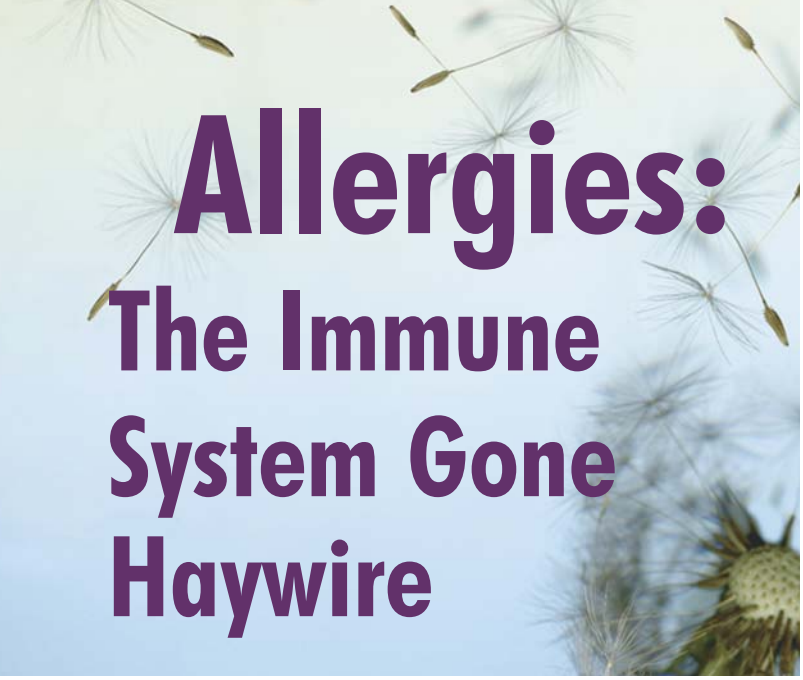

Allergies: The Immune System Gone Haywire

Runny noses, itchy eyes, upset stomachs, inflamed skin… most of us have experienced these symptoms or have a family member or a friend that suffers from them. Allergies are a modern era pandemic. It is estimated that 30-50% of the population in the United States suffers from allergies. Allergies in the US come with a hefty yearly price tag of over 2 billion dollars in lost productivity, medical expenses and medication.[1-5] Allergies are a long term health problem; typically beginning between 8 and 12 years of age and lasting for decades if not for a lifetime.[6,7] And to add insult to injury, research shows that the incidence of allergies is on the rise in most developed countries. Thankfully, as our understanding of allergic disorders improves, new treatment and preventive approaches emerge, because at times, scratching an itch truly makes it worse.

Allergies and the Immune System

Allergies are a disorder of the immune system that is caused by the improper activation of the immune response. Allergies are almost always linked to the presence of an excessive amount of allergic antibodies known as IgE. Allergies occur because a substance present in the environment that is normally harmless enters our body and is mistakenly identified as a threat. Most pathogens that we are exposed to, from bacteria to viruses, are proteins and are eliminated through the activation of the immune system. In the case of harmless proteins, like proteins from food, the immune response must be suppressed through a process known as oral tolerance. Inducing oral tolerance has been used as a strategy to prevent allergies for years. For instance, Native Americans used to eat poison ivy leaves to prevent contact dermatitis associated with skin exposure to the plant.[8] Understanding the process of oral tolerance is essential for the prevention and treatment of allergies.

Although true or immediate allergies are mediated by IgE, other antibodies and immune cells have also been linked to allergic diseases. Contact dermatitis for instance occurs through the effect of T-cells and IgM or IgG are often responsible for drug allergies or what is known as cytotoxic allergies.[9]

Food intolerances are also probably allergies since significant immune factors are involved in the process.

Infants with milk, soy and egg intolerance were found to have IgG levels significantly higher than the control group.[10] Trials in animals also show a clear involvement of IgG immunoglobulins when peanut sensitivities are present.[11] Other studies point to a clear immunological link in irritable bowel syndrome, with results showing that elimination diets that focus on the foods which elicit an IgG response in IBS patients lead to significant improvements of the disease in a majority of patients.[12,13] IgG immune reactions are delayed occurring several hours after exposure to the offender and are often not immediately identified as allergies.[14]

When Intolerance Sets In

The immune system is designed to protect our body from pathogens and must respond and eliminate threats. On the other hand, the immune system must also be able to tolerate the cells of our body, the proteins from food as well as the bacteria naturally present on our body. Most of the interaction with foreign proteins occurs in the intestine which explains why the gastrointestinal tract is the largest immune organ in the body. Given the complexities of the immune response and the abundance of proteins and bacteria in our diet, it is not surprising that allergies are common. There are two important immune reactions occurring in our intestines, the activation of the immune system when pathogens are present in the gastrointestinal tract and the suppression of the immune response when food proteins are digested.

If tolerance fails, which means that the immune system is inappropriately activated, B cells produce antibodies specific to the antigen and antibody's known as IgE are produced to neutralize the perceived threat. This leads to the release of histamines, leukotrienes, tryptase, chemokines, cytokines and prostaglandins from mast cells. These in turn lead to inflammation through the recruitment of basophils, eosinophils and leukocytes. These cells increase the blood flow to the

area which accentuates symptoms such as swelling and itching. There are two main phases to allergies, the first phase is the immediate phase characterized by the release of histamine and vasodilators. The second phase is mediated by the mobilization of immune cells and occurs 4 to 6 hours after the initial reaction.[15]

Immune tolerance is a process that begins during pregnancy, as early as 20 weeks of age through transfer of immune factors from the mother.[16] Several researchers have focused on the age at which exposure to a protein first occurs and its consequence on allergies. Experiments in mice have shown that when the exposure occurs at a younger age, especially when exposure occurs prior to the normal weaning time, allergies are more likely to occur. For many of these mice tolerance develops with age.[17]

More than an Inconvenience

Although the symptoms of allergies are often seen as a mere nuisance, they have been shown to cause headaches, fatigue, difficulty learning, loss of sleep, and reduced productivity.[18,19] There are also several associated problems such as headaches, loss of smell and taste, cough, wheezing, snoring, ear infections and nasal polyps.[20] The most severe kind of allergic reaction, known as anaphylaxis, is very serious, can progress very quickly and can be lethal due to the involvement of several body systems. Other allergies such as seasonal allergies, which affect up to 35% of the North American population, are not life threatening but lead to seriously unpleasant side effects. By far the most common symptoms associated with air borne allergies are a runny nose and itchy eyes. The eyes are typically quite inflamed in seasonal allergy sufferers as allergens can impact the eye surface directly.[21] Severe allergies are often overwhelming because avoidance strategies are needed. The most common kind of this type of allergy is peanut or tree nut allergy, which affects roughly 1% of children under the age of 5.[22,23] In Canada, peanut allergy affects 1.34% of children.[24] Food allergies in general affect 6-8% of children and 4% of the United States population older than 10 years of age. Every year in the US alone, 30 000 anaphylactic reactions are caused by allergies, of those, 2000 lead to hospitalization and 200 are lethal.

Diagnosis of Allergies[25,26]

Appropriate history of exacerbating factors

Perennial or seasonal symptoms, with timing correlated to specific pollen or mold spore exposure

Symptom triggering with identifiable agents such as animals

Familial history of asthma, allergic rhinitis, or atopic eczema

Medication and medical history

Oral aggravators such as acetylsalicylic acid, nonsteroidal anti-inflammatory drugs, anti-hypertensive agents

Topical aggravators such as alpha agonists

Hypothyroidism

Pregnancy

Physical findings

Rhinorrhea, clear or mucoid discharge

Erythema of nasal mucosa

Nasal congestion

"Allergic facies"

Collaborative findings

Immediate hypersensitivity skin testing

Serum specific IgE

Comorbid conditions

Sinusitis

Nasal polyposis

Asthma

Eustachian tube dysfunction

Serous otitis media

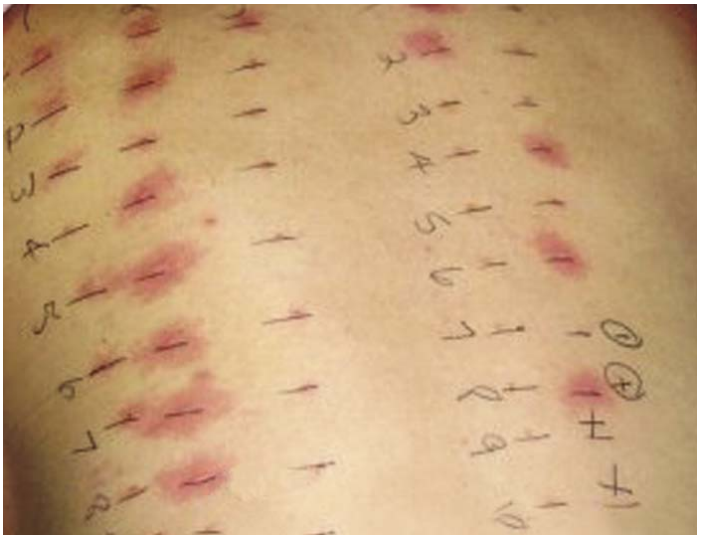

Figure 1. Skin prick testing remains the most specific and most cost effective way to diagnose allergies.

An Inborn Predisposition

Allergies are still poorly understood. We know that they tend to run in families, which indicates a genetic bias. Most allergy sufferers have inherited their allergies through an immune predisposition to a Th2 immunity profile (mediated by antibodies) which is often seen in autoimmune disorders. Allergies are therefore linked to an abnormal immune system, tend to occur in clusters and are often associated with other hypersensitivity reactions. [27]

Allergies, genes and the immune system

Women suffering from allergic symptoms early in their pregnancy are 6 times more likely to have children who also have allergies.[28]

Animal studies have demonstrated that in the most susceptible strain 87-100% of the animals developed allergies to milk or peanut while the least susceptible animals did not develop allergies.[29]

A very clear indication of the central role the immune system plays in allergic disease is that bone marrow recipients develop the allergies of their donor.[30]

Children with egg allergies and eczema have a 20% chance of having peanut allergy.[31]

There is a concordance between allergies and asthma.[32]

Some allergies take a long time to develop, while others appear very quickly.

Generally, allergies are more likely to be a problem for foods that are introduced early in life and that are eaten more commonly. Delaying the introduction of potential allergens may be a good idea and studies have demonstrated that exclusive breast feeding for the first 4 months of life reduces the risk of developing atopic dermatitis, a hereditary inflammatory skin condition.[33]

Some allergies are life-long while others lessen with time.

For all allergies, there seems to be a tendency towards eventual tolerance. 20% of children with peanut allergies will eventually outgrow them.[34] For egg allergy, which affects 1-2% of children, 4% develop tolerance by 4 years of age, 12% by the age of 6, 37% by the age of 10 and 68% by the age of 16 years.[35] Other trials demonstrate similar results with 35% of the children on an elimination diet developing tolerance without any other form of treatment.[36] However, severe allergies are less likely to subside and patients with IgE levels to egg exceeding 50 ku/L and patients with multiple food allergies are less likely to see their allergies subside.[37]

Potential Determinants of Allergic Disease[38]

Genetics
Family history
Low birth weight
Exposure to pets
Exposure to allergens
Infections
Exposure to parasites
Obesity
Dietary fatty acids
Dietary antioxidants
Exposure to tobacco smoke
Exposure to pollutants

Avoidance as a Stratagem

The best way to control allergies once they have developed is to prevent exposure to the allergen.

Unfortunately, as seasonal allergy sufferers know too well, avoidance is not always a possibility. While most of us rejoice once spring has arrived, for seasonal allergy sufferers, the powdery grains released from trees and grasses can wreak havoc on their immune system. Pollens from trees and grasses that are carried by the wind to pollinate other plants can cause an allergic reaction if the person is sensitive to pollen. Springtime allergies are typically caused by pollen from trees, summertime allergies are a result of pollen from grass and fall allergies are caused by weed pollen. Unlike avoidance to dust or pet dander, allergies to pollen or mold spores are more difficult to avoid. This problem is made worse by the "priming effect", which results in progressively worsening symptoms as the inflammation from the initial allergic reaction is made worst by subsequent exposure.[39]

Typical prescription medications for the treatment of allergies include antihistamines, which prevent the release or action of histamine. Histamine can cause sneezing, itchiness, irritation and excess mucous production. One major inconvenience to prescribed antihistamines is that they have a sedative effect and can lead to drowsiness, increasing the risk for accidents and injuries. Antihistamines are also typically ineffectual for nasal congestion and other treatment options often need to be considered in allergy sufferers.

A commonly used treatment for allergy sufferers is cutaneous allergen immunotherapy, a technique where allergens are periodically injected under the skin in gradually increasing quantities. If successful the technique eventually leads to desensitization. Unfortunately, this technique is not used for food allergies as the risk of adverse reactions is too great.[40]

Several studies have reported an increase in the prevalence of allergies in recent decades. In the UK for instance, the prevalence of peanut allergy has risen from 1.3% of 3 year olds to 3.2% of 3 year olds in 1995.[41,42] These increases are common throughout the developed world with several European countries now reporting one in ten children suffering from asthma and one in three affected by allergies. Such increases are unlikely to be caused by genetic factors alone.[43] Possible explanations have included the "hygiene theory" and an increase in air pollution. The hygiene theory has been put forth to explain the rise in incidence of several immune disorders in developed countries. The theory's basic premise is that limited exposure to microbes in early childhood increases the susceptibility to allergic disease and other immune disorders such as asthma. Such exposure would be important to educate the immune system and a sterile environment would predispose to immune dysfunction and autoimmune diseases.[44,45] This may also explain why certain strains of probiotics seem to have a protective role in immune diseases.[46] This also explains why children who grow up with dogs in their home are less likely to suffer from allergies.[47] Surprisingly, children born through C-section were also more likely to develop food sensitivities. It has been speculated that contact with the bacteria in the birth canal may reduce the risk of allergy. It is also possible that the presence of antibiotics in the mother to prevent infections post surgery may predispose to the development of allergies.[48] Studies looking at the importance of early exposure to specific bacteria have shown that children who develop allergies are significantly less likely to have been exposed to S. aureus, a bacteria that has a strong stimulatory effect on T-cells, another indication that exposure to microbes in early childhood is important for the proper development of the immune system.[49] This would also explain why children drinking milk fortified with probiotics missed fewer days from day care due to sickness and were less likely to receive antibiotic therapy.[50,51]

Figure 2. Peanut Allergy - A problem on the rise.

Observational studies continue to strengthen the link between air pollution and allergic conditions. Pollution has long been known to induce asthma and to acerbate inhaled allergens in asthmatics.[52] The link between pollution and allergies has been explained by an increase in oxidative stress and free radicals in people that are more likely to suffer from allergies. People with allergies would be more sensitive to pollution due to a lessened ability to detoxify pollutants.[53] Other possible explanations for the increase in allergic disorders have included the manner in which foods are prepared. For instance, in the case of peanut allergies, it has been postulated that the formation of advanced glycation end products in roasted peanuts may increase the susceptibility of developing peanut allergies. The presence of advanced glycation end-products in heat treated peanuts could therefore increase their allergenicity and previously non-allergenic raw peanut proteins have been shown to trigger an immune reaction once heated.[54] However, more research is needed to confirm those results as they have not been reproduced by other researchers.[55]

Since foods that are introduced at a young age are more likely to be candidates for allergies, the American Academy of Pediatrics has recommended that children should not consume peanuts for the first three years of their life to help prevent the development of allergies.[56] Others have suggested that this measure is counterproductive and that the consumption of peanuts at an early age may actually prevent allergies and countries where peanut snacks are available for infants have lower rates of allergies to peanuts.[58,59]

It has also been postulated that skin exposure to peanut oil may contribute to allergies but those findings remain tenuous and are only based on population studies.[61] More work is needed to determine the role exposure plays in the development of allergies.

Other work in the prevention of allergies has looked at producing transgenic plants that are free of the proteins that lead to the allergy.[62]

Newer research has revealed ways of reducing the likeliness of developing allergies. Probiotics for instance have demonstrated promise in this new field. Vitamin D has also been portrayed to be a significant factor in allergies and epidemiological studies demonstrate that there is a very strong North-South gradient for the sales of EpiPen prescription in the United States. This may point to a link between vitamin D and allergies, an interesting finding given new research showing that vitamin D is important for self tolerance. Other possibilities include the shift in dietary lipid consumption with a significant decline in the consumption of Omega 3 fatty acids. It has been proposed that omega 3 fatty acid consumption would have a protective effect against allergic disease due to the anti-inflammatory effect of those oils. Higher omega 3 fatty acid levels in the breast milk decreased the risk of allergic disease in infants.[63] Increased maternal consumption of omega 3 fatty acids during pregnancy may have even greater health benefits for the infant, with studies suggesting a long term immune effect associated with early exposure to omega 3 fatty acids.[64] Several mechanisms have been identified as far as how these fatty acids can influence the function of the immune system (*see figure 6 from*[65]). Omega 3 fatty acids may also have a direct effect on the immune system and on the structure and function of cellular membranes. The effect of omega 3 long chain polyunsaturated fatty acids on cellular membranes reduces T-cell signaling and activation.[66] The prevention of T-cell proliferation and the inhibition of the production of immune messengers such as IL-2 and IFN-by omega 3 fatty acids are key to their beneficial effects for allergy sufferers.

Figure 3. EpiPen, the treatment for anaphylaxis

You wouldn't play the piano with a mallet, or swat a fly with a bat… unfortunately, that is what your body is doing if you experience allergies. Instead of addressing a problem by eradicating a pathogen, it creates havoc by unleashing an array of immune cells and their mediators, creating inflammation, swelling and itchiness. Most of us will experience allergies, which is not surprising given the difficult task of separating threatening substances from harmless ones. As more research surfaces on allergies, our understanding of the disease process will improve. For the time being, suffice it to say that when we stray from the natural way and the natural environment we evolved in, problems arise. For example, although growing up in a cleaner and more germ-free environment seems like a good way to prevent

infection and disease, in reality it also predisposes to autoimmune diseases. We evolved with germs and bacteria and it seems that this interaction is needed for the proper development and maturation of the immune system. Exposure to the sun is another key factor in the prevention or allergies. Our ancestors would have spent most of their time in the sun and would have had much higher vitamin D levels than most of us do. Since vitamin D is extremely important for immune tolerance, it is not surprising to see such a strong North-South gradient for immune diseases. Despite all of modern medicine's advancements, Mother Nature still knows best.

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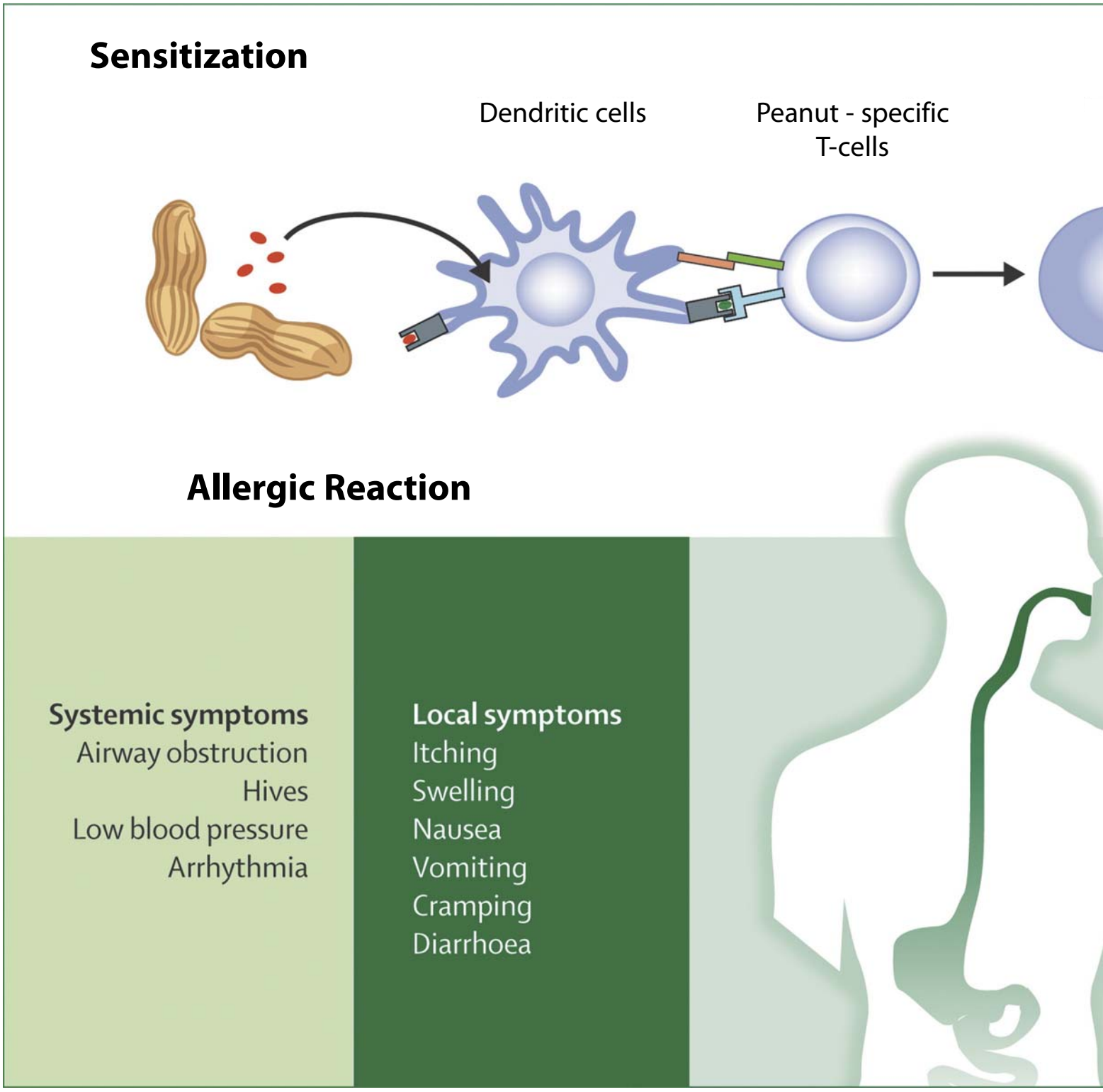

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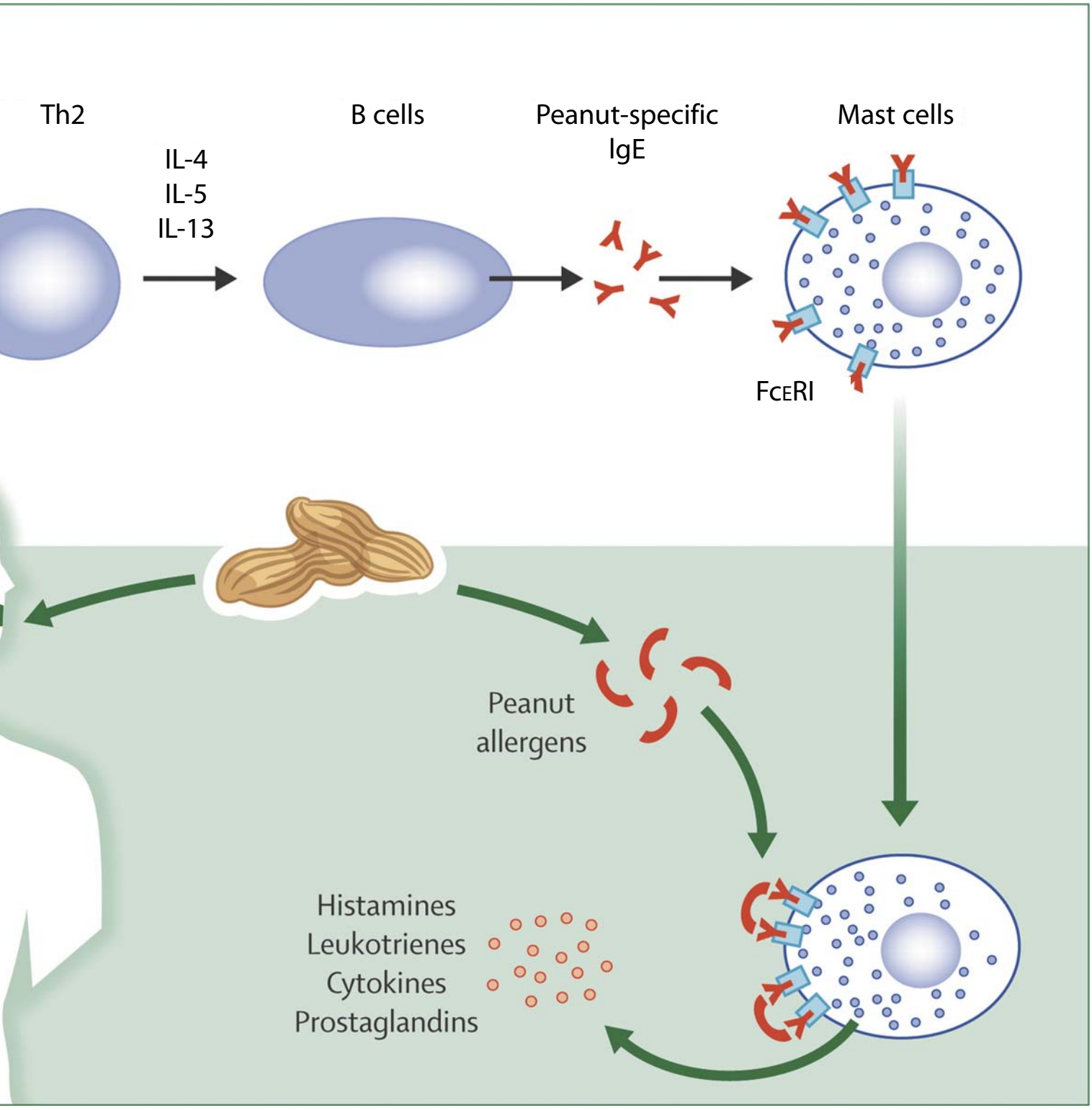

Antigens from allergens like peanuts are engulfed and then presented by immune cells called dendritic cells that in turn activate T-cells, causing a Th2 immune response. This causes the release of cell signaling molecules called cytokines (IL-4, IL-5 and IL-13), triggering the production of antibodies specifically matched to the antigen. Antibodies then activate Mast cells, causing the release of histamines and pro-inflammatory molecules, this in turn produces the symptoms of allergies.