

Use of Immunotherapy in the Treatment of Peanut Allergies in the Pediatric Population

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## Abstract

Peanut allergies are a serious issue that must be monitored and treated effectively to avoid severe adverse effects and death. In the last decade, their incidence has increased significantly, due to indeterminate factors. Because people typically do not outgrow peanut allergies and the effects of exposure can be life-threatening, it is important that a cure or management method is developed and refined. Recent research regarding treatment for peanut allergies has focused on the use of immunotherapy, a process aimed at desensitizing children's immune systems so that they do not reject foods that contain peanuts. Some studies utilizing immunotherapy have provided positive findings, while others show less promising results. Working within the limitations imposed by safety concerns, researchers are seeking to find a reliable treatment that can be utilized in more cases, whether it is through oral, sublingual, or subcutaneous immunotherapy. Since those with peanut allergies are gradually composing a larger percentage of the population, this area of research is relevant and could prove beneficial in improving and saving the lives of many individuals.

### Use of Immunotherapy in the Treatment of Nut Allergies in the Pediatric Population

Food allergies are a growing problem, especially in the United States. One study by the Centers for Disease Control and Prevention (CDC) showed that food allergies among children increased by about 50% between the years 1997 and 2011 (FARE, n.d.). In the last decade, the number of children living with peanut allergies has also increased dramatically, tripling between 1997 and 2008 (FARE, n.d.). In fact, peanuts currently comprise approximately 0.6-1/3% of all allergens causing reactions in the United States. According to Yu, Weldon, Neale-May, and Nadeau (2012), "Peanut allergy, which affects an estimated 0.6% of U.S. adults and more than 1% of children, is the leading cause of food related fatal anaphylaxis in the United States" (p. 1). This once-rare issue has now become the most common cause of fatal allergic reactions to food, making it an area greatly in need of an effective and reliable cure, rather than just an emergency treatment (Anagnostou & Clark, 2015).

Many have tried to determine an explanation for this significant increase in peanut allergies in children, but as of yet no one factor has been proven to be the cause. One theory under speculation is the delayed introduction of young children to peanuts. For several years, many medical experts advised that all parents wait until their children reached recommended ages before they were given peanuts and other potentially allergenic foods. With these recommendations came increased awareness of specific food allergies and the dangers they can cause. While pediatricians still recommend using caution with early exposure, many believe that avoidance may cause more harm than good and that delaying exposure actually increases the chances the child will display

hypersensitivity (UCLA Health, 2010). A second theory is the impact of our current society's focus on living 'clean' and trying to stay as healthy as possible. It is thought that perhaps when people prevent their bodies from exposure to bacteria, illnesses, and other things they consider to be harmful, it actually causes their immune systems to be more sensitive to minor invaders such as pollen and peanut proteins. Another proposal is that the way peanuts are cooked today makes them more allergenic. The peanut-roasting process manufacturers use supposedly modifies the sugar in peanuts, thereby increasing the ability of the peanuts to attack the immune system (Hendrick, 2010). At one point, it was thought that children's allergies to peanuts may be caused by their mothers' ingestion of peanuts during pregnancy. However, this was soon disproved by a study wherein expectant mothers avoided peanuts. It was found that "[a]voidance of peanut consumption during pregnancy and lactation failed to reduce the prevalence of peanut allergy. Early introduction of peanut may actually promote tolerance and reduce the risk of peanut allergy" (Anagnostou & Clark, 2015, p. 71).

Despite the lack of a confirmed cause or causes, it has been found that peanut allergies are definitely on the rise. This significant rise necessitates a safe and reliable treatment which can effectively prevent allergic reactions to peanuts. Immunotherapy is currently on the front lines of a growing field striving toward the elimination of peanut hypersensitivities. The goal of immunotherapy researchers is that the affected population will someday be able to live day-to-day without constant fear of accidentally ingesting this seemingly harmless ingredient that turns bodies against themselves.

### **Pathophysiology of Allergic Response**

The body's immune system works constantly to protect a person from foreign material it may encounter in its environment. Sometimes, however, its defensive mechanisms bring about a negative result and the immunity which is meant for good may actually place the body in more danger. This is the case with hypersensitivities such as peanut allergies. The immune processes of the body are carried out by the lymphatic system. One of the central lymphoid organs is the bone marrow, which produces lymphocytes. After lymphocytes have been formed, they differentiate into either B or T lymphocytes. Of these two types, B lymphocytes are key players in allergic responses (Lewis, 2011).

When a hypersensitive person ingests peanuts, the peanut proteins are viewed by the body as an antigen and it quickly reacts to try to rid the body of it. The first time this person consumes peanuts, the proteins enter the bloodstream, where they are detected by B lymphocytes. This encounter activates a transformation of the B lymphocytes into plasma cells, which have the ability to produce antibodies against the peanut antigen. The specific type of antibodies – also called immunoglobulins – created are called immunoglobulin E (IgE) antibodies. These newly-formed IgE antibodies attach themselves to another type of cell, either mast cells or basophils, where they wait for the allergen to enter the body again. Thus, this initial encounter with the allergen produces no systemic effects. However, when the person ingests peanuts for the second time, the antibodies attached to the mast cells bind to the peanut proteins, thereby initiating an allergic response. Granules inside the mast cells break down and quickly release many

powerful chemical mediators, including histamine and serotonin, which exert their effects on various body systems (Lewis, 2011).

### **Chemical Mediators and Their Actions**

One type of chemical mediator released by the mast cells are called anaphylatoxins. The three complement proteins specific to allergic reactions are C3a, C4a, and C5a. These three complement fragments are known as anaphylatoxins because they combine their effects to produce anaphylaxis or anaphylactic shock. They cause the smooth muscles in the body to contract and make the blood vessels more permeable. C5a, which is the most influential of the three proteins, and C3a also stimulate the release of histamine, another chemical mediator, by activating submucosal mast cells (Janeway, Travers, Walport, & Shlomchik, 2001).

Histamine, one of the main players in the anaphylactic response, is a very potent vasodilator of the small blood vessels. It also causes endothelial cell contraction, which provides openings for easier passage of proteins, cells, and fluids. This increased capillary permeability may cause edema to occur due to the loss of fluid into interstitial spaces. In turn, the loss of intravascular fluid along with vessel dilation causes a drop in blood pressure. Histamine also causes constriction of the bronchi. All of the above effects occur when histamine stimulates H1 receptors (Lehne, 2010) (Moriber, 2013).

Leukotrienes, prostaglandins, kinins, and serotonin are all chemical mediators that also work to constrict smooth muscle, constrict bronchi, vasodilate, and increase permeability of vessels. Leukotrienes constrict the bronchi and enhance the effects of histamine to constrict smooth muscle. The bronchoconstriction effects of leukotrienes are

actually slower, longer-lasting, and more potent than those of histamine. Together, leukotrienes and histamine help activate and sustain the allergic response.

(Hammarström, 1983) (Grossman, 2013).

Platelet-activating factor is another important mediator of the allergic response. This chemical is produced from the lipids stored in cell membranes; its main action is to put the aggregation of platelets into effect. It also draws in and activates eosinophils and neutrophils. Platelet-activating factor causes bronchospasm as well as wheals and flaring (Grossman, 2013).

### **Clinical Symptoms of Allergic Reaction**

All of the above effects caused by the many chemical mediators released into various parts of the body combine to inflict a deadly outcome for hypersensitive individuals if antagonistic action is not taken quickly. As the bronchi constrict, it becomes more and more difficult to breathe. Affected children may speak in a hoarse voice due to their constricted airways or cough in an attempt to expel more air. Wheezing and stridor may be heard upon breathing as the bronchi narrow and gas exchange becomes more difficult. Tachypnea may also occur, eventually progressing to respiratory arrest.

The cardiovascular effects can also be severe and life-threatening. As mentioned above, the vessels dilate and vascular permeability increases, causing a low vascular volume. This leads to a decrease in blood pressure and increase in heart rate, which may in turn cause vascular collapse, dysrhythmia and cardiac arrest to develop (Lewis, 2011).



The neurological system is also affected by the chemical mediators. When vasodilation occurs in the head, the child may experience a headache due to the increased pressure on the brain. The decreased oxygen supply to the brain due to impaired gas exchange, as well as lower circulating blood volume, can cause a child to feel dizzy and possibly lose consciousness. A decrease in oxygen supply to nerves can also cause paresthesia. The individual may also experience a sense of impending doom (Lewis, 2011).

The allergic person can also develop unpleasant integumentary symptoms. Urticaria, or hives, occur as a result of the vasodilatory and fluid shift effects of histamine. Fluid that escapes from the increasingly-permeable vessels forms collections of fluid under the skin known as wheals anywhere on the body. Blood vessels underneath the wheals may dilate as a result of sympathetic nervous system stimulation, producing flaring of the wheals. Pruritis, or itchy skin, and erythema, a general or localized reddening of the skin, are two other symptoms that are also caused by the release of histamine. Angioedema may also occur. This involves the build-up of fluid, much like with urticaria, but the fluid collects under deeper layers of the skin. Unlike with urticaria, angioedema occurs in areas such as the eyelids, genitalia, and gastrointestinal tract. Pain or burning are sometimes felt when the swelling affects sensitive areas such as the gastrointestinal (GI) tract. This swelling is especially serious when it reaches the larynx and other airway structures, so it is important that the individual's airway be protected. It may take as long as 24 hours for the swelling to subside (Lewis, 2011).

The allergic response also causes GI effects. As mentioned above, angioedema can lead to acute pain in the abdominal region. Cramping, nausea, vomiting, and diarrhea may all also occur. These symptoms are further evidence that the body is making a deliberate effort to get rid of the antigens it considers to be harmful (Lewis, 2011).

### **Traditional Treatment of Peanut Allergies**

As Blumchen et al. (2010) points out, peanut allergies are a unique and persistent allergen:

Some food allergies in early childhood, like cow's milk and hen's egg allergy, usually resolve over time. In contrast, peanut allergy tends to persist over a lifetime, and only about 20% of young children outgrow their disease. It has been reported that the severity of future allergic reactions to peanuts cannot be predicted from former allergic reactions in the patient's history. Thus, most patients with peanut allergy face the fear of anaphylaxis throughout their life. This constant uncertainty has a major psychological burden on the quality of life of the children and their families. (p. 83)

The standard treatment for peanut allergies has remained the same for years. Affected individuals avoid ingesting the allergen whenever possible, even if it means avoiding restaurants and food from manufacturers that process peanuts. Parents may meticulously read nutrition labels of any food they give their child and do anything else they have to in order to prevent their child from being exposed. In addition, many children with peanut allergies also are allergic to one or more tree nuts, adding to the need to be very careful

about what the child ingests (The Peanut Institute, n.d.). As Blumchen et al. (2010) noted above, this places extreme stress on children and all those involved in their care.

However, despite precautionary measures, these children still sometimes ingest peanuts – whether it be through accidental or intentional means. The standard and most effective treatment is Epinephrine. Epinephrine is the prototype of a drug class called sympathomimetics. Specifically, it acts on all four adrenergic receptors –  $\alpha_1$ ,  $\alpha_2$ ,  $\beta_1$ , and  $\beta_2$  – to activate each of their effects. These effects include vasoconstriction, increased contractility and heart rate, and bronchodilation. Epinephrine causes rapid activation of the adrenergic receptors and thus, relieves the life-threatening vasodilation and bronchoconstriction brought on by the anaphylaxis. Blood pressure quickly normalizes, heart rate increases, and dyspnea is relieved – all within seconds or minutes (Lehne, 2010).

An epinephrine 1:1000 preparation is available inside what is called an EpiPen. An adult EpiPen dose is 0.3 mg of epinephrine, while the EpiPen Jr. injects 0.15 mg with each dose. In some cases, one dose is not sufficient to relieve the individual's symptoms. When this occurs, another dose may be given. The EpiPen is easy to use and can be self-administered; it is loaded with an intramuscular needle which self-ejects when pressure is applied. After the cap is removed, the pen must be firmly pressed into the vastus lateralis muscle, which is located on the lateral aspect of the thigh. After the dose is administered, the injection site should be massaged for a few seconds to promote optimal absorption. A small marker in the window of the pen indicates successful injection. Even if symptoms improve, it is recommended that the individual seek medical care because epinephrine

has a very short half-life and the anaphylactic symptoms may return. Care providers can administer prednisone if needed and observe for continued symptoms. It is important that individuals with known peanut allergies always have access to an EpiPen, because exposure may be encountered even in an unexpected setting. Since EpiPens typically expire after one to two years, it is important to check often to make sure the medication is still current. Most EpiPens have small windows that allow the owner to check for age-related discoloration, which is a good indication that the epinephrine has lost its original potency (EpiPen, n.d.) (Lehne, 2010).

### **Background and History of Immunotherapy Treatment**

The idea of immunotherapy has been around for centuries. It is said that King Mithridates VI, who lived 132–63 B.C., attempted to make himself immune to snake venom by exposing himself to increasing doses of the poison. Since this recorded event, there have been numerous other occurrences of a harmful reaction being treated with increasing amounts of the reaction-causing substance. Allergen-specific immunotherapy was first studied clinically in humans by scientists Leonard Noon and John Freeman in 1911. They injected extracts of pollen into patients with hay fever and observed the results. Their research paved the way for the use of immunotherapy in many other studies and cases (Ring & Gutermuth, 2011).

Allergy injections are a common form of immunotherapy used today. Used mainly in patients with seasonal allergies, this therapy involves the routine injection of tiny amounts of allergens with the goal of triggering activation of the immune system without creating a full-scale allergic response. The results of this treatment range from

slow improvement of symptoms to complete desensitization to the injected allergens. Desired results may take years to achieve, however, and even then in some cases, the shots may still have to be administered in order for desensitization to continue (Mayo Clinic Staff, 2015). Today, the use of immunotherapy in treating peanut allergies is a major area of research yielding promising, yet controversial results and opinions (Ring & Gutermauth, 2011).

### **Study Participants**

Before each individual study begins, the group of researchers will determine inclusion and exclusion criteria for potential participants in their research. Usually a general age population – adults or children – is agreed upon, then the recruiting begins from there. Volunteers go through a screening process to see if they meet the proper criteria for the study. A detailed medical history is typically taken, for safety and also so that comorbidities such as asthma and other allergic disorders can be taken into account when the research results are analyzed. Often, if a person has a history of severe anaphylactic reactions or if they have another serious chronic illness, they will be excluded from the study for safety reasons. Tests to confirm their hypersensitivity to peanuts, such as a skin-prick test, are typically performed to ensure the allergy actually exists. Some studies will utilize a group of healthy individuals to receive the treatment alongside the allergic individuals. After the final selections for the study group have been made, the immunotherapy process begins.

### **Overview of Immunotherapy Process**

Conducting studies utilizing immunotherapy treatment necessitates careful planning and organizing, collaboration and recruiting, troubleshooting and preparedness. This list is just a sampling of the many thought processes and methods that must be present to conduct a well-established, reliable research study. The choices the researchers make can affect the results of the study as well as the outcome of the patients.

While details such as the specific routes, dosages, timeframes, and populations may vary according to the study being carried out, the general concept is the same. The steps of the immunotherapy typically occur in the following order, although individual studies may rearrange or omit steps depending on their research process: initial escalation phase, build-up phase, maintenance phase, avoidance phase, and challenge phase.

#### **Initial Escalation Phase**

The first phase of immunotherapy usually takes place over one day in a controlled clinical setting where all the participants may be observed throughout the process and treated in the event of an emergency. A very tiny dosage of peanut protein is administered, typically around one milligram (mg). In addition, a percentage of the participants may receive a placebo substance instead. This initial dose is actually only 0.005-0.006% of the average amount of protein in a single peanut, 180-200 mg. After this initial dose, the amount is doubled every 30 minutes until either a maximum dosage is reached (around 50 mg) or the participant exhibits symptoms of an allergic response. During this phase especially, it is important for the conductors of the study to have epinephrine and other emergency equipment readily available in case there are any

serious reactions. Some participants experience such severe symptoms from the introduction of peanut proteins during the escalation phase that they cannot safely continue with the study (Moffat, 2014).

### **Build-up Phase**

On the day following the escalation period, the build-up phase begins. Each participant is given the highest amount they were able to tolerate the day before and their response is observed. The participant is then instructed to continue this daily dosage at home, usually with other food. At frequent intervals, typically every week or sometimes every other week, the participant returns to the clinical setting for escalation of the dosage. This phase may continue for months to a year, depending on how long it takes for the participant to reach set dosages. At first, the escalation is usually by 50-100%, then once the individual reaches a determined dose, the build-up rate is decreased. Often during this phase and occasionally during other phases, the participants or the parents of the participants are required to keep a diary recording observations of important details such as reactions, illnesses, missed dosages, and any other data that may be relevant (Varshney et al, 2011).

### **Maintenance Phase**

The build-up phase continues until the maintenance dose is reached. In one study, this amount was set at 4000 mg, but it is typically anywhere from 1800-4000 mg. At this point, the participant will ingest this amount every day for an extended period of time, ranging from a month to several years. During this phase, around 50% usually experience adverse effects to the peanut proteins (Varshney et al, 2011) (Moffat, 2014).

**Challenge Phase**

During the maintenance phase, a challenge test is delivered to determine whether the participant truly has become tolerant to the peanut allergens. The challenge test involves the delivery of increased amounts of peanut proteins over short increments of time. Over this timeframe, the total accumulated dosage adds up to the highest amount the participant has ever had, often around 5000 mg (Varshney et al, 2011).

**Avoidance Phase**

An avoidance phase is sometimes incorporated into immunotherapy. During this phase, the participant discontinues all daily doses of peanut protein. After about two to three months of avoiding the allergen completely, the participant receives another oral challenge to reassess their sensitization. Typically over half of the study participants are able to tolerate this delayed dosage, but research has shown that the longer the avoidance phase lasts, the more likely the participant is to experience a reaction when he consumes peanuts again (Moffat, 2014).

**Types of Immunotherapy & Correlating Studies**

There are several different types of peanut immunotherapy that have been studied. Some have been more successful than others in terms of participant safety and positive outcomes. The different routes that have been attempted include subcutaneous, oral, sublingual, and epicutaneous. Along with exclusive peanut immunotherapy, a few other treatments or methods have been combined to explore the effectiveness of different methods. These methods include the use of a peanut vaccine and adjuvants such as anti-IgE (Anagnostou & Clark, 2014).



**Subcutaneous Immunotherapy**

The subcutaneous route of peanut immunotherapy was first attempted on a small scale in a study that took place in 1992. Unfortunately, this study resulted in a high rate of systemic reactions; 13.3% of the participants. Also, as a result of a pharmaceutical error, one participant who had been receiving placebo dosages was accidentally given a maintenance dose of peanut protein and ended up with fatal anaphylaxis. Besides these cases, three of the participants of this study showed a significant reduction in allergic symptoms. A second study utilizing subcutaneous therapy was conducted on 12 adult patients. Some of the participants experienced an increased in their threshold for peanuts, but just as in the earlier study, a high rate of systemic reactions was present. For this reason, despite potential benefits, subcutaneous immunotherapy has been determined to be an unsafe method at present for the experimental treatment of peanut allergies (Anagnostou & Clark, 2014).

**Oral Immunotherapy**

Oral immunotherapy (OIT), unlike subcutaneous immunotherapy, has been shown to be a safer method of conducting trials for those with peanut allergies. The rate of systemic reactions, compared to that of subcutaneous therapy, is much lower. In addition, more beneficial and promising results have been found. A study of children in the United Kingdom resulted in 86% of the participants developing tolerance to the small amount that might be ingested accidentally. The reactions in this study were mild and did not require the use of epinephrine. In the United States, a similar study was performed with a similar outcome. Although epinephrine was required on six occasions, the end result was

that 93% of the children could tolerate 3.9 grams of peanut protein (equal to about 19-20 peanuts). Subsequent studies have shown a tolerance rate of 84%. Based on these and other studies, oral immunotherapy appears to be a safe and effective method of conducting research. The majority of recent studies have utilized oral methods with substantial success (Anagnostou & Clark, 2014).

The first double blind, placebo-controlled study of oral peanut immunotherapy was published in 2011. The study consisted of 28 peanut-hypersensitive children, aged one to 16 years. Nineteen of the children received peanut flour in whatever food they chose, while the other nine were given a similar placebo administration. The starting dosage of the administrations was 0.1 mg. Early in the trial, three of the participants dropped out because they experienced side effects. The other 16 children, however, were able to complete the entire year of treatment and tolerate the final oral food challenge (OFC) of 5000 mg of peanut protein (Varshney, 2011).

Another double blind, placebo-controlled study was conducted by Blumchen et al. to evaluate the effectiveness of oral immunotherapy in 23 children ages 3-14 years old. The participants followed a rush protocol in the first week, then build-up and maintenance phases were implemented. Due to various factors, such as reactions, that prevented further experimentation and personal adherence to the required regimen, only 14 of the original 23 participants ended up able tolerate the final maintenance dose of 500mg or more of whole peanut. During the rush period, one participant dropped out of the study due to anxiety concerning the initial reaction that had occurred during the beginning OFC confirming peanut allergies. The other 22 participants received an

average of 14 servings of peanuts during the rush protocol week. The goal was for the patients to be able to tolerate 500mg of peanut protein after undergoing the therapy.

However, only five children met this goal at the end of the rush protocol (Blumchen et al., 2010).

A notable difference in IgE levels in the two groups was found, with an average of 212 kU<sub>A</sub>/L in the less tolerant group and 9.1 kU<sub>A</sub>/L in the group able to tolerate 500mg. While the less tolerant received a tolerable daily maintenance dose, the others underwent a long term buildup protocol. In all, 14 participants reached the 500mg daily goal. The eight who did not reach the goal discontinued therapy for various reasons: four experienced allergic reactions preventing them from continuing, one experienced subjective allergic symptoms, and the other three dropped out for non-allergic reasons. Thus, a protective dose was reached by 61% of the original group. After two subsequent weeks of peanut avoidance, the children still showed an increased tolerance as compared to their baseline before the study. Eight children were even able to tolerate a dose higher than their maintenance amount. The study concluded that oral immunotherapy as a long term buildup protocol seems to be safe and effective. Conversely, rush protocol was noted to be minimally effective unless the participant had low levels of IgE. In addition, the rush protocol was associated with a higher number of adverse reactions (Blumchen et al., 2010).

Syed et al. conducted a study in 2014 to explore in more detail how oral immunotherapy works on a cellular level, since the exact mechanisms by which immunotherapy induces desensitization are not known. Specifically, this group examined

changes that occurred in T cells, basophils, and antibodies. Two groups were selected to be observed and compared. One group was undergoing oral immunotherapy, while the other group was following traditional abstinence from peanut proteins. The study found no significant differences in the amount of basophils and antibodies in each group.

However, an improvement in T cell function in the oral immunotherapy participants was noted, as evidenced specifically by the hypomethylation of a protein in Treg cells called forkhead box protein 3 (FOXP3). This was the first state to prove that in addition to being increased as a result of tolerance, aiTreg cells are also “functionally suppressive” (p. 508). Interestingly, “aiTreg cells, despite being in relatively small numbers compared with other immune cell subsets, have been shown to be associated with natural loss of food allergy (Syed et al., 2014).

### **Sublingual Immunotherapy**

Sublingual immunotherapy (SLIT) is another route that appears to be somewhat effective and yet still seems to be safe for routine studying. In 2011, a study was done on 19 hypersensitive participants using the sublingual route to deliver peanut proteins. This study resulted in the control group being able to consume 1710 mg of peanut protein, while the placebo group could only safely consume 86 mg. Another study resulted in 85% clinical desensitization to an average of 496 mg of peanut protein. Excluding oropharyngeal symptoms, 94.7% of the participants were symptom-free, demonstrating a high safety profile. When compared with oral immunotherapy, however, sublingual immunotherapy requires the use of lower allergen doses and thus has not been shown to be as effective as oral immunotherapy. In addition, less research involving sublingual

immunotherapy has been performed, so more trials need to be conducted in order to determine its potential (Anagnostou & Clark, 2014).

In 2012, another study using sublingual immunotherapy was conducted using double-blind, randomized methods with a placebo control group. For the cohort group, only volunteers aged 18-40 years were allowed to participate. Twenty weeks after the start of the cohort group, younger individuals, aged 12 to 18 were permitted to join the study. Each participant underwent several verification processes to confirm their allergy, including a physician's diagnosis, significant reaction to skin prick titration test or detectable IgE proteins specific to peanuts, and a positive baseline double-blind, placebo-controlled food challenge (DBPCFC). Subjects were excluded if they had a history of severe anaphylaxis, intubation, or another serious medical condition. Half of the 40 participants were randomly chosen to receive a sublingual form of peanuts, while the other half received a placebo. The peanut preparation was made by extracting from the allergenic portion of unroasted peanuts and combining it with "0.5% sodium chloride and 0.54% sodium bicarbonate at a pH of 6.8 to 8.4 as aqueous extracts in 50% glycerin" (Fleischer et al., 2012, p. 127). The placebo was a simple mixture of phenol with caramel coloring and glycerinated saline (Fleischer et al., 2012).

The escalation phase began with administration of a dose containing only 0.000165 micrograms ( $\mu\text{g}$ ) of peanut protein. Every two weeks, three equal dosages were given at least 30 minutes apart and then the participant was instructed to maintain the same dose at home until the next escalation. If a participant failed the 3-dose administration three times (two weeks apart), then a 1- or 2-dose administration was

allowed. Escalation continued until a dose of 660  $\mu$ g was reached. At this point, single doses were given, then two weeks of maintenance therapy was provided (Fleischer et al., 2012).

During the maintenance phase, a daily dose of peanut protein ranging from 650-1386  $\mu$ g or a 420 mL dose of placebo was given until the 44<sup>th</sup> week. At this point, an unblinding DBPCFC of 5g transpired. After the participants had undergone unblinding and approximately one year of maintenance, they received a 10g OFC. Responders were determined based on alterations in the level of IgE and IgG4, responses to another skin prick test, and activation of basophils. In the group receiving peanut SLIT, 14 out of 20 were considered responders, compared with 3 out of 20 in the control group. The average successfully-consumed dose (SCD) was 371mg at Week 44, an increased from 21mg at baseline. On the other hand, the placebo subjects had a baseline average of 71mg and a SCD of just 146 at 44 weeks. After 44 weeks, however, there was no significant difference between the average SCDs of the two groups (Fleischer et al., 2012).

Also at 44 weeks, 17 members of the control group crossed over to receive a peanut OFC. Eighty-eight percent were able to withstand the maximum dose of 3696mg. Fifteen subjects underwent another OFC at 68 weeks. Three subjects were able to consume 5g of peanut powder and two subjects could consume 10 g. The median SCD increased from week 44 to 996 mg. The researchers concluded that a majority of participants who undergo peanut SLIT safely experience a level of desensitization. However, more studies are needed to determine whether peanut SLIT can be used therapeutically (Fleischer et al., 2012).

**Epicutaneous Immunotherapy**

Epicutaneous immunotherapy (EPIT) is the newest route of desensitization being tested. This method is based on the avoidance of highly vascular areas which quickly create a systemic immune response. Instead, a patch is placed to “[target] professional allergen presenting cells (Langerhans cells of the epidermis) necessary for optimal allergen presentation” (Anagnostou & Clark, 2014, p. 3). The first study involving epicutaneous immunotherapy was done in a group of children with allergies to cow’s milk. The study appeared to be well-tolerated and no systemic reactions occurred. A similar trial of 4-25 year-olds with peanut allergies is currently in progress. This study began in September 2013 and is expected to reach completion in March 2016 (NIAID, 2015) (Anagnostou & Clark, 2014).

**Peanut Vaccine Therapy**

In 2013, a study was conducted to research the effects of a newly-developed peanut vaccine in allergic adults. The vaccine consisted of several modified peanut proteins that were then encapsulated in heat/phenol killed *E. coli*. This vaccine was given in a rectal administration called EMP-123 to a group of 10 allergic adults and five healthy adults. Five of the allergic participants were unable to complete the study because the reactions they sustained were too severe to continue. Of the other five, one had mild symptoms and four had no reaction. The conclusion of the study was that significant modifications, including possibly a change in administration route, need to be made before any other trials can be performed using this peanut vaccine (Wood et al, 2013).

**Anti-IgE Therapy**

Another method under trial is the use of an adjuvant to improve immunotherapy results. Leung et al. conducted a randomized, double-blind, dose-ranging trial in 84 allergic participants. Some received a placebo, while the others were given an anti-IgE molecule called TNX-901. The treatment phase lasted just four weeks, with doses being given once a week. The results showed an increase in peanut reactivity threshold when 450mg of anti-IgE was concurrently administered. One limitation the researchers found was that anti-IgE treatment is expensive when used long-term. To purchase one 150mg vial of Omalizumab at a local pharmacy costs over 900 dollars. Depending on factors such as length of treatment course, dosage and frequency of administration, and insurance coverage, this could be an unaffordable long-term option for many families (GoodRx, n.d.). In addition, details such as the administration timeframe needed to produce long-lasting desensitization still need to be explored (Anagnostou & Clark, 2014).

Another study using anti-IgE in the form of Omalizumab as an adjuvant to OIT was done by Schneider et al. in 2013. All 13 subjects were able to tolerate 4g of peanut protein at the end of the therapy. As a result, the researchers believe that “Omalizumab may facilitate rapid oral desensitisation in peanut allergic patients with high peanut specific IgE levels at baseline” (Anagnostou & Clark, 2014, p. 3).

**Peanut Proteins & Probiotic Therapy**

Another type of adjuvant therapy currently being studied is the use of probiotic therapy as an adjuvant to peanut immunotherapy. The results of one such study were revealed earlier this year. Sixty-two participants were given a daily dose of the probiotic



*Lactobacillus rhamnosus* in addition to undergoing a fixed schedule of build-up immunotherapy. In order for seven children to remain unresponsive to peanuts after two weeks, nine children needed to be treated. Thus, over 80% of the children who participated showed tolerance to peanut intake at the end of the study. It was concluded that the use of probiotic and peanut OIT is associated with decreased skin prick test reaction and IgE levels. However, a greater number of adverse reactions was reported, particularly during the maintenance phase. Further studies are needed to determine the long-term effectiveness of combined therapy (Tang et al., 2015).

Many other studies utilizing probiotics have been done, but the majority of these studies are done on mice. One study found that, “Oral administration of recombinant *Bacillus subtilis* spores expressing CTB-Arah2 protected against peanut induced anaphylaxis” (Zhou et al., 2015, p. AB29). There are many different probiotics that need to be tested. Further testing, particularly more on human subjects, still needs to be conducted to evaluate the effectiveness of probiotics combined with immunotherapy.

### **Study Evaluation Methods**

The success of each study is determined by several different factors. Factors such as the type and severity of participants’ reactions must be considered. Before the immunotherapy treatment is initiated, baseline levels of immunoglobulin E, basophils, and other relevant substances are typically measured. At certain times during the study, these levels may be taken again to evaluate the current desensitization status. When the study is complete, a final measurement will be taken to see what influence the therapy had on the immune system and its response to the higher doses of peanut protein. One of

the most important factors considered is how many milligrams of peanut protein the individuals were able to tolerate. Most of the studies resulted in the participants being able to tolerate at least 1000mg, even up to 10,000 mg in one case.

### **Positive Outcomes of Immunotherapy Treatment**

#### **Reduction in Allergic Reaction**

In all of the studies aforementioned, at least some of the participants experienced a successful reduction in their reaction to peanut consumption. This reduction was more significant and more permanent in some than others. At the very least, the immunotherapy treatment helps decrease allergic reactions with accidental consumption of peanuts. Even if participants have to ingest a certain amount of peanuts per day, this is more satisfactory than if they had not undergone immunotherapy. More studies need to be done and correlating factors to success examined, but the positive results of immunotherapy are substantial.

### **Adverse Effects and Limitations of Immunotherapy**

#### **Risks of Participation**

While peanut immunotherapy and related experimental treatments for peanut allergies have demonstrated substantial success and show significant potential, there are still many drawbacks to implementation – from minor reactions to major events, including fatalities.

*Anaphylaxis or allergic reaction.* The obvious major drawbacks currently faced by peanut immunotherapy is the risk of allergic reaction involved in participation. Many parents of those with peanut allergies understandably do not want place their child in

danger for the sake of science. To avoid negative results as much as possible, many precautions are taken during these studies. One such precaution has already been examined – the ready supply of epinephrine and other emergency medical equipment in case a participant becomes unable to tolerate a dosage. Another precaution involves the early phase of selecting research participants. Typically those with a history of severe anaphylaxis are excluded from participation in the study, since “[o]ther oral and GI side effects, wheezing, worsening asthma, anaphylaxis have been shown to worsen or evolve in some patients” (Moffat, 2014, para. 8).

*Worsened symptoms of allergic reaction and other conditions.* In addition to the risk of anaphylaxis occurrence, there is a chance that subsequent reactions after completion of the study may involve worsened symptoms, placing the individual at greater risk. Also, the treatment may exacerbate previous comorbidities such as asthma. Asthma tends to be common in children with peanut allergies; thus, many immunotherapy participants must have their asthma monitored and taken into account in the study findings. Because asthma increases the risk of adverse respiratory effects with peanut exposure, many studies eliminate any potential participants who have severe asthma. As Thyagarajan et al. (2010) notes, “The selection criterion for these protocols excludes individuals with a history of anaphylaxis with hypotension, which may represent many patients seeking this treatment in the clinical setting” (p. 32). In the study performed by Blumchen et al. (2010), the four participants who were unable to continue the study due to adverse effects all had been identified as having mild to moderate asthma before beginning the study.

A 2014 study evaluated the factors associated with increased adverse reactions in 104 children receiving peanut OIT. It was shown that children who have a history of asthma, allergic rhinitis, and larger skin prick tests are at a higher risk of experiencing adverse reactions. This information could be useful in screening high-risk participants for future studies (Virkud, Vickery, Steele, Kulis, & Burks, (2015).

*Eosinophilic esophagitis.* Also at risk of worsening are gastrointestinal side effects. In particular, a disorder known as eosinophilic esophagitis (EoE) has been a recurring side effect noted in those who have been desensitized to peanuts through oral immunotherapy. Eosinophilic esophagitis is “a disorder of the food tube characterized by marked infiltration of a particular type of WBC (eosinophil) that can lead to pain, narrowing and chronic inflammation” (Moffat, 2014, para. 8). An obvious correlation between oral immunotherapy and EoE has been found, since EoE occurs in 10% of patients who receive OIT, while only 0.0001% of the general population develops EoE (Moffat, 2014).

### **Not a ‘Cure’**

While studies have yielded encouraging results, peanut immunotherapy has not yet reached the point of providing a complete cure for those with allergies. It is true that many subjects have become desensitized to a certain amount of peanuts, but in some cases, a reaction still occurs if the amount the person is exposed to exceeds the amount the study desensitized them to or if they have gone a significant amount of time after the study without ingesting peanuts. For many, in order for desensitization to be maintained, they must continually consume a few peanuts or the equivalent amount of protein

recommended every day. While desensitization is a positive and desired result of immunotherapy whether a daily dose is continued or not, the ultimate goal of researchers would be to induce tolerance of peanuts in these participants. Unfortunately, very few individuals have actually demonstrated complete tolerance as a result of immunotherapy. Varshney (2011) briefly describes the difference between antigen desensitization and tolerance:

We use the term desensitization to signify a change in the amount of food antigen needed to cause allergic symptoms; this state is dependent on regular antigen exposure. In contrast, tolerance refers to long-term immunologic changes associated with the ability to ingest a food without symptoms and without ongoing therapy. (p. 8)

Moffat (2014) reiterates this point by noting that, “Outcomes studies seem to indicate that peanut OIT does not lead to cure, and continuous exposure to peanuts is likely needed to sustain desensitization” (para. 8). Additional studies have shown that although peanut-allergic children are able to become desensitized by consumption of small amounts of peanuts, this tolerance sometimes disappears. Thus, immunotherapy cannot yet be labeled as a cure for peanut allergies (Rettner 2015).

Desensitization may not always continue, depending on the amount of peanut protein the patient is exposed to and how long it has been since he ingested any. However, some participants may mistakenly believe that they have been cured after undergoing immunotherapy, causing an issue with false sense of security. These clients may neglect to always have epi-pen with them or forget to keep taking the required

maintenance dose because think will never have anaphylactic reaction again due to desensitization. Appropriate education of the participants and family members is necessary to correct this mindset (Thyagarajan, 2010).

### **Ethical Dilemmas Facing Physicians and Researchers**

One of the main drawbacks to performing immunotherapy studies is the potential of causing anaphylaxis in participants. Some researchers have pointed out that the risks involved conflict with the medical provider's Hippocratic obligation to "do no harm" (Thyagarajan et al., 2010, p. 31). These same authors believe that because of the risks associated with immunotherapy, those with peanut allergies should continue to practice strict avoidance. Thyagarajan et al. (2010) states:

With current forms of OIT, as with other forms of immunotherapy, up to 18% of patients undergoing treatment will not be able to endure the associated side effects. In addition, accidental ingestions do pose a threat, with events occurring in about 15% of children with peanut and tree nut allergy over a 4-year period. The major issue to address is whether the likelihood of patients experiencing accidental food reactions over a given period is more or less than the percentage of patients who cannot tolerate OIT. (p. 31)

On the other hand, some argue that, "Many more deaths have resulted from accidental exposure" than from immunotherapy and the psychological implications associated with avoidance should not be ignored (Wasserman et al., 2011, p. 290). This side believes that to do nothing for these clients would cause greater harm; "although OIT is not without risk, it is a potentially life-altering treatment. Fully informed patients and

parents should be free to choose the management approach that is best for themselves and their families” (Wasserman et al., 2011, p. 290).

### **Future Research & Expectations**

Before immunotherapy can be utilized as a reliable treatment for peanut allergies, many more studies need to be performed in order to gain increased evidence of the treatment’s effectiveness. Larger randomized studies will help provide a more accurate picture of the benefits, drawbacks, and corresponding risk factors. The specific factors that need to be examined include treatment methods, participant demographics, and other details. Regarding treatment, further research is needed to determine the best route of administration; the most effective preparation of peanut protein along with any adjuvant medications; and appropriate dosage amounts and administration schedules. Selection of study participants should include an assessment of related factors such as the age of the children and severity of their allergy. Factors such as a high susceptibility to anaphylaxis; sickness or menstruation during the therapy; incorrect timing of therapy administration; excessive exertion following administration; and conditions such as asthma all have been shown to cause an increased susceptibility to anaphylaxis. The majority of these researchers agree that, while immunotherapy has potential, it is still “not ready for clinical use” and significant advancements must be reached before it is a truly safe and effective treatment modality (Thyagarajan et al., 2010, p. 31).

Anagnostou (2015) gives a brief overview of immunotherapy’s current progress and areas needing further investigation:

Larger studies are needed to further improve safety and efficacy of this form of

treatment. Patients will need to balance the frequent reactions occurring during immunotherapy, with the risk of severe reactions due to accidental ingestion and the possibility of successful desensitization, by the end of treatment. Long-term tolerance following immunotherapy is still an area that requires further investigation. Trials are also underway using immunotherapy by different routes such as epicutaneous and sublingual. Other treatment options are also under investigation such as the use of adjuvants (anti-IgE) in combination with OIT. (p. 71)

Another area currently under research that relates to the treatment of peanut allergies is the correlation of genetics and genomics to allergy incidence. A study by Hong et al. (2015) identified a loci specific to peanut allergy at 6p21.32, found in the HLA-DR and -DQ gene region of 2197 study participants. It is believed that these gene regions correlate to a high genetic risk of peanut allergy development (Hong et al., 2015). This was “the first genome-wide association study (GWAS) that identified a genetic link to well-defined peanut allergy” (para. 4). An interesting facet of these study results is that although 20 percent of the study participants possess this susceptibility, not all of them develop an allergy. Thus, “By identifying what environmental factors can alter DNA methylation levels in people with genes that make them susceptible to peanut allergy, researchers could potentially open a new avenue for prevention and treatment of peanut allergy” (Johns\_Hopkins Bloomberg School of Public Health, 2015, para. 10).



### **Conclusion**

Of all the treatment types under research for peanut allergies, oral immunotherapy appears to be the most successful method. Varshney (2011) states, “Further investigation of this promising intervention will address outstanding issues and continue to refine therapeutic protocols in hopes of offering an allergen-specific treatment option for food allergy” (p. 8). The field of immunotherapy is quickly growing and changing in an attempt to find a safe and successful means of treatment. As knowledge of peanut allergy epidemiology increases and merges with expanding knowledge gained from clinical trials, the ultimate goal of decreasing peanut allergy prevalence comes closer to attainment.

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