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Early introduction of peanuts to infants for elongated prevention of peanut allergies

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Thesis

EARLY INTRODUCTION OF PEANUTS TO INFANTS FOR ELONGATED PREVENTION OF PEANUT ALLERGIES

by

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EARLY INTRODUCTION OF PEANUTS TO INFANTS FOR ELONGATED PREVENTION OF PEANUT ALLERGIES

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ABSTRACT

Peanut allergies have become more popular in the United States especially among young children. It is not uncommon to hear about peanut allergies in classrooms, at birthday parties and in hospitals. Research shows that early introduction of peanut protein to an infants' diet can help prevent the development of peanut allergies until age 60 months. This study aims to track pediatric participants until age 20 to determine if the early introduction of peanut protein is effective in elongated protection from developing peanut allergies. The study will begin by surveying participants from a previous study about if they have developed a peanut allergy since the previous study concluded. Participants will then be separated into 3 groups based on their peanut protein eating habits. The participants will be tested each year for a peanut allergy until their 20th year of life. At the end of 20 years, the data will be collected and analyzed by a statistician to determine if there is a significant difference in the development of food allergies between the 3 different groups.

If there is a significance between the three groups, it has the potential to help in preventing peanut allergies going forward. Applying the conclusion from this study could significantly decrease the number of peanut allergies in the population and has the potential to be used with other allergens as well. There is often confusion among parents as to the best method to help protect their child from developing allergies. The study can

serve as a guide to providers for educating parents early on in an infant's life to introduce them to peanut protein early.

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LIST OF ABBREVIATIONS

BU	Boston University
EAT	Enquiring About Tolerance
EIG	Early Introduction Group
FA	Food Allergy
LEAP	Learning Early About Peanut
PA	Peanut Allergy
SIG	Standard Introduction Group
SPT	Skin Prick Test

CHAPTER ONE

Introduction

Background

Food allergies (FA), and peanut allergies (PA) in particular, have increased in prevalence in the western world between 1% and 2%. This is in contrast to Asian countries where, because peanuts are such a common part of their diet, the prevalence is so low that it is not on their list of top allergens.[1] Food restrictions are much more common at birthday parties, in classrooms or in restaurants as compared to as early as 20 years ago. Although awareness of these allergies has also increased, and what is done to accommodate them has improved, understanding what should be done to avoid them in the first place remains a mystery.

The debate includes whether to introduce allergens early in a babies' life, whether to introduce them orally or through skin, and which individuals need different protocols for introduction if they are at an increased risk of developing allergies. It is also a mystery as to how long these individuals are protected from their peanut allergies. While allergies are much more common to develop during childhood, around 11% of adults have some food allergy.[2] The prevalence of food allergies is between 1%-10% depending on the country. In the United States specifically, from 1997 to 2011 the prevalence of all food allergies has increased from 3.4% to 5.1% of the total population.[3]

The top eight allergens in the world in order of commonality are milk, eggs, fish, shellfish, tree nuts, peanuts, wheat and soy. Anaphylactic reactions to these allergens are responsible for 150 deaths per year in the United States and, while death is relatively

uncommon, food allergies cause a great physical, financial and psychological burden to those who have them and their loved ones.[4] This data is often measured retrospectively and the majority occur outside of the hospital so it can be difficult to collect accurate data.[5]

The reason peanut allergies are so important to focus on is due to the fact that peanuts allergies are responsible for the majority of deaths related to anaphylactic reactions in the United States and Germany.[5] This potentially deadly reaction can not only cause fear in the patient and their family but can also result in high costs for the healthcare system or the patient.

The gold standard for treatment of anaphylactic reactions is .15mg or .30mg of epinephrine intramuscularly usually via prefilled autoinjector. These are prescribed to patients to be used outside of the hospital in an emergency situation or used while the patient is in the hospital. Depending on which auto-injector is used, the price for each of these can range from $800-$5,000+ U.S dollars. Sometimes more than one dose is necessary to deter the effects of the immune response which only adds to the healthcare cost burden associated with peanut allergies.[6]

Statement of the Problem

Although there is evidence that earlier introduction of peanuts helps to prevent insensitivity to the food proteins, the existing studies fail to examine the lifelong effects of exposure. It is clear that the immune system changes over the course of human life. Adults are able to develop food allergies as well as children.[1] Thus, studies that conclude follow up at age 6 fail to provide evidence as to the lifelong effects of early

exposure. While the literature focuses on high-risk individuals with early exposure as compared to avoidance, it fails to compare high risk to normal risk in a lifelong comparison.

Hypothesis

Early introduction of peanut protein, at aged 6 months until 60 months at a steady regimented amount, will help prevent sensitivity until age 20 years among high risk and normal risk individuals.

Objectives

The ultimate goal of this study is to investigate the lifelong protection of early intervention of peanut protein. There is a severe lack of evidence on how individuals can avoid contracting allergies later in life and intervening as infants. While there are a few hypotheses regarding a sterile gut, overly clean living environment, or exposure to peanuts, it is unclear how long these can last. To eliminate food allergies for life, clear evidence that early inventions are protective is required. Specifically this study aims to:

1. Follow up with "LEAP-On" study subjects to determine their current peanut consumption habits
2. Separate these subjects into 3 categories;
    a. Consumption of peanut protein always (greater than or equal to three times per week)
    b. Consumption of peanut protein sometimes (less than 3 times per week)

c. Consumption of peanut protein never

3. Record allergy prevalence at the end of the subjects 20th year of life

CHAPTER TWO

Review of Literature

Overview

In order to determine methods to prevent food allergies (FA) from occurring, it is important to understand the mechanism of food allergies and what happens to the body when introduced to an otherwise normal food item it considers dangerous. Essentially, the immune system mistakes normal, non-harmful foods such as peanuts as pathogenic and requiring an immune response.

There is an increase in gut absorption of allergens in those with FA ultimately leading to a more intense immune response.[7] IgE antibodies bound to mast cells react and bind with the proteins found in the allergens causing a cascade of chemicals such as histamine to be released. This IgE mediated response is responsible for common symptoms of allergic reaction such as oral pruritus, urticaria (generalized or contact), bronchospasm or diarrhea. These symptoms are most often acute after ingestion but may be delayed in some cases.

In contrast with those relatively minor symptoms, the more serious threat among those with FA are symptoms associated with anaphylaxis. Two symptoms that can often lead to anaphylactic shock and death of the patient are laryngeal oedema, which may lead to complete airway blockage, and severe hypotension leading to shock. There are other factors that contribute to FA and the symptoms associated with allergic reactions however, IgE antibodies are the only cause of histamine release from mast cells.[7] Refer to Figure 1 from Discovery Medicine associated with the Division of Allergy and Clinical

Immunology at the University of Colorado Denver is a visual representation of the process described above.

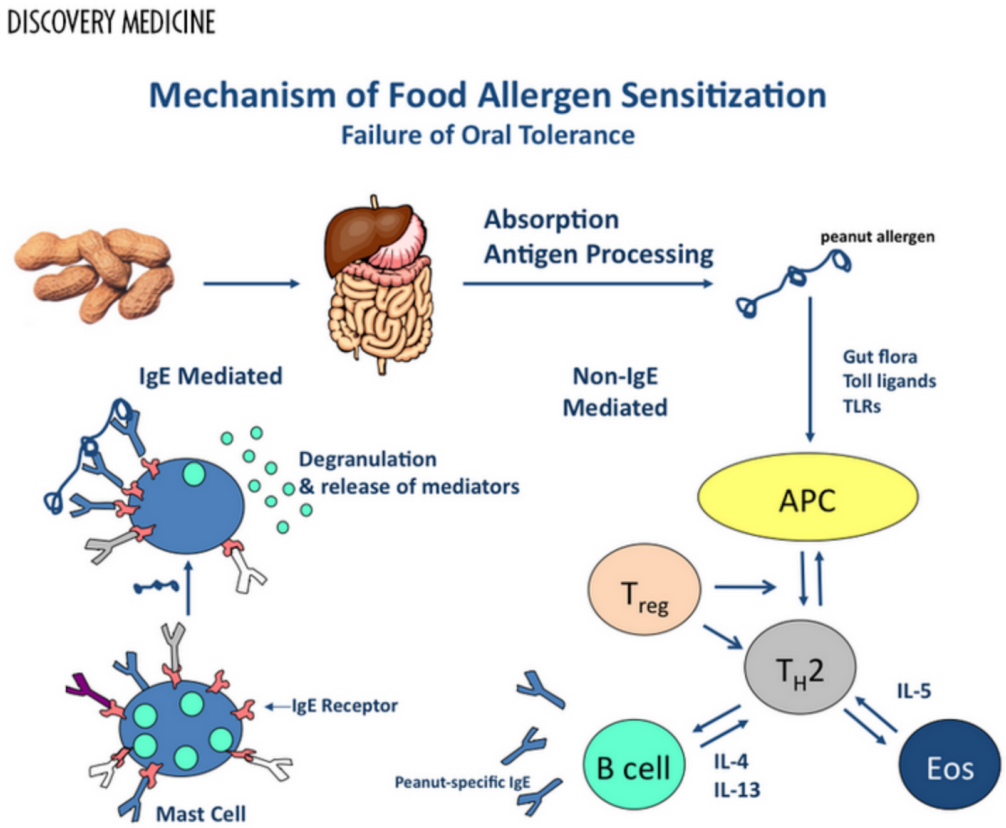

Figure 1. Mechanism of sensitization to peanut antigen through gut absorption: Once the allergen enters through the gut, it is presented to immune cells, specifically T-cells, which in turn communicate with B-cells to produce antibodies to this foreign protein. These IgE antibodies bind with high affinity to mast cells which release histamine causing an allergic reaction when bound to the original peanut allergen.[8]

There is no true therapy for peanut allergies (PA) other than complete avoidance of any peanut-containing foods. Unfortunately, this is often not easy and can lead to unintentional ingestion ultimately, causing the patient and their family a lot of anxiety, having to consistently read food labels and worry about their loved one's health.[7] While these allergies are manageable and there are many people living with this condition, it

can still be a heavy burden to bear for someone of any age. This is the reason why, for now, the ultimate goal is to prevent food allergies (FA), particularly deadly ones such as peanut allergies (PA).

There have been a few hypotheses as to the cause of food allergies (FA), most of which consist of exposure to different elements as an infant. One, the dual allergen hypothesis, states that infants who are exposed to peanuts through the skin, mostly through moisturizer with peanut oil, are at higher risk of intolerance than those who consume it orally.[9] Another possible scenario would be individuals who are raised in a sterile environment compared to those who have pets or older siblings. This is referred to as the hygiene hypothesis and includes infants who are not exposed to microorganisms or infections early in their life. Whether through older siblings, pets, or farm animals, there is data to suggest that infants with a more diverse gut flora have a lower incidence of food allergies.[7] The final suggested hypothesis is the vitamin D hypothesis comparing prevalence of allergies among those who have higher exposure to vitamin D with those with lower levels. Lower levels of vitamin D can predispose children to developing a food allergy. Populations of subjects who lived further from the equator had a higher prevalence of severe peanut allergies, epinephrine injector prescriptions and hospital admissions secondary to anaphylactic reactions.[7] There is little evidence to suggest this hypothesis and it is still being investigated however it could explain the higher rates of food allergies at higher latitude levels where there are lower levels of vitamin D in the population.[7] These three hypotheses are summarized in Figure 2 from the Journal of

Allergy and Clinical Immunology as a visual representation of how these potential desensitization methods work.

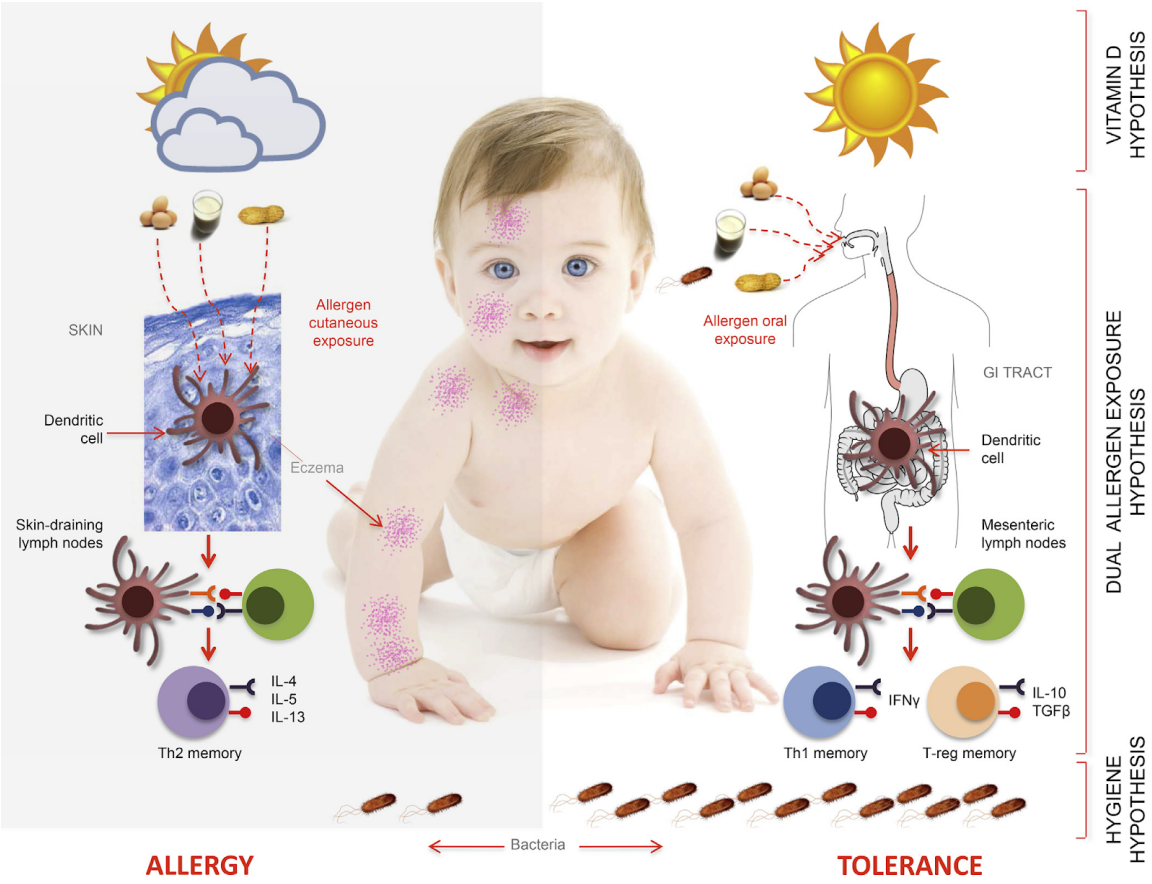

Figure 2. Three proposed hypotheses for risk factors in developing peanut allergies. This diagram summarizes the three different possibilities for how infants develop food allergies including the hygiene hypothesis, the dual allergen exposure hypothesis and the vitamin D hypothesis.[10]

It is important to examine the existing research that has been done on exposure to allergens early in life to determine the protective ability for the life of the patient. The literature has changed since the nineties and early two thousands due to the steep increase of allergies in the western world.

Existing research

The first study of importance to review is the Learning Early About Peanut Allergy (LEAP) study. For this study, the authors recruited 640 infants aged 4 months to 11 months with either severe eczema and or an egg allergy to either consume peanuts or avoid them until they reached 5 years of age. The purpose of this study was to determine whether high risk infants were more likely to develop a peanut allergy if they avoided peanut protein as compared to those who introduced peanut protein earlier in life. These groups were randomly assigned to the consumption and avoidance groups.

Subjects were tested before the study to determine any preexisting sensitivity to nuts by a skin prick test. Those who developed a 1-4mm wheal were considered positive for an allergy while those without a wheal were negative. There were 530 subjects in the intention-to-treat group who did not have a pre-existing sensitivity to peanuts.

In the consumption group, individuals were fed 6g of peanut protein per week, usually spread over the course of 3 different meals. This was performed each week until aged 60 months old. The majority of participants used a puffed corn snack with peanut butter as the source of the protein. Subjects were evaluated with skin prick tests at 12, 30 and 60 months. A positive result was recorded if the subject had a wheal size on their skin greater than 1mm.

The study found that 13.7% of those who avoided peanuts had a food allergy at the end of 5 years, whereas in the consumption group the prevalence was only 1.9% ($P<0.001$). This suggests that early introduction of peanut protein does help to desensitize infants and prevent food allergies early on in life. The ultimate conclusion of

this study was that at the end of 60 months, those who were in the consumption group had a significantly lower amount of peanut allergy versus those in the avoidance group.[9]

A strength of this study is the strict parameters for how the participants should consume the protein. It is easy to remember and makes introducing peanut protein simple for parents of subjects to feed their children. One area of weakness for this study is the opportunity for parents to feed their children as much or little protein as they want without the leaders of this study knowing. Obviously, this study assumes that parents are adhering to the guidelines they have set for participants. There is no way other than a parent admitting to a lack of adherence for the leaders of the study to know.

The parameters of consumption for peanut protein are easily applied to how individuals in the community can attempt to prevent food allergies in their children. The LEAP study creates an opportunity for providers to educate parents on how best to avoid peanut allergies by understanding when to introduce peanut protein. One area the LEAP study does not explore is the long term effects of early exposure passed childhood. This unexplored area is one aspect of peanut allergies that needs to be studied in more depth.

The next study to focus on is the Early Consumption of Peanuts in Infancy study which focuses on the eating habits of Jewish residents in the United Kingdom compared to Jewish residents in Israel. The participants in the study were 10,786 children in 24 schools in the United Kingdom and Israel. The school children were ages 4-18 and were given a survey about their dietary habits from when they were an infant up until their current age. Some of the questions from the survey included the child's age, sex, and allergies to allergens including peanuts.[11] Out of the nearly 11,000 children surveyed,

8,826 returned the surveys to this study. The surveys showed that there was a significant difference in the amount of peanut protein consumed monthly in Israel versus the United Kingdom. Israeli infants consumed 7.1g of peanut protein while United Kingdom infants consumed 0g ($p<.001$). The prevalence of peanut allergies among the students from the United kingdom was 1.85% and 0.17% in Israel ($p<.001$).[11]

This data clearly demonstrates that introducing peanuts earlier in the diet of an infant can lead to a decrease in prevalence of peanut allergies. One thing this study does very well is tracking its participants long term. Asking questions about their eating habits from infancy and following them up until age 18 provides a long term prevalence as compared to the LEAP study. What this study does not address is the possibility of other factors on food allergies such as cleanliness or vitamin D exposure. While these hypotheses are still under study, there has been some evidence that these other factors can cause peanut allergies. Additionally, focusing only on Jewish individuals from these two countries, it is difficult to apply this research to other religions and cultures around the world. This is a great start comparing two populations with similar, if not identical in some cases, religions and cultures, but it is important to expand this comparison to several different cultures.

There was a follow up study for the LEAP study called the LEAP-On study, which aimed to determine the lasting effects of early peanut consumption on peanut allergies. The subjects in the LEAP study were asked to avoid peanuts for 12 months, after the LEAP study concluded, and then reintroduce them when the subjects were six years old. They recruited 88.5% of the primary trial of participants (N=556). Avoidance

in this follow-up 12-month period was higher in the original avoidance group (90.4%) than the original consumption group (69.3%). There was a significant increase in the prevalence of peanut allergies in the avoidance group (18.6%) compared to the consumption group (4.8%; $p<0.001$).[12] That being said, in the avoidance group, the 12-month period did not directly result in a statistically significant increase in peanut allergy prevalence from 60 to 72 months (3.6% at 60 months versus 4.8% at 72 months, $p=0.25$).[12]

The conclusion of this study was that individuals who were introduced to peanut protein between the first year of their life and continued until age 5 were at decreased risk for developing an allergy by 6 years of age compared to those who avoided it. Another conclusion was an additional 12 months of avoidance was not associated with a significant increase in peanut allergies from 60 to 72 months.[12]

A strength of this study is that it aims to discover how avoidance and reintroduction of peanut protein will affect the prevalence of food allergies in a high risk population. It was an attempt to discover the long term effects of early introduction, however the study only followed participants for 12 months.

One hole that the LEAP-On study does not fill is a prolonged effect of early introduction versus avoidance on a high risk population. Some unanswered questions include whether or not subjects have continued desensitization from peanut protein? How long does this desensitization last? Does continued consumption maintain desensitization or does allergy development decrease after 72 months of age? This study aims to try and answer some of these questions.

Unfortunately, there is not a lot of other research on the topic of early introduction of peanut protein specifically. There have been studies done on eggs, soy and milk but the majority of these studies cite the LEAP study as a potential breakthrough for the eradication of peanut allergies in the future. The LEAP study has truly paved the way for other studies and has opened up many opportunities for other studies to start developing their own hypotheses.

CHAPTER THREE

METHODS

Study Design

This study will be a continuation of the LEAP-ON study consisting of as many of the study subjects as are able to be contacted. The overall goal is to determine the incidence of new food allergies among the subjects in each group up until age 20. It will be a longitudinal cohort study that is bidirectional. At first, the survey found in the **Appendix** is sent to the subjects from the LEAP-On study from the past 8 years and will follow the subjects until age 20.

Study population and sampling

Subjects in the LEAP study were recruited in 2006 making them about 14 years old in 2020. It will be difficult to recruit all of the subjects for this study however it is the goal to recruit as many as will respond.

From the beginning of the LEAP study to the LEAP-ON study, there was a change in participants from 640 to 556. From the beginning to the end of the LEAP-ON study, there was a change to 445. If the loss of about 10% from the LEAP to LEAP-ON study were to continue each year after the latter study concluded, about 102 participants could be recruited for this study. With the 3 different groups of this study, assuming an alpha of 0.05 and a power calculated to 0.8 and 2 degrees of freedom, the effect size would be 0.307.[13] This effect size corresponds to a moderate or medium effect for Cohen's W.[14]

Any subjects who have a diagnosed peanut allergy via scratch test or blood IgE antibody test will be surveyed to the best of their knowledge of their eating habits of peanut protein before their diagnosis. They will also be asked at what age the diagnosis occurred. These individuals will be placed in the appropriate groups depending on their consumption habits. Then their peanut allergy incidence will be tallied with the final result of the group at the end of the subject's 20th year.

These subjects are the ideal participants as they are at high risk for developing food allergies and, through monitoring their continued peanut consumption and knowledge of which group they were in during the LEAP study, we can determine who is at the highest risk of developing a peanut allergy.

Treatment (or intervention)

This study aims to avoid changing the current habits of the subjects as little as possible. If the subjects eat peanuts daily, the study wants to make sure that they continue as is the same for those who avoid peanuts. Subjects will be instructed to maintain their peanut consumption and avoid changing their eating habits. This differs from the LEAP intervention as we are not controlling the specific amount of peanut protein the subjects consume. Each year they will be tested via IgE antibody testing and scratch testing until they are 20 years old. The initial intervention was from the LEAP study regarding early introduction versus early avoidance. In this study, there are no additional interventions other than asking participants to maintain their current peanut intake habits.

Study variables and measures

The subjects once recruited will be separated into three groups. Those who avoid peanuts all together, those who consume peanuts sometimes (that is almost never to less than three times per week), and those who consume peanuts greater than or equal to three times per week. These three groups will be referred to as the Complete Avoidance Group (CAG), Minimal Consumption Group (MCG) and Common Consumption Group (CCG). If a participant changes their diet drastically from one group to another, this has the possibility of skewing the data and therefore, the subject will no longer be included in the study. While this may seem drastic, if they change their eating habits, it could result in an immune response or more tolerance to peanut protein. At the end of the study, we will measure the incidence of peanut allergies in the three different groups. Other than a yearly scratch test and IgE blood test, the subjects will ultimately be left to go about their lives with little interference.

The initial intervention from the leap study will be important to consider once data is collected from these subjects. Once the data from this study is collected and analyzed, it will be compared to the 2 groups of the LEAP studies' data.

Recruitment

Recruitment of participants will require contacting the LEAP study participants. The goal is to contact the individuals who ran the study in order to obtain the list of participants and their contact information. The subjects will be given a description of the study via email or phone if they prefer not to use email. Once they agree to participate in the study, subjects will be given the questionnaire above regarding their peanut protein consumption.

Data collection

Each participant will have an annual scratch test and blood test to determine if they have developed a peanut allergy. For all three groups, at the annual scratch and blood test performed by a clinician associated with this study, those with peanut allergies will be referred to an allergist and asked to avoid peanuts from that point on. They will not receive future scratch tests or blood tests for the rest of this study and any tests they have on their own after one positive test will not be included in this data collection. At the end of the study, when the subjects reach their 20th year of age, the data will be compiled in the three groups assigned at the start of the study.

Data analysis

Once they agree to participate in the study, subjects will be given an electronic form shown in the **"Study Design"** section which will be sent via email in a Word Document. If they do not have email, a paper copy can be mailed to their address. Participants will be asked to return this form within 2 weeks of receiving it and data collection can begin. The prevalence of peanut allergies at the end of the study, as well as the incidence of peanut allergies along the way will be calculated in the complete avoidance group, the minimal consumption group and the common consumption group. These values will then be compiled into a spreadsheet and a Chi squared test with 2 degrees of freedom will be run with the three different groups and the allergy prevalence in each. The goal is to find any significant difference between those who stopped eating peanuts, those who eat it sometimes and those who eat peanut products regularly.

Timeline and resources

Recruiting subjects would begin as soon as possible to make sure we have the largest sample size for this study as possible. If there were 10 individuals recruited to work for this study, each individual would have to make around 56 calls to reach all 556 potential subjects. If the work day was 9 hours per day and each call was a maximum of 1 hour, it would take 7 days for all 556 potential participants to be reached via telephone. If we give each subject a 2 week period to decide whether they want to participate in this study, that means that it would take a maximum of 21 days from when the calls began for the last subject to decide.

The study itself will last from 2020 until the subjects are 20 years of age which would be 2026. Data organization and analysis will begin on January 2 of 2027 to allow for all subjects in the study to turn 20. To compile the data of all the participants it will take 5 days with another 10 days allotted for data analysis. The time to begin this study until its conclusion will be a maximum of 6 years.

For each of these subjects, we need the questionnaire survey, as well as at least one scratch test kit per subject and materials for IgE antibody testing for each year until the subjects turn 20 years old. Additional tests may be necessary if there is lab error or user error when performing these tests on the subjects.

A skin prick test can cost a maximum of $300 while an IgE antibody test can cost a maximum of $1,000.[15] If we recruited all 556 individuals and tested them once a year until they were 20 years old the maximum cost for testing alone would be $4,336,800.

For the most part, there are not many other resources that are necessary to carry out this study. Besides the initial intake paperwork and calling to recruit subjects, there are not many more resources needed. If a subject were to have an allergic reaction, their insurance would be involved for the cost of healthcare. This study takes a laissez faire approach to the participants in order to have them consume peanuts as they would normally to their comfort level. This alleviates this study from responsibility if a subject has an adverse reaction to peanuts.

Institutional Review Board

This statement certifies an intent to perform research submitted for Full Board Review from the International Review Board. This study is performed on subjects who are under 18 years of age and therefore do not qualify for Exempt Review. Due to a moderate risk of severe harm or death while in this study if subjects have a severe allergic reaction, this study does not qualify for Expedited Review. This study does not introduce any potentially dangerous interventions unlike previous studies such as the LEAP study; however, due to this increased risk as subjects continue eating peanut products for a life threatening reaction, Full Board Review is required.

CHAPTER FOUR

Conclusion

Discussion

The biggest strength to this study is that it observes these pediatric patients until age 20 while not restricting their own preferences of what quantity of peanut protein they want to eat. The "intervention" in this case is merely encouraging them to continue their eating habits as they normally would as if they were not in this study. The biggest limitation this study presents is trying to contact the majority of participants of the LEAP-On study. It is possible that if they are reachable they may not want to participate in such an elongated study. Additionally, subjects may change their eating habits for other reasons such as health concerns, other food allergies, or social and cultural changes.

This study is strong in terms of generalizability in that the conclusion will help determine whether or not early introduction of peanut protein will have a preventive effect against the development of peanut allergies until age 20. This will provide evidence for providers to tell parents of infants to introduce peanut protein early in order to give the child the best chance at not developing a peanut allergy. Additionally, the study has the potential to influence other individuals to research other proteins such as wheat or eggs.

Summary

The aim of this study is to measure the incidence of peanut allergies from when the subjects are recruited until the end of study and the prevalence of peanut allergies at

the end of the study. The data between the three groups will be compared to see if continued peanut consumption can help prevent future allergy development or if there is no significant evidence of protection past 5 years old. This will be measured through skin prick tests and blood IgE tests as well as symptom monitoring.

This is a continuation of the LEAP study up until 20 years old. While previous studies have determined if infants can avoid developing a peanut allergy until age 5, it is important to continue this study long term. It is not enough to stop at age 5 and consider that timeline success of peanut allergy prevention. Long term study is important to track to make sure that high risk individuals, like those born with eczema or atopy can avoid deadly allergies beyond early childhood. In addition, surveying participants beyond age 5 and observing their peanut protein eating habits will help to determine if avoidance later in life can increase the risk of developing an allergy. This is in hopes of allowing future study of older adults to occur about the incidence of peanut allergies.

Clinical and/or public health significance

This study aims to help clarify if there is protection for those who consume peanuts more often than those who do not up until age 20. Food allergies are an enormous burden for children and young adults as well as their families. What this study can do for the public is provide evidence for continued protection from allergies and hopefully decrease the prevalence of food allergies in general. It is possible this study for peanut allergies can be applied to other common allergens, such as dairy or wheat products. There is so little known about how to cure food allergies and, thus, this study can provide preliminary evidence on methods as to how they can be prevented.

APPENDIX

1. Have you ever been diagnosed with a peanut allergy via scratch test or blood test resulting in any of the following symptoms: Yes/No
    a. Anaphylaxis
    b. Difficulty breathing
    c. Hives
    d. Rash
    e. Stomach Upset/ Heartburn
    f. Vomiting
    g. Diarrhea
2. Do you consume peanuts or peanut containing products (such as but not limited to peanuts, peanut butter, peanut containing candy, protein bars, granola or peanut containing pastries? Yes/No
3. How often do you consume peanut containing products?
    h. Almost daily
    i. More than three times per week
    j. Between one and three times per week
    k. Less than once a week
    l. Almost never
    m. Complete avoidance
4. If you answered “Complete avoidance” to the above question please specify why?

_____

_____

5. Do you feel comfortable maintaining the current amount of peanut protein in your diet? Yes/No

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CURRICULUM VITAE