or just being in a damp outside location. Fungal spores are so ubiquitous and long lasting it may be difficult to determine what the offending source is. In these cases, skin testing would be warranted to determine that indeed the patient is suffering from an allergen and is not experiencing infectious sinusitis.

TREATMENT OPTIONS:

Seasonal allergies are one of the most self-diagnosed and self-treated conditions. Many people know what will trigger an allergic response and how and when to avoid exposure. Over the counter antihistamines and decongestants are advertised and purchased widely during the common allergy seasons. Here are some of the typical treatment options:

Avoidance: The most obvious and beneficial thing that a person can do is to avoid the allergen all together. Spending time in air-conditioned areas, especially cars, will filter out many of the offending allergens. It is now possible to purchase a relatively cheap air-purifier that will recycle the air as it filters it, without changing the temperature of the air. Keeping the humidity low in their homes is another way a patient can reduce some of the common offenders such as mold and dust mites.

Drugs: Antihistamines are usually the first drugs that most people try when seasonal allergies come around. One of the most popular (and typical) is diphenhydramine (Benadryl), which works by blocking histamine H1 receptors. By blocking the histamine receptors, antihistamines are excellent at reducing sneezing, itchy eyes and nose, and slowing the pace of a runny nose. Antihistamines have little effect on congestion or associated asthmatic conditions. Of course, one of the major side effects of antihistamines is drowsiness. In fact, it is because of this side effect that many of the antihistamines are used as sedatives and hypnotics. Newer antihistamines, which do not cross the blood-brain barrier, have little to no sedating side effects. Claritin, Seldane, and Hismanal have similar antihistaminic effects as Benadryl with fewer side effects, but at a much greater cost. Seldane has just been pulled from the market by the FDA for its complications with the heart. While Hismanal has some of the same problems as Seldane, the major warning of all of these newer drugs is a contraindication with the concomitant use of erythromycin (a common antibiotic) and ketoconazol (a common antifungal).

While antihistamines block many of the effects of histamine, they are unable to stop the mast cell from releasing histamine or any of the other preformed or lipid-derived mediators. This means that some of the secondary problems associated with allergies are unaffected or masked by antihistamines. Such problems as nasal congestion and asthma must be addressed by other means.

Bronchodilators and decongestants are also available by prescription or over-the-counter. The most common would be ephedrine or pseudoephedrine (Sudafed) containing products. They work primarily as a-adrenergic agonists. They reverse congestion by vasoconstricting the nasal mucosal blood vessels, reducing swollen membranes, which allows sinus drainage and improved air conduction. Since both ephedrine and pseudoephedrine also effect the ß-adrenergic receptor, they are capable of acting as bronchodilators. Care should be taken when patients with heart conditions, high blood pressure, or on MAO inhibitors take these drugs.

Another option is steroid drugs. Topical preparations of glucocorticosteroids are supplied by nasal sprays. The mechanism is probably very similar to the anti-inflammatory effects of corticosteroids. They are mainly indicated in long-term allergic conditions that are not responding to antihistamines.

NEWS PERSPECTIVES

Adverse Drug Reactions:
A Leading Cause of Death In The US

The April 15th issue of JAMA includes a meta-analysis with a startling conclusion. It reported that the number of fatal adverse drug reactions in the United States in 1994 was estimated at 106,000. This average makes adverse drug reactions the fourth leading cause of death in the United States; behind heart disease (743,460), cancer (529,904), and stroke (150,108). These results were not only unexpected, but also quite alarming.

The criteria for inclusion in this study were to include only those adverse reactions of drugs that were prescribed, dosed and dispensed correctly. They did not include intentional or accidental poisonings, overdoses, drug abuse, incorrect dosing or non-compliance. This basically means that these deaths were due to the inherent nature of the FDA approved dose of a variety of drugs on the human population. It is interesting that this is not included in the "leading causes of death" lists published by the CDC or FDA. If we included the accidents, overdoses, and chronic effects of years of compliance; FDA approved drugs may even constitute the third leading cause of death in the United States.

We, of course, do not mean to imply that many of these drugs have not played a role in saving lives, they have. These data are just a glimpse into the effects of potent drugs which block receptors, stop enzymatic reactions, and alter membrane potentials. These activities have the ability to alter disease conditions, but come with some powerful consequences. When we analyze the ability of natural ingredients to effect similar conditions, we find that similar activities are implicated, but with fewer (and less severe) side-effects.

As we pursue a natural approach to one of the most ubiquitous ailments in the United States, allergies, antihistamines are the first line of defense. As is well known, they cause drowsiness in a large majority of users. Two of the three anti-histamines that were designed to eliminate this side effect (by not crossing the blood-brain barrier) have been pulled off the market for other, more serious side-effects. While botanical products may not have the potency of many of the pharmaceutical ingredients, they contain a variety of phytochemicals that allow them to stimulate the same outcome as many of the pharmaceuticals, with fewer side effects.

Finally, we must mention that adverse supplement reactions are almost unheard of. That is, when correct natural products are taken correctly and with the proper dose, severe adverse reactions are extremely rare. Most adverse reactions come from allergic reactions, incorrect dosing, or accidental mix-up of poisonous botanical (as with the recent incidence of digitalis/plantain). We are quite proud of the safety record of natural medicines, and feel that it is in keeping with the primary oath of physicians: "First, do no harm."

Jason Lazarou, Bruce H. Pomeranz, and Paul N. Corey. Incidence of Adverse Drug Reactions in Hospitalized Patients. *JAMA* , 1998; 279 (15): 1200-1205.

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Immunotherapy: Allergen immunotherapy is the subcutaneous injection of the offending allergen in increasing doses over several months. Essentially what one is doing is to try to stimulate production of other types of antibodies (IgG especially) which will proliferate and can bind to the allergen in the place of IgE. Since IgG do not have receptors on mast cells, they will not stimulate an allergic response. It is not uncommon for many people to take "allergy shots" at regular intervals throughout the year.

THE NATURAL APPROACH

Because allergies are such a common recurrent condition, many people are concerned about the perennial high dose of allergy drug use. The research into natural ingredients has yielded some excellent results in the alleviation of allergic symptoms.

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Antioxidants: One of the major secondary products of inflammatory responses is the formation of a whole host of free radicals. The formation of these potentially harmful products is normal, and even helpful at the time and location of their synthesis; after which they are neutralized by antioxidants. One of the leading water-soluble antioxidants is ascorbic acid (ascorbate) or vitamin C. The use of vitamin C, flavonoids, and other natural agents as potent antioxidants is beyond the scope of this article, but their role in allergic as well as other inflammatory processes have been studied for years. The role of supplemental antioxidants in preventative health will be a topic of a future article.

Quercetin: Among the flavonoids, quercetin is possibly the most biologically active. Quercetin is the aglycone (non-carbohydrate portion) of rutin, quercetrin and other glycoside flavonoids. It is widely distributed in the plant kingdom including oak trees *(Quercus spp.)*, onions *(Allium cepa)* and tea *(Camellia sinensis)*. It has effects on many different enzymatic systems in the body, most of them via its interaction with the calcium-regulating enzyme calmodulin (3).

Quercetin's effect on allergies is unmatched by other natural substances. It inhibits phospholipase A (responsible for converting phospholipids into arachidonic acid), lipoxygenase (responsible for converting arachidonic acid into leukotrienes)(4), platelet aggregation, and mast cell and basophil degranulation (6,7). Quercetin has been shown to bind to calcium/calmodulin complexes, preventing the influx of calcium into mast cells and basophils (6,11). This inhibition prevents the mast cells from destabilizing and degranulating, keeping histamine and other preformed mediators from being released (13). In fact, quercetin so consistently blocks calcium induced mast cells destabilization that researchers often use it in experiments as a control substance for such activity (7,8,12).

The activity of quercetin has been well known for years, leading to the synthesis of similar compounds by pharmaceutical companies. One such compound, cromyln (the active ingredient in Intal), has been used as a mast cell stabilizer for years (10). The only problem is that cromyln cannot be absorbed orally and must me delivered as a powder through spinhalers or an aerosol inhaler. Even then, only 8% is absorbed in the respiratory tract (9) leading to the need to take 2 metered dosages four times per day.

Like most biologically active flavonoids, quercetin's pharmacology is quite interesting. The absorption of quercetin is about 20-52% depending on the form (14,15). While this may seem quite low, the elimination of quercetin and its derivatives is very low, and high plasma levels are easily maintained with a regular supply of quercetin in the diet (16). Studies conducted in rats showed that more than 25% of the absorbed quercetin was localized in the lung tissue, an added benefit to combat allergy and associated asthma (17). While these radioactive studies have not been repeated in man, it is likely that similar results would be found. It has been known for some time that the concomitant administration of bromelain, an enzyme derived from the stem of the pineapple plant, can enhance the absorption of quercetin as well as other flavonoids such as rutin. An added benefit included with bromelain is its ability to block inflammatory pathways (fibrin and kinin) and decrease the viscosity of mucus in the lungs.

Patients should begin to take quercetin upon the first signs of allergen exposure. Since quercetin is prophylactic (stabilizing mast cells rather than blocking histamine) and will stay in the blood stream, initial doses should be 400-600 mg, three

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times per day, for the first 5-7 days. Symptom relief may begin in the first several hours. Once plasma levels are up, 200-400 mg per day should be sufficient through the rest of the allergy season. Quercetin is extremely safe, and has so many other benefits (antioxidant, anti-inflammatory, capillary stability etc.) it should make it the foundation of any natural approach to allergic rhinitis therapy.

Stinging Nettle: Among the many plants one would propose to be helpful in the treatment of allergic rhinitis, the stinging nettle *(Urtica dioica* L.*)* would probably not be among them. This common plant, often called "itch weed", is known to cause hives or urticaria (hence the Latin name) due to the histamine located in needles under each leaf. For years, the dried **leaves** of stinging nettles were used for the symptoms associated with allergic rhinitis. Finally in 1990 a double-blind, placebo-controlled study was done to assess the use of stinging nettle leaf for allergic rhinitis (18). After one week, stinging nettle was rated higher than placebo. Unfortunately this study was based on diary entries of symptoms and overall patient ratings. These studies should be expanded to include more patients, longer intervals, and more objective measurements.

A recent article studying the use of stinging nettle leaf extracts in the treatment of rheumatoid arthritis (another inflammatory process) may explain the mechanism. An extract of stinging nettle leaves was shown to inhibit both lipoxygenase and cyclooxygenase activity (19). These two enzymes are responsible for converting arachidonic acid into the inflammatory prostaglandins and leukotrienes. This and possibly a negative feedback effect from oral histamine (from the nettle leaf) contribute to the overall activity of nettle leaf in allergic symptom relief.

While other botanical products have been used for allergic rhinitis over the years, most of these work as anti-allergic agents due to the high amount of quercetin in them. Among them, garlic, onion, and green tea are the most popular.

Asthma: Asthma is one of the most common allergy associated ailments. It can be triggered by the same events as allergies (IgE-allergen interaction) and results in the constriction of the bronchioles and increased production of bronchial mucus. While several of the mast cell preformed mediators play significant roles in asthma, increasing research has been targeted at leukotriene and PAF-induced asthma (20,21,22). These lipid-derived mediators are responsible for drawing eosinophils (by chemotaxis) to the lungs, which perpetuate the response by releasing more PAF.

Several botanical constituents, including quercetin (23) and bilobide B from Ginkgo biloba (24), have been shown to inhibit the synthesis or effect of PAF. There is continued research to find other botanical ingredients that will address this area of allergy and asthma.

Ephedra: Ephedra *(Ephedra sinica* Stapt.*)* or Ma Huang has been used in Chinese medicine for thousands of years (29). The ephedra plant contains 2 to 3% alkaloids, mostly ephedrine and pseudoephedrine. These alkaloids were discovered and synthetically produced in the late 1920's and their use has been wide in over-the-counter and prescription medications for asthma, hay fever and related conditions. See the discussion under "Treatment Options: Drugs" above for mechanisms.

Ephedra has come under scrutiny of late by the FDA, primarily due to its formulation with caffeine-containing products and its promotion as a stimulant weight-loss product. Restrictions will be

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recommended, and possibly mandated on the use, dose, and combination use of ephedra in the near future. Extracts of ephedra (Ma Huang) is safe in short-term use (1-2 weeks) as a bronchodilator. Longer use of ephedra should be monitored closely and should be accompanied by adrenal stimulating herbs like licorice *(Glycyrriza glabra* L.*)*, Siberian Ginseng *(Eleutherococcus senticosus* Maxim.*)*, and Dandelion Root *(Taraxacum officinalle* Wiggers*)*. Ephedra extracts contain 6-8% ephedrine and should be dosed at 200-400 mg 2 or 3 times daily. Each individual reacts differently to ephedra and smaller and less frequent doses should be attempted prior to increasing dosing.

NAC: N-Acetyl Cysteine (NAC) may be one of the best expectorant/mucolytic agents, although it has been forgotten in recent years. NAC is gaining interest as an antioxidant that acts by itself and as a "recharger" of the body's own glutathione (25). As disulfide reducing agents, both NAC and glutathione can decrease the viscosity of mucus, which is increased by disulfide bridging of sulfur proteins in mucus. Recently, the mucolytic mechanism is being reassessed by research suggesting a "mucoregulating" action for NAC (27,28). NAC has been used quite frequently in an assortment of lung conditions including COPD, bronchitis, and asthma (26).

CONCLUSION:

As we finish editing this article, we are looking at one of the worst allergy seasons in decades. Just one more El Niño effect, we are told. As the seasons approach, patients will begin stocking up on prescription, over-the-counter, and natural products to combat the inevitable symptoms they will face. This information should help you direct your patients to the best natural treatment options for the coming season.

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IN MY OPINION

Finally someone is saying what many of us have known for sometime: that most people are unlikely to get enough vitamins from food and should take either supplements or eat specially fortified foods. This statement was just released by the U.S. Institute of Medicine on April 7, 1998. According to Dr. Robert Russell at the Tufts University "this is the first time a recommendation has been made for intake other than from natural foods for a significant portion of the population". The first by them, but certainly not the first.

The concept of supplementation seems to hinder many traditional camps. Let us discuss this for a moment. Supplementation is simply the adding of components not found in the available material, in this case, diet. The majority of the world's plants are not native to Central Wisconsin where I live. My wife and I choose to supplement our diet with Florida oranges, Georgia peaches, California grapes and a host of ingredients from around the world to gain the vitamins, minerals and phytonutrients we want to complete our diet. Unfortunately, many of the most biologically active phytonutrients are very unstable in the original plant material (must be eaten fresh), are too bulky to be transported efficiently (need to be concentrated), or are found in a part of the plant that most people would choose not to ingest (root, skin, bark etc.). Supplementation is taking these ingredients to a population that cannot legitimately add them to their normal diet.

This is certainly not an endorsement for taking supplements instead of fresh fruits and vegetables, but with them. The best advice (I don't recall from whom) I have heard concerning the diet is "Eat things that would spoil, but eat them before they do!" Our modern culture has spent billions of dollars extracting out the active components of foods to increase shelf-life, improve texture, and improve shelf appeal. This, and the fact that much of the soil has been depleted of vital trace minerals in the past 100 years, has led to the need for supplementation of vitamins and minerals, as well as various phytonutrients. From the looks of it, what we have known for decades has become a novel finding by our federal government.

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