STATE OF MINNESOTA

OFFICE OF THE ATTORNEY GENERAL

MIKE HATCH
ATTORNEY GENERAL

102 STATE CAPITOL
ST. PAUL, MN 55155-1002
TELEPHONE: (651) 296-6196

3128 '01 JAN -8 10:42

December 13, 2000

Commissioner Jane Henney
U.S. Food and Drug Administration
5600 Fishers Lane
PKLN 1471, Room HF-1
Rockville, MD 20857

Re: Multistate Citizen Petition for Rules Regarding the Labeling and Manufacture of Foods Containing Allergenic Substances

Dear Commissioner Henney:

I urge you to exercise the FDA's authority to protect the public health by promulgating the modest yet important regulatory reforms requested in the May 26, 2000 Petition for Rules Regarding the Labeling and Manufacture of Foods Containing Allergenic Substances. The proposal represents an important step toward reducing the risk of injury and death to the approximately 5 million American consumers, including children, who suffer from food allergies.

The proposal focuses on those food substances that are related to 90% of all food allergies: milk, eggs, fish, crustacea, mollusks, tree nuts, wheat, peanuts and soybeans. The proposal will allow citizens to know what foods contain an allergenic substance by: (1) requiring food manufacturers to clearly disclose on a product's label that the food contains one of these substances, and by including a simple symbol, the circled letter "A," to be displayed in the upper right hand corner of the product package; (2) allowing consumers to obtain accurate information about product ingredients from food manufacturers, by requiring food manufacturers to include on the labels of foods containing allergenic substances a toll-free number where consumers can obtain information about ingredients in the food; (3) requiring disclosure on food labels when allergenic substances are present even in amounts currently designated as "insignificant levels" and requiring disclosure of such substances when used as flavoring in the food products; and (4) requiring as part of food manufacturers' good manufacturing practices the adoption of reasonable measures to ensure that these substances do not adulterate food through cross-contamination, which occurs when such allergenic substances migrate to food from adjacent or shared equipment or facilities used in food processing or packaging.

Approximately 40-50 million Americans have allergies of some kind. (Exhibit 1.) An estimated 4 million American consumers suffer from food allergies. A disproportionate number of American citizens afflicted with food allergies are children. (Exhibit 4.) Although 1-2% of adults suffer from food allergies, among children the figure is between 2 and 5%. (Exhibit 1.) Among very young children, those under three years old, the Journal of the American Medical

00-1382 C 6

00-7717

Association has documented food allergy rates as high as 6%. (Exhibit 3.) Allergies to peanuts and crustacea often last a lifetime. (Exhibit 1.) That fact is especially disturbing considering the widespread use of peanuts in the preparation of many foods. (Exhibit 4.)

The medical consequences of food allergies are serious, especially for children. The onset of an allergic reaction is typically sudden, striking children with little warning. (Exhibit 2.) The most common symptoms of food allergies are hives, eczema vomiting, nausea, stomach cramps, indigestion, and diarrhea. (Exhibit 1.)

It is estimated that approximately 125 Americans die every year from food related anaphylactic reactions.

The most effective treatment for food allergies is to avoid eating allergenic substances. Consumers suffering from food allergies cannot avoid such foods unless they know what is in the food they eat.

Warning labels on foods containing allergenic ingredients offer a major step toward reducing public harm caused by hidden ingredients. For example, approximately 3 million American consumers are allergic to peanuts and tree nuts, which are often included, without disclosure, as ingredients in a variety of foods such as candy, biscuits, pastry, chili and egg rolls. The proposal requires that manufacturers clearly disclose on food labels if natural flavors used in the food product are derived from allergenic substances, by simply identifying the substances by their common names rather than, under present regulations, allowing them to be hidden within the more generic term, "natural flavor." Additionally, manufacturers would not be allowed, as is the case under current regulations, to omit disclosure of "incidental additives" found at "insignificant levels" with respect to allergenic substances. It has been demonstrated that such substances can cause severe allergic responses even when the person ingests small amounts of the substance. A 1997 FDA analysis concluded that if a food substance can cause an allergic reaction, then there is no such thing as "an insignificant level" of that substance. (Exhibit 2.) In fact, according to the FDA, "as little as one-fifth to one-five thousandth of a teaspoonful of an offending food has caused death from anaphylactic shock." (Exhibit 2.)

By allowing the millions of American consumers afflicted with food allergies to purchase safe foods, the FDA will clearly advance the public health interests of the American public.

Very truly yours,

MIKE HATCH
Attorney General
State of Minnesota

Enclosures

cc: Assistant Attorney General David Woodward

MAH/agk
AG: 436661,v. 01

ACAAI Homepage

About ACAAI

Bulletins

Information for:
Patients
Physicians
Employers
News Media

About Food Allergies

While an estimated 40 to 50 million Americans have allergies, only one to two percent of all adults are allergic to foods or food additives. Eight percent of children under age six have adverse reactions to ingested foods; only two to five percent have confirmed food allergies. The following information addresses commonly asked questions regarding food allergy.

What are symptoms of food allergy?
Allergic reactions to foods typically begin within minutes to a few hours after eating the offending food. The frequency and severity of symptoms vary widely from one person to another. Mildly allergic persons may only suffer a runny nose with sneezing, while highly allergic persons may experience severe and life-threatening reactions, such as asthma or swelling of the tongue, lips or throat.

The most common symptoms of food allergy involve the skin and intestines. Skin rashes include hives and eczema. Intestinal symptoms typically include vomiting, nausea, stomach cramps, indigestion and diarrhea. Other symptoms can be asthma, with cough or wheezing; rhinitis, often including itchy, stuffy, runny nose and sneezing; and rarely, anaphylaxis, a severe allergic reaction that may be life threatening.

Because these symptoms can be caused by a number of different diseases other than food allergy, your allergist-immunologist may want to examine you to rule them out as the source of your problem.

What causes my symptoms?
A food allergy is the result of your body's immune system over-reacting to food proteins called allergens. Normally, your immune system and defense mechanisms keep you healthy by fighting off infections and inactivating proteins such as food allergens, which could potentially, cause allergic reactions. Therefore, the majority of people develop a tolerance to a wide variety of different foods in their diet.

In the individual with food allergy, the immune system produces increased amounts of immunoglobulin E antibody, or IgE. When these antibodies battle with food allergens, histamine and other chemicals are released as part of the body's immune reaction to these substances. These chemicals can cause blood vessels to widen, smooth muscles to contract and affected skin areas to become red, itchy and swollen. These IgE antibodies can be found in different body tissues - skin, intestines, and lungs - where specific allergy symptoms such as hives, vomiting, diarrhea and wheezing are observed.

Not all adverse reactions to foods are due to allergy. Some reactions to cow's milk, for example, are related to a deficiency of an enzyme (lactase) that normally breaks down a sugar in milk (lactose). When individuals with lactase deficiency drink cows milk or eat other dairy products, they may experience intestinal symptoms including stomach cramping, gas and diarrhea. This is sometimes misinterpreted as a food allergy.

Why me? Why have I developed food allergy?
Heredity seems to be the prime reason some people have allergies and others don't. If both your parents have allergies, you have approximately a 75 percent chance of being allergic. If one parent is allergic, or you have

EXHIBIT
1

relatives on one side with allergies, you have a 30 to 40 percent chance of developing some form of allergy. If neither parent has apparent allergy, the chance is 10 to 15 percent.

Although food allergy occurs most often in infants and children, it can appear at any age and can be caused by foods that had been previously eaten without any problems. Finally, excessive exposure to a particular food may affect the overall rate of allergy to that food, as testified to by the high prevalence of fish allergy among Scandinavians and of rice allergy among the Japanese.

Which foods are most likely to cause allergy?
Eggs, cows milk, peanuts, soy, wheat, tree nuts, fish and shellfish are the most common foods causing allergic reactions, but almost any food has the potential to trigger an allergy. Foods most likely to cause anaphylaxis are peanuts, tree nuts and shellfish.

Keep in mind that, if you are allergic to a particular food, you might be allergic to related foods. For example, a person allergic to walnuts may also be allergic to pecans and persons allergic to shrimp may not tolerate crab and lobster. Likewise, a person allergic to peanuts may not tolerate one or two other members of the legume family such as soy, peas or certain beans. Clinical research of individuals with food allergy, however, has demonstrated that the overwhelming majority of patients with food allergy are only allergic to one or two different foods. Complete restriction of all foods in one botanical family based on an allergy to one of its members is rarely necessary. Discuss these issues with your allergist.

How do allergists determine which foods make me sick?
Some people know exactly what food causes their allergic symptoms. They eat peanuts or a peanut-containing product and immediately break out with hives. Other individuals need their allergist's help in determining the "culprit", especially when the specific food cannot be identified or when the symptoms show up many hours after ingesting an offending food.

Your allergist-immunologist will typically begin by taking a comprehensive medical history. Specifically, you'll be asked about the symptoms you experience following the food ingestion, how long after the food ingestion they occurred, how much of the offending food was ingested, how often the reaction has occurred and what type of medical treatment, if any, was required. Moreover, you will be asked about your overall diet, your family's medical history and your home environment.

These questions are necessary because your allergist wants to eliminate the possibility that another problem or allergic condition may be causing or adding to your symptoms. For example, a patient's allergy to inhalant pollen such as ragweed may be related to allergic symptoms in the mouth and throat following the ingestion of certain melons, such as watermelon, cantaloupe or honeydew.

What is allergy testing?
You may be asked to undergo some allergy testing. Your allergist-immunologist may employ skin testing, in which a diluted amount of the appropriate food extract is placed on the skin and the skin is then lightly punctured. This procedure is safe and generally not painful. Within 15 to 20 minutes, a positive reaction typically appears as a raised bump surrounded by redness, similar to a mosquito bite, and indicates the presence of allergic, or IgE, antibodies to the particular food. In some cases, an allergy (IgE)

blood test can be used to provide similar information to that obtained by the skin test. The IgE blood test is generally more expensive than skin testing and the results are usually not available for one to two weeks.

If properly performed and interpreted, skin tests or IgE blood tests to foods are reliable and good screening tests for food allergy. However, it's entirely possible to test "allergic" to a food (by skin testing or IgE blood testing) and yeat have no symptoms when that food is eaten. Thus, confirmation requires appropriately designed oral challenge testing with each suspected food.

How do special diets help pinpoint the problem?
With the information gained from your history, physical exam and testing, your allergist may further narrow down the suspected foods by placing you on a special diet. If your symptoms occur only occasionally, the culprit is likely a food that is eaten infrequently. Your allergist-immunologist may ask you to keep a daily food diary listing all food and medication ingested, along with your symptoms for the day. By reviewing and comparing "good days" with "bad days", you and your allergist may be able to determine which food is causing your reaction.

If only one or two foods seem to be causing allergic reactions, it may be necessary for the patient to go on a food elimination diet. The suspect food must be completely eliminated in any form for a short time - one to two weeks. If the allergic symptoms subside during abstinence and flare up when the food is ingested again, the likelihood of identifying the problem food can be increased.

If several foods appear to cause problems and/or the diagnosis of food allergy is equivocal, your allergist may want to confirm the role of each suspected food by oral food challenge testing. Not all positive skin tests and/or IgE blood tests equal a definite food allergy. With this in mind, food challenges are the best way to determine whether or not a food allergy really exists.

During an oral food challenge test the patient will eat or drink small portions of a suspected food in gradually increasing portions over a given period of time, usually under a physician's supervision, to see if an allergic reaction occurs.

Once my allergy is identified, how is it treated?
Once the diagnosis of food allergy is confirmed, the most effective treatment is not eating the offending food in any form. Therefore, the patient must be vigilant in checking ingredient labels of food products and learning other names of identification of the responsible food or food additive to make sure it is not present. When you eat in a restaurant, you must be particularly vigilant and you should take emergency medicines with you if you have a history of servere reactions. Waiters (and sometimes the kitchen chef) are not always aware of the exact ingredients of each item on the restaurant's menu.

All patients with food allergies must make some changes in the foods they eat. Special food-allergy cookbooks, patient support groups and registered dietitians can provide valuable assistance regarding your diet. Your allergist can direct you to these resources.

What if I accidentally eat a food I'm allergic to?
Individuals with food allergy should have a clearly defined plan of action for handling situations in which they accidentally ingest a food allergen. Have a

list of symptoms and your doctor's instructions for treatment posted in a prominent place in your kitchen. Oral antihistamines can be very useful in treating many of the early symptoms of a mild allergic reaction to a food.

Persons with histories of severe reactions need to be instructed in when and how to give themselves a shot of epinephrine (adrenaline) in the event of a severe allergic reaction. This medication is available in easy-to-use injectable devices and should be carried by persons with histories of severe allergic reactions. You should be taken to the hospital or call 911 and arrange for follow-up medical care for a severe reaction. Bracelets or necklaces may be worn to quickly alert medical personnel or other caretakers about food allergies.

Will I ever be able to eat these foods again?

In some cases, particularly in children, strict adherence to an elimination diet appears to promote the process of outgrowing a food allergy. For example, the vast majority of patients with documented allergic reactions to eggs, cows milk and soy eventually become tolerant to these foods. Allergies to peanuts, tree nuts, fish and shellfish, however, typically last a lifetime and are not outgrown. Overall, approximately one-third of children and adults will eventually be free of their allergic reactions to foods after rigorously following appropriate diets free of the offending food allergens.

After you have eliminated foods responsible for allergic reactions for a period of at least six months, your allergist may recommend that you undergo an oral food challenge under observation to reassess your symptoms. If you have no reaction and can ingest a normally prepared portion of the food, you will be able to safely reintroduce this food into your diet. If any symptoms of an allergic reaction do occur, the dietary restriction will need to be continued.

If you have had a severe immediate-type allergic reaction to a certain food, such as an anaphylactic reaction to peanut, your allergist-immunologist may recommend that you never again eat this food and rarely would a food challenge be needed to confirm the history. Remember, in some very allergic persons a very small quantity of an allergenic food can produce a life-threatening reaction.

Patients who use caution and carefully follow an allergist's advice can bring food allergy under control. Please contact your allergist-immunologist with further questions and concerns about food allergy.

For more medical information, please contact an allergist in your area.

Send comments to ACAAI Executive Office
Revised January, 1999, March 1, 2000

The Risk of Peanuts

Food Allergies: No Trivial Health Matter

Beatrice Trum Hunter

Food allergies are more common than formerly, according to Steve L. Taylor, co-director of the Food Allergy Research and Resources Program at the University of Nebraska at Lincoln. The mechanisms behind food reactions are similar to those with hay fever, bee sting, or allergic reactions to pharmaceuticals. More consumers die yearly from food allergy-induced anaphylaxis than from bee stings, reports Anne Munoz-Furlong, of the Food Allergy Network. Just one bite of an offending food can induce a reaction. There is no known cure for food allergy. The best help is to avoid the offending food.

Normally, our bodies develop a tolerance to most foreign proteins. The body's immune system provides protection against foreign proteins (antigens), including those in food. But the bodies of people with food allergies mount an inappropriate immune response to these antigens, and generate immunoglobulin E (IgE) antibodies. These antibodies latch onto the antigen and to the surface of the immune system's mast and basophil cells. These cells then release "mediators," such as histamine, that lead to the symptoms of allergic reactions such as stuffy nose, breathing difficulty, and rash.

Two groups of genes have been identified as responsible for inducing the inappropriate immune response and overreaction, and confirm the innate sensitivity of some people to allergens. One gene codes for an amino acid chain that is involved with an IgE receptor. Some variants of this gene tend to make individuals susceptible to asthma and allergies. Another identified gene alters a receptor chain in some allergy-prone people. It is thought that this alteration affects the receptor's functioning. Although the change may be subtle, its effects can be profound.

Some food allergies are based on a different mechanism, which can be traced to reactions mediated by sensitized T lymphocytes in the gastrointestinal tract. This type of food allergy is not well understood, and is difficult to test.

Less commonly, some food allergies are induced by exercise, performed before or after eating a specific food.

Medical reports attribute 90% of food allergies to a list of the "big eight": milk, eggs, fish, crustacea (crabs, shrimp, and lobster), peanuts, tree nuts, soybeans, and wheat. The remaining 10% consist of 160 other foods.

If a person becomes sensitized, the amount of an allergen needed to incite adverse reactions can be exceedingly small. In 1997, Fred Shank, Director of Food Safety and Applied Nutrition at the Food and Drug Administration (FDA) reported that the agency determined that if something can cause an allergic reaction, there is no insignificant level. This point is well taken. A spatula, used to remove peanut-containing cookies from one pan, and then to remove non-peanut-containing cookies from another pan, can render the latter cookies hazardous to peanut-allergic individuals. Similar cross contaminations can occur with shared ice cream scoops, utensils, and machinery used with peanut- and non-peanut-containing products. The problem of peanut allergy deserves better recognition by health professionals and the general public.

A spatula, used to remove peanut-containing cookies from one pan and then to remove non-peanut-containing cookies from another pan, can render the latter cookies hazardous to peanut-allergic individuals.

Peanut Allergy. In the early 1990s, major allergy centers began to note a rise in peanut allergy. According to Professor Gary A. Bannon, of the Department of Biochemistry and Molecular Biology at the University of Arkansas for Medical Sciences at Little Rock, peanuts are responsible for "one of the most severe food allergies."

James D. Astwood, manager of Monsanto's Protein Characterization and Safety Center, reports that only a handful of peanut proteins—out of thousands of different proteins present—are allergenic. Although proteins usually are digested rapidly in the gastrointestinal tract, major food allergens such as those in peanuts, are indigestible. They remain in the gastrointestinal tract, causing

Mrs Hunter is food editor of CR.

EXHIBIT 2

How Extensive?

The extent of peanut allergy—or for that matter, any food allergy in the general population—is unknown. Estimates are uncertain and varied. Some allergens are lifetime; others may disappear. Real allergies, with discernible effects on the immune system as well as on other systems of the body, may be confused with intolerances and sensitivities that are non-immune system responses. Their mechanisms, as yet, are unclear.

Information about peanut-allergic individuals was collated in a United Kingdom questionnaire of 622 self-reported peanut-allergic subjects. Two-thirds of the group reported symptoms experienced on contact with peanuts. Ninety percent reported adverse reactions after eating less than one peanut; 50%, even after touching a peanut. For 93%, symptoms occurred in less than a half hour after exposure by ingestion, inhalation, or touching peanuts. The most severe symptoms experienced were collapse and cyanosis. Symptoms were experienced most frequently in adults. Peanut-allergic reactions were associated significantly with abdominal symptoms. Individuals with a history of asthma were more likely to develop severe reactions to peanut exposure. Due to extreme reactions, 13% required hospitalization. Sixty-five percent carried in some form adrenaline (epinephrine) with them. One-third of the group reported that with each episode their reactions were becoming more severe.

the body to mount an immune response.

As little as one milligram of exposure to a peanut allergen can provoke immune system responses in individuals who are peanut-allergic. A few well-documented medical cases demonstrate the problem:

• In December 1995, a 33 year-old woman with peanut sensitivity read the contents on the label of a container of split pea soup. Peanuts were not listed. She consumed part of the soup, and within minutes experienced severe systemic allergic reactions. At an emergency room in a hospital, she was treated with intravenous fluids, corticosteroids, and diphenhydramine. The woman had a lifetime history of peanut sensitivity. Her reactions were so intense that she developed welts on her face if her husband kissed her after he had eaten a peanut butter sandwich.

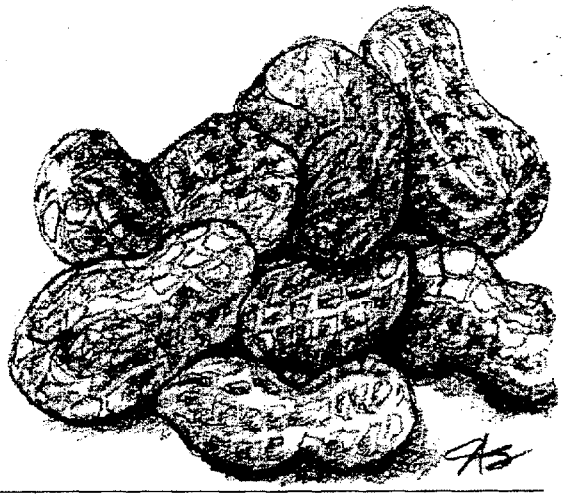
As follow-up after her hospitalization, the split pea soup was analyzed and found to contain peanut flour as a component of the "flavoring" ingredients, but not listed on the label. The soup manufacturer discontinued using peanut flour in the product. This case, and others, prompted the FDA to consider a requirement for declaring known allergens used in spices, flavorings, and colors added to food products.

• A young boy, highly allergic to peanuts, had been trained by his parents to read labels carefully and avoid peanut-containing products. A neighbor offered the boy some ice cream. They read the label ingredients on the package. Peanuts were not listed. The boy ate the ice cream, went into anaphylactic shock, and died. The product actually contained peanuts, but they were not listed.

• In 1986, a Providence, Rhode Island college student ate some restaurant chili, went into anaphylactic shock, and died. Unknown to her, the creative cook had added peanut butter to the chili. The young woman had been peanut-allergic. Subsequently, Rhode Island state health officials requested that restaurateurs list any "highly unusual ingredients" in dishes. Also, they encouraged patrons with allergies to question ingredients used in restaurant dishes. The city of Providence instituted a policy of requiring ambulances to carry adrenaline so that persons in anaphylactic shock can be treated promptly.

• Recently, peanut-allergic individuals traveling on airplanes have complained of experiencing allergic reactions to peanut protein released into the cabins when other passengers eat mid-flight peanut snacks. Allergic reactions can occur through inhalation as well as through consumption or skin contact.

The 1986 Air Carrier Access Act guarantees airline access to the disabled. Citing this Act, the



Anaphylaxis: A Violent Reaction

Anaphylaxis is a violent allergic reaction that involves a number of parts of the body simultaneously. Like less serious reactions, anaphylaxis occurs after a person is exposed to an allergen. However, in this case, the severe reaction occurs only after having had previous experiences with the same allergen.

According to the FDA, as little as one-fifth to one-five-thousandths of a teaspoonful of an offending food has caused death from anaphylactic shock. Peanuts have been implicated in numerous cases of anaphylaxis, and many have been fatal.

Anaphylaxis can produce severe symptoms within five to 15 minutes, although its life-threatening reactions may progress over a period of hours. Warning signs include itching; swelling of the lips, mouth, and throat; and difficulty in breathing. There may be a sense of impending doom, drop in blood pressure, and loss of consciousness.

The sooner anaphylaxis is treated, the greater the chance for survival. The person who is suffering from anaphylactic shock should be hospitalized immediately, even if the symptoms appear to be subsiding on their own without any intervention.

There is no specific test to predict the likelihood of anaphylaxis. Persons at greatest risk are those who have a history of gastrointestinal and respiratory symptoms, hives, or swellings immediately after eating an offending food.

The American Academy of Allergy and Immunology suggests that a person who has experienced anaphylaxis and fortunately survived should carry at all times injectable epinephrine (adrenaline) to treat any future reactions promptly, and to wear a Medic Alert bracelet that identifies the allergy(ies).

Epinephrine works directly on the cardiovascular and respiratory systems, causes rapid constriction of blood vessels, reverses throat swelling, relaxes lung muscles to improve breathing, and stimulates heartbeat.

For emergency home use, epinephrine is available in a traditional needle and syringe kit and provides two doses. Also, there is an automatic injector system, which resembles a pen. The person removes the safety cap and pushes the automatic injector tip against the outer thigh until the unit activates and provides a premeasured dose. The person holds the device in place for several seconds, and then discards it. These medications have expiration dates.

A Position Statement from the Allergy Section of the Canadian Paediatric Society reviewed the characteristics of children at risk for anaphylaxis. The parents and/or caregivers failed to appreciate the potential seriousness of the food allergies. Four of six fatalities occurred at school. Although a self-injected epinephrine device had been recommended for three of the six children, they were not carrying it with them when it was needed.

The incidence of fatal anaphylactic reactions to foods has been increasing yearly. Some causes are from the widespread use of protein additives in many commercially prepared foods; increased consumption of foods prepared by others who may be unaware of allergic problems created by their "creative" recipes; inadvertent food contamination; and undeclared ingredients on labels that may be present in the food products.

Due to the gravity of anaphylactic shock, parents of a peanut-allergic school child in the Detroit area of Michigan requested the school system to ban consumption of all peanut-containing products in schools, including home-prepared brown-bagged lunches (due to lunch swapping).

U.S. Department of Transportation (DOT) issued guidelines for major airlines to provide "buffer zones" to accommodate passengers who, in advance of the flight, present medical documentation of peanut allergy. However, the buffer zone extends only to the passenger's row and the rows immediately in front and in back of this row. Passengers in these three rows are not to be offered peanut snacks. Although DOT promised to comply with the "buffer zone," in the catch-all spending bill approved by Congress in October 1998, regulators were directed not to spend any funds to enforce the policy. In any case, this arrangement may be ineffective. A study, conducted in 1996 by the Mayo Clinic, showed that peanut allergens are not filtered efficiently out of the air by the airplanes' ventilation systems. The peanut dust is carried in the recirculated air.

To date, at least one airplane had to make an emergency landing because a peanut-allergic passenger reacted to the peanut dust released when other passengers opened peanut snack bags.

One airline has banned peanuts from being served on any flight after a peanut-allergic passen-

ger gives proper advance notice. Other airlines have substituted non-peanut snacks such as pretzels. (See, also, "A Nutty Solution?" CR, October 1998.)

Peanut-Allergic Children. Allergic reactions to peanuts have increased in the United States by 95% over a recent 10-year period. This rise parallels the common practice of offering the seemingly benign jelly-and-peanut butter sandwich to very young children.

This finding is worrisome. Unlike some food allergies, peanut allergy generally persists into the adult years. Peanut allergy is thought to be the leading cause of life-threatening anaphylaxis caused by food allergies. (See sidebar about anaphylaxis.)

In 1993-1994, at Addenbrooke's Allergy Clinic in Cambridge, England, peanuts were found to be the most common cause of allergy in 62 patients, ranging in age from 11 months to 53 years. Peanuts were responsible for all allergies in children sensitized by the age of three years. In many cases, a single allergy to peanut butter in very young children progressed to multiple allergies, including tree nuts, cat dander, pollen, and dust mites as the children grew older. The Addenbrooke staff advised that peanuts should not be given to children before the age of three years, and in cases where allergies were common in families, to hold off until seven years.

Dr. Hugh Samson, a renowned pediatric allergist at Johns Hopkins Medical School, also has been concerned about the increased numbers of children with peanut allergies. Samson advised breast-feeding mothers with family histories of allergies to eliminate peanuts and other potential food allergens from their diet.

Unlike some food allergies, peanut allergy generally persists into the adult years. Peanut allergy is thought to be the leading cause of life-threatening anaphylaxis caused by food allergies.

Samson's advice was repeated in 1998 by Chief Medical Officer Kenneth Calman of the United Kingdom, who warned pregnant women and breast-feeding mothers to avoid eating peanuts in order to prevent peanut allergy in their offspring. The warning was issued after receiving a report by the government's Committee on Toxicity, citing a rise in the number of British children who were peanut-allergic. Scientists had reported that about one in 200 people are peanut-allergic. Calman reported that the warning was precautionary and based on evidence that the developing fetus and the breast-fed infant, exposed to peanuts from the mother's diet, are at increased risk of developing peanut allergies. The warning extended to women whose partners had peanut allergies, as well as to pregnant women who had already given birth earlier to children with peanut allergies. The government estimated that the warning was applicable to about one in every three women of childbearing age.

The National Jewish Center for Immunology and Respiratory Medicine in Denver, Colorado, recently conducted a long-term follow-up of children previously found to have severe peanut allergies. Although all of the children had been instructed about the need for peanut avoidance, including information about the variety of disguises in which peanuts could appear, only one-fourth of the children succeeded in avoiding peanuts completely. The staff conducting the follow up was concerned about the frequency of accidental peanut ingestion, and none of the children demonstrated any evidence that they outgrew peanut reactivity.

Strategies by Food Manufacturers to Minimize Food Allergens. Increasingly, food manufacturers have become aware of the potential problems created by inadvertent introductions of allergenic ingredients in their products. Many manufacturers have extended the concept of HACCP (Hazard Analysis Critical Control Points), devised to improve food safety, to include allergenicity.

The Allergen Protection Plan, developed by scientists from the National Food Processing Association, General Mills, and Campbell Soup Company, was created in 1997 to identify potential areas of contamination and to build a preventive strategy similar to HACCP.

There is general consensus that trace amounts of peanut contamination are a major problem, and among the most difficult allergens to control. Raw materials may be intermingled by a supplier before being delivered to a food processing plant. Or, in a large factory where breakfast cereals are extruded, peanut dust released from a peanut-containing cereal being manufactured can contaminate a non-peanut-containing cereal being extruded in the same area. Sometimes, a simple printing error can result in mislabeling an entire production run.

Manufacturers have become aware of the need to mark clearly any allergenic ingredients, and to store them away from non-allergenic ones. "Reworked" products—a combination of batches produced at different times—should be in containers separated from others, and marked by distinguishing labels or color codes.

Major food processors have hot lines and/or

Bioengineered Hypoallergenic Peanuts?

The antibody—immunoglobulin E, or IgE—binding sites on the peanut proteins that cause allergenic responses were identified by Professor Gary A. Bannon and his colleagues at the University of Arkansas for Medical Science at Little Rock. They found where these sites occur in the folded molecule, and discovered that each of the IgE binding epitopes (the simplest form of a complex antigenic molecule) can be mutated to a non-IgE binding epitope by substituting a single amino acid in each binding site (see discussion on page 21).

This work could lead to the creation of hypoallergenic plants that contain functional but harmless versions of the allergenic proteins. To date, the group has been able to produce the gene capable of producing a hypoallergenic protein. The next step is to introduce the modified genes back into the plant, and inactivate the allergenic ones normally present in the plant, so that only the modified genes are expressed.

Scientists need to manipulate genes cautiously to avoid inadvertent introduction of troublesome ones into plants, according to James D. Astwood, manager of Monsanto's Protein Characterization and Safety Center. Astwood added, "imagine if you moved an allergen from peanuts into corn or into wheat. A peanut-allergic person knows how to avoid peanuts, but would [he] know to avoid wheat? The answer is no."

Astwood reported that Monsanto has made a "fairly substantial effort to evaluate these issues" for its bioengineered food products. "We don't want to create foods that increase the incidence of allergens." Astwood added that the company is interested, too, in "developing methods and models to predict the allergenic potential of new products."

The possibility of introducing allergens inadvertently into new foods created by bioengineering was raised at a food allergy conference at Annapolis, Maryland, in 1994. The question seemed to anticipate an incident two years later. In 1996, University of Nebraska researchers detected an allergenic protein in soybeans that had been altered genetically with proteins from Brazil nuts. The study showed that allergens can be transferred from one plant to another in bioengineering. Fortunately, the discovery was made before the modified soybean was released commercially. If it had been marketed, its allergenic potential would not have been declared on the label.

Scientists at the College of Agriculture and Environmental Sciences at the University of Georgia used another approach to reduce the allergenicity of peanut protein. They adjusted partially defatted peanut flour for moisture and pH value, and extruded it at different temperatures. At a high temperature, they succeeded in drastically reducing allergenicity. However, the resulting product was unsuitable for food use because of excessive protein breakdown.

toll-free numbers for consumer inquiries or complaints. Thomas Trautman of General Mills reported that allergy-related inquiries increased tenfold from 1988 to 1998. The Kellogg Company reported that hot-line requests for information about allergens tripled from 1991 to 1994. Other companies also report large increases of inquiries about allergens.

In 1998, General Mills and Hershey Food Corporation were honored by the Food Allergy Network in recognition of their outstanding commitment to making a difference in the lives of individuals with food allergies.

Food manufacturers recognize their responsibility to label products adequately to meet the needs of allergic consumers. The Grocery Manufacturers Association (GMA) agrees with the FDA that "proper labeling of foods that contain allergenic substances is a vitally important public health issue." GMA established a Food Allergy Task Force and reported that food manufacturers "understand the necessity and value of good manufacturing practices and strongly oppose the use of precautionary, or 'may contain' labeling of allergens in lieu of applying good manufacturing practices." However, even with good manufacturing practices, "certain manufacturing processes present the potential for 'cross contact' of ingredients from product to product, resulting in the potential presence of an undeclared allergen in a food product." GMA recommends that the FDA formulate a uniform method to state, in the simplest way possible, that allergens may be present in foods.

Some manufacturers use "prophylactic labeling," by including in the ingredient listing those substances that, unavoidably, may be present. An example is the declaration "may contain traces of peanuts due to manufacturing." Some groups oppose prophylactic labeling, and cite the Federal Food, Drug, and Cosmetic Act which provides

that the list of ingredients are those included, not those that might be in the product. However, this control is weakened by FDA's tolerance of the phrase "may contain..." for listing specific fats or oils that may or may not be present in a food product. (This policy was instituted to allow manufacturers to choose ingredients of the least cost with fluctuating market prices, before the time of increased awareness of the problem of allergenicity of undeclared ingredients.) It is argued that if this tolerance is extended to cover unintended but potential allergens, manufacturers may not follow quality control procedures that can reduce, if not eliminate, this problem.

Ultimately, if the phrase "may contain" is used extensively, consumers with allergies will find that their food choices are narrowed still further. Often, food allergies are multiple, and may not be only from peanuts, but may extend to other allergens, too.

Most often, allergen contamination in food plants is due to incomplete cleaning of equipment, failure to declare ingredients, use of reworked mixtures, and unknown ingredients in a raw material. For example, black pepper was adulterated with dry mustard and wheat germ. Another risk may be created when the research and development group of a company modifies a well-established product that previously had been allergen-free, or develops one product in a line of products that contains an allergen. Also, there are human errors, with mix-ups on labels or packaging.

At times, manufacturers may become aware of a problem and conduct a voluntary recall. At other times, the problem is caught by the FDA, a state agency, an inspector, or a consumer report. Recalls due to allergenic ingredients in food products have increased. In 1996, there were 35 Class 1 recalls (those most serious as imminent health threats) involving 57 products; in 1997, 35 recalls of 70 products; and in 1998, 58 recalls of 240 products.

The FDA has become more aggressive in recalling foods with allergenic components. A frequent focus is on ice cream containing undeclared peanuts.

Laboratory tests are available to food manufacturers to detect unwanted peanut protein in food products along the production line. Some tests detect levels down to one or two parts per million. This level is sufficient to provoke allergic reactions in highly allergic individuals. Also, negative findings do not guarantee that the food product is entirely free from peanut. Most of the tests are ELISA (enzyme-linked immunosorbent assays), and are known to have inherent shortcomings. They may be inaccurate, and are directed against only one specific allergen. Thus, such tests are not helpful to identify a multiplicity of allergens that may be in a food product. (Such tests are not intended for consumer use. In future, home kits may be available, but probably will not offer detection levels low enough to be useful for highly allergic individuals.)

Strategies With Data Banks to Minimize Food Allergens. In 1987, the United Kingdom Food Intolerance Data Bank was established cooperatively with the Leatherhead Food Research Association (LFRA), British Dietetic Association, and the Food and Drink Federation. Using detailed criteria, food manufacturers contributed data about their products to central collection at LFRA, to declare products "free from" specific additives or ingredients. The data were used to produce a series of shopping guides that detailed branded food products. Also, it was possible to create combination "free from" lists for people with multiple food allergies or sensitivities. However, if a manufacturer decides to reformulate a product, the list in circulation may no longer be valid.

By 1992, LFRA investigated the possibility to extend the data bank. A similar one existed in the Netherlands, known as ALBA, and supported by governmental research. LFRA, in consultation with Netherlands colleagues, interested communities to fund a network of food intolerance data banks across the European continent. The project, begun in 1993, by 1996 had partners in Austria, Belgium, France, Germany, Greece, Ireland, Denmark, Portugal, and Spain.

Greece was the first country to produce "free-from" booklets, followed by Austria launching an Austrian Food Intolerance Data Bank. Interest spread to New Zealand. South Africa published a "free-from" book in 1995, available in book stores. To date, the United States lags behind in these efforts.

Strategies by Organizations to Minimize Food Allergens. The Food Allergy Network* (FAN), established as a non-profit organization, provides educational materials for parents and children with food allergies, as well as for health professionals and educators. FAN issues newsletters and "Special Alert Notices" to members, which caution readers about hidden allergens in specific food products.

The National Institute of Allergy and Infectious Diseases**, a branch of the National Institutes of Health, publishes free materials about allergies, including food allergy resources, the immune system and how it works, and allergens. Some publications are intended for the general public; others, for health professionals. CR

* Food Allergy Network 4744 Holly Ave, Fairfax, VA 22030 (703) 691-3179 *www.foodallergy org.*

**Request a list of publications from NIAID Office of Communications, NIH Bldg. 31, Room 7A50, 31 Center Dr., MSC 2520, Bethesda, MD 20892-2520 *www.niaid.hih.gov.*

EXHIBIT 3

Title: Food allergy.
Database: Health Reference
Authors: Sampson, Hugh A.
From: *JAMA, The Journal of the American Medical Association* , Dec 10, 1997, v278, n22, p1888(7)

FOOD ALLERGY (food hypersensitivity) is a term applied to a group of disorders characterized by abnormal or exaggerated immunologic responses to specific food proteins that result in a variety of symptoms. For practical purposes, food allergy is generally subdivided into disorders mediated by IgE antibodies, which are generally of rapid onset, and those resulting from non-IgE-mediated mechanisms, which generally take hours (and possibly days) to become apparent. Food intolerance is a term used to describe an abnormal physiologic response to an ingested food or food additive. Such reactions are not immunologic in nature and may include abnormal metabolic (eg, lactase deficiency) or idiosyncratic responses of the host or unusual susceptibility to pharmacologic substances contained in some foods (eg, tyramine in aged cheese).[1] This review represents an update of the chapter appearing in the 1992 Primer[2] and includes new references gleaned from MEDLINE, Current Contents, and my own reference database.

PREVALENCE

Although surveys in both children and adults indicate that approximately 25% of the population believe they have a food allergy, the true prevalence is far less.[3,4] The prevalence of food allergy is greatest in the first few years of life, with up to 6% of children younger than 3 years experiencing food allergic reactions.[3] In 4 prospective studies with appropriately performed milk challenges, 2.2% to 2.8% of infants were found to have cow milk allergy in the first 1 to 2 years of life.[3,5-7] Children with atopic disease are more likely to have food allergies compared with the general population; about 30% of children with moderate to severe atopic dermatitis and 10% of children with asthma have been shown to have food allergies.[8,9] Adverse reactions to food additives also have been demonstrated in about 1% of children.[10] The prevalence of food allergy declines over the first decade of life. Using double-blind, placebo-controlled food challenges to substantiate reported reactions, epidemiologic studies suggest that the prevalence of food allergies in adults is about 1.5%[4,11] and adverse reactions to food additives about 0.1%.[12] Although there are no data available, the prevalence of food allergy in adults with atopic disorders also is probably increased compared with the general population.

PATHOPHYSIOLOGY

The allergenic components of foods are made up primarily of glycoproteins with molecular weights between 10 000 and 60 000. Most food allergens tend to be resistant to proteolysis and are heat stable. A number of food allergens have been extensively characterized (Table 10-1). These allergens have been fully sequenced and complementary DNAs isolated, cloned, and expressed in most cases. Closely related foods (legumes,[13] bony fish,[14] cereal grains[15]) frequently contain allergens that cross-react immunologically (ie, with skin prick tests or radioallergosorbent tests [RASTs])

but only rarely cross-react clinically. Cross-reactive allergens also have been reported between certain foods and airborne pollens; eg, melons and banana with ragweed pollen; celery, apple, and kiwi with mugwort pollen; and apple, carrot, hazelnut, and potato with birch pollen; and between foods and latex (eg, banana, kiwi, avocado, and chestnut with latex).[16] Recent work comparing complementary DNAs coding for major allergens in these foods and pollens have identified "conserved" homologous proteins that account for the cross-reactivity (eg, profilin [Bet v 2] in birch pollen, apple, and carrot). However, patients should not be assumed to be reactive to foods within similar food groupings unless reactivity is suggested by history and confirmed by oral food challenge.

Table 10-1.--Purified Antigens in Foods(*)

Approximate

Percentage

of Food Molecular

Protein Fraction Protein Weight

Cow milk

Caseins 76-86 19 000-24 000

Whey 14-24 ...

[Beta]-Lactoglobulin 7-12 36 000

[Alpha]-Lactalbumin 2-5 14 440

Chicken egg white

Gal d 1 11 28 000

(ovomucoid)

Gal d 2 54 45 000

(ovalbumin)

Gal d 3 12-13 77 700

(ovotransferrin)

Peanut

Ara h 1 ... 63 500

Ara h 2 ... 17 000

Ara h 3 ... 14 000

Soybean

Soybean trypsin ... 20 500

inhibitor

Gly m 1 ... 30 000

Fish

Gad c 1 ... 12 328

Shrimp

Antigen I ... 42 000

Antigen II ... 38 000

Pen a 1 ... 36 000

(*) Adapted from Sampson and Metcalfe.[2] Elipses indicate data not available.

The gastrointestinal (GI) tract uses both nonimmunologic and immunologic mechanisms to prevent intact foreign antigens from gaining access to the body while processing ingested food for energy and cell growth. Although more than 98% of ingested antigen is blocked by this GI barrier, minute amounts of intact food antigens are absorbed and transported throughout the body.[17-19] Increased stomach acidity and the presence of other food in the gut decrease antigen absorption, while decreased stomach acidity (eg, antacids) and ingestion of alcohol increase absorption.[17] Immunologically recognizable protein entering the circulation does not normally cause adverse reactions because most individuals develop tolerance to ingested food antigens. The means by which tolerance develops are not well understood, but the B-cell system appears to require larger amounts of oral antigen than the T-cell system to become tolerized.[20] There also appears to be a difference in the ease with which tolerance induction develops in T-cell subsets, with [T.sub.H]1-like cells outnumbering [T.sub.H]2-like cells which in turn outnumber B cells.[21] In general, immune tolerance may develop by clonal deletion, clonal energy, or active suppression.[22] In mice older than 4 days, a single antigen feeding leads to suppression of antigen-specific systemic IgM, IgG, and IgE antibody responses and cell-mediated immune responses. Processing of food antigens by the rodent gut to a "tolerogenic" form appears essential for the development of oral tolerance.[23] Several lines of evidence indicate that lymphoid cells in the GI tract are necessary for generating tolerogenic food proteins; severe combined immunodeficient mice (lacking B and T lymphocytes) are unable to generate tolerogenic ovalbumin, irradiation of mice abrogates their ability to form tolerogenic ovalbumin, and the infusion of normal spleen cells restores the ability of irradiated mice to generate tolerogenic protein.[24,25] Antigen-presenting cells (APCs) located in the reticuloendothelial system (RES) also appear to play a critical role in the development of oral tolerance since agents that activate the RES and enhance APC

activity interfere with generation of [CD8.sup.+] cells and the development of oral tolerance.[23] Recent studies in experimental allergic encephalomyelitis support the role of transforming growth factor [Beta]-secreting [CD8.sup.+] cells in tolerance induction.[26]

The increased susceptibility of young infants to food allergic reactions is believed to be the result of immunologic immaturity and, to some extent, immaturity of the gut. Consequently, in genetically predisposed infants, ingested antigens may stimulate excessive production of IgE antibodies or other abnormal immune responses. Several prospective studies suggest that exclusive breast-feeding may promote the development of oral tolerance and prevent some food allergy and atopic dermatitis in infants and young children.[27-30] This protective effect may be due to decreased exposure to foreign proteins, passive protection provided by breast milk secretory IgA, and/or soluble factors in breast milk that induce earlier maturation of the gut barrier and the infant's immune response. Introducing solid foods to an infant's diet after 4 months of age has been shown to prevent some food allergy and atopic dermatitis.

Low concentrations of detectable serum IgG, IgM, and IgA food-specific antibodies are found in normal individuals.[17,18] Individuals with inflammatory GI disorders (eg, celiac disease, food allergy, inflammatory bowel disease) frequently have high levels of food-specific IgG and IgM antibodies. However, these antibodies reflect dietary intake and are not specific for foods that will provoke symptoms. Several studies have demonstrated increased lymphocyte proliferation after food antigen stimulation in vitro in patients with food allergy, celiac disease, and inflammatory bowel disease. However, in vitro T-cell responses also are commonly found in normal individuals.[31] It is not clear whether these T-cell responses in vitro represent an immunopathogenic marker or simply reflect a response to increased antigen penetration of the GI tract.

In the susceptible host, a breakdown in the development of oral tolerance may result in a variety of hypersensitivity responses to an ingested food antigen. Although the Gell and Coombs classification of hypersensitivity reactions is traditionally used to describe allergic responses, food allergic disorders typically involve more than 1 mechanism.

Type I IgE-Mediated Reactions

Food-specific IgE antibodies bind high-affinity Fc[Epsilon]RI receptors on mast cells, basophils, macrophages, and dendritic cells as well as low-affinity Fc[Epsilon]RII receptors on macrophages, monocytes, lymphocytes, eosinophils, and platelets. When food allergens penetrate mucosal barriers and reach IgE antibodies bound to mast cells or basophils, mediators are released that induce symptoms of immediate hypersensitivity. Activated mast cells also may generate a variety of molecules (eg, cytokines such as interleukin 4 and tumor necrosis factor a, platelet-activating factor) that may induce the IgE-mediated late-phase response. During the late-phase response, eosinophils, lymphocytes, and monocytes are attracted to the site of reaction where they may release a variety of inflammatory mediators and cytokines. With repeated ingestion of a food allergen, mononuclear cells are stimulated to secrete "histamine-releasing factors," some of which interact with IgE molecules bound to the surface of basophils (and perhaps other Fc[Epsilon]R-bearing cells) to increase their releasibility.[32] The increased releasibility has been associated with skin and lung hyperactivity and increased symptoms. In addition, IgE antibodies bound to Langerhans cells (APCs) lead to more efficient capture of antigens and allergens at low eoneentration[33] and preferential activation of [T.sub.H]2-like cells,

which promotes allergic inflammatory reactions in atopic dermatitis, asthma, and some forms of GI hypersensitivities.[34]

Type II, III, and IV Reactions

Type II antigen-antibody dependent cytotoxic reactions have been implicated in a few reports of antibody-dependent thrombocytopenia secondary to the ingestion of cow milk.

Type III antigen-antibody complex-mediated hypersensitivity has been incriminated in some patients with a variety of subjective complaints and elevated serum food antigen-antibody complexes. However, several investigators have demonstrated food antigen-antibody complexes in the serum of normal individuals, as well as patients with suspected food hypersensitivity.

Type IV cell-mediated hypersensitivity has been implicated in food allergic disorders where the onset of clinical symptoms occurs several hours after the ingestion of a suspected food allergen, especially reactions in the GI tract. Evidence suggests that activation of food antigen-specific lymphocytes induces preferential "homing" of committed lymphocytes to specific target organs.[35] Peripheral blood mononuclear cells from children with atopic dermatitis and IgE-mediated milk hypersensitivity stimulated in vitro with casein resulted in proliferation of T cells bearing the cutaneous lymphocyte antigen (CLA), whereas no increase in [CLA.sup.+] cells was seen in milk-allergic children with asthma or GI allergy. While there is little evidence at present to support a specific pathogenic role for classic types II and III hypersensitivity in any food allergic disorders, IgE-mediated, cell-mediated, and combinations of IgE- and cell-mediated reactions appear to account for the majority of food allergic reactions.

CLINICAL MANIFESTATIONS OF FOOD HYPERSENSITIVITY

IgE-Mediated Mechanisms

IgE-mediated allergic reactions to foods present as a variety of clinical findings related to the site and extent of mast cell degranulation (Table 10-2). The signs and symptoms of an immediate reaction to food may occur within minutes to 2 hours of ingestion and may be limited to the oropharynx (itching or tingling of the lips, palate, tongue, or throat, swelling of the lips or tongue, sensation of tightness in the throat with hoarseness, dysphonia, and/or dry staccato cough) or GI tract (de, GI anaphylaxis manifested by nausea, colicky abdominal cramps, vomiting, and/or diarrhea). In other cases the spread of the antigen through the bloodstream leads to degranulation of mast cells in the skin (urticaria/angioedema and atopic dermatitis[36]); in the lungs (de, asthma manifested by chest tightness, wheezing, shortness of breath, and/or repetitive deep cough[37]); and in the nose and eyes (de, rhinoconjunctivitis manifested by ocular pruritus and tearing and nasal congestion, pruritus, rhinorrhea, and sneezing[38]). In the most severe cases, the cardiovascular system is also involved, leading to shock (systemic anaphylaxis).[39,40] This acute and potentially fatal reaction is now the leading single cause of anaphylaxis treated in hospital emergency departments.[41,42] Systemic anaphylaxis may present as itching and swelling of the lips and tongue and palate, itching and tightness in the throat with a dry staccato cough, wheezing and cyanosis, chest pain, urticaria/ angioedema, abdominal pain, vomiting, diarrhea, hypotension, and shock. Severe life-threatening reactions are most often associated with the ingestion of peanuts, nuts, fish, and shellfish.

Fatal reactions may progress rapidly or begin with mild symptoms, frequently not involving the skin, and then progress to cardiorespiratory arrest and shock over 1 to 3 hours.[40] Systemic anaphylaxis also has been reported only after ingestion of food followed by exercise.[43] In food-associated exercise-induced anaphylaxis, symptoms occur only when patients exercise within 2 to 4 hours of ingesting certain foods, and less frequently when patients ingest any food.[44]

Table 10-2.--Food Hypersensitivity Reactions

IgE mediated

Cutaneous: urticaria/angioedema, atopic dermatitis

Respiratory: rhinoconjunctivitis, asthma

Gastrointestinal: oral allergy syndrome,

gastrointestinal anaphylaxis, infantile colic

(subset), allergic eosinophilic gastroenteritis

(subset), infantile gastroesophageal reflux

(subset)

Generalized: systemic anaphylaxis, food-associated

or exercised-induced anaphylaxis

Non-IgE mediated

Cutaneous: dermatitis herpetiformis, contact

dermatitis

Respiratory: food-induced pulmonary

hemosiderosis

Gastrointestinal: food-induced enterocolitis

syndrome, food-induced proctocolitis syndrome,

food-induced enteropathy (celiac disease),

allergic eosinophilic gastroenteritis syndrome,

gastroesophageal reflux, dermatitis herpetiformis

Mechanism(s) unknown

Migraine headache

Cow milk-induced intestinal blood loss

The oral allergy syndrome is a common form of contact allergy almost exclusively confined to the oropharynx and most frequently seen in patients with seasonal allergic rhinitis due to conserved homologous proteins in some pollens and foods (eg, birch pollen, apple, and carrot, as noted above).[45] Symptoms are generally associated with the ingestion of various fresh fruits and vegetables (but not cooked foods) and include the rapid onset of pruritus and angioedema of the lips, tongue, palate, and throat, generally followed by a rapid resolution of symptoms. Diagnosis is based on a suggestive history, positive skin prick tests with the implicated fresh fruits or vegetables, and oral food challenge. Oropharyngeal symptoms may be a prelude to systemic symptoms of food allergy, including urticaria, GI symptoms, rhinitis, and anaphylactic shock and must be distinguished from the oral allergy syndrome.

IgE-mediated reactions to foods are a frequent cause of acute urticaria/angioedema, but rarely induce chronic urticaria.[46] They also may contribute to the pathogenesis of atopic dermatitis.[47] Historically, it is often difficult to associate specific food allergies with symptoms in atopic dermatitis, because many foods that provoke skin reactions during a double-blind challenge do not provoke obvious symptoms when patients consume them on a regular basis. Both food-specific IgE-mediated and cellular mechanisms appear to be responsible for chronic eczematous inflammation in about one third of children with atopic dermatitis.[35] Identification of food-induced symptoms requires demonstration of food-specific IgE antibodies (eg, skin prick tests) and clinical reaction in response to specific foods on oral challenge. Clinically, the avoidance of foods shown to induce a positive response on double-blind, placebo-controlled food challenges leads to substantial improvement in the disease.[48] Foods most commonly eliciting responses in children with atopic dermatitis include eggs, milk, peanut, soy, fish, and wheat. Once a specific food allergen has been avoided for 6 to 12 months and eczematous lesions have cleared, the readministration of these foods will often precipitate urticarial skin lesions rather than a morbilliform rash, which is seen during challenge procedures in the initial evaluation of active atopic dermatitis. About one third of children will "lose" their food hypersensitivity (except to peanuts, nuts, and seafood) after 1 to 3 years of an appropriate food elimination diet.

Non-IgE-Mediated Food Hypersensitivity

Gastrointestinal Food Hypersensitivity.--Signs and symptoms of the GI hypersensitivities (Table 10-2) overlap and often require invasive procedures, eg, endoscopy and biopsy, for appropriate differentiation. Food-induced enterocolitis syndrome generally presents in infants between 1 week and 3 months of age with protracted vomiting and diarrhea, which not infrequently results in dehydration.[49] Cow milk, soy protein, or both are most often responsible, but enterocolitis secondary to egg, wheat, rice, oat, peanut, nuts, chicken, turkey, and fish sensitivities also have been reported in older individuals. Similar, less severe reactions are reported in some adults to seafood (eg, shrimp, crab, lobster). Stool samples generally contain occult blood, polymorphonuclear neutrophils, and eosinophils.

Studies of IgE antibodies to the responsible food allergen are characteristically negative. Jejunal biopsy specimens classically reveal flattened villi, edema, and increased numbers of lymphocytes, eosinophils, and mast cells. Elimination of the responsible allergen generally leads to resolution of symptoms within 72 hours. Oral food challenges consist of administering up to 0.6 g/kg of body weight of the suspected protein allergen. Vomiting and diarrhea occurring within 1 to 6 hours constitute a positive challenge and may be accompanied by shock in 15% of cases. In positive responses, the absolute peripheral blood neutrophil count increases by at least 3.5x[10.sup.9]/L 4 to 6 hours after symptoms develop.

Food-induced proctocolitis also presents in the first few months of life and is generally secondary to cow milk or soy protein formulas, but about half of reported cases are now seen in breast-fed infants.[50] These infants commonly have normal-appearing stools, but proctocolitis is identified because of the presence of hematochezia (gross or occult) or, rarely, diarrhea. Lesions are confined to the distal large bowel. Hematochezia largely resolves within 72 hours of appropriate food allergen elimination, but the resolution of mucosal lesions may take up to 1 month. Reintroduction of the allergen (challenge dose of 0.6 g/kg of body weight) leads to resumption of symptoms within several hours to days. Sigmoidoscopic findings are variable but range from areas of patchy mucosal injection to severe friability with small aphthoid ulcerations and bleeding. Colonic biopsy specimens reveal a prominent eosinophilic infiltrate in the surface and crypt epithelia and the lamina propria. Food-induced proctocolitis often resolves after 6 months to 2 years of allergen avoidance.

Food-induced enteropathy is a malabsorption syndrome that (excluding celiac disease) presents in the first several months of life with diarrhea (frequently steatorrhea) and poor weight gain.[51] Symptoms include protracted diarrhea, vomiting, and failure to thrive. Increased fecal fat and abnormal D-xylose absorption are generally present. Cow milk sensitivity is the most frequent cause of this syndrome, but it also has been reported with sensitivity to soy egg, wheat, rice, chicken, and fish. Eliminating the responsible allergen from the diet results in gradual resolution of symptoms, but this may require several days to weeks. On endoscopy, a patchy villous atrophy is evident, and biopsy specimens reveal a prominent mononuclear round cell infiltrate of the epithelium and lamina propria with a small number of eosinophils, not unlike celiac disease but generally much less severe. Complete resolution of the intestinal lesions may require 6 to 18 months of allergen avoidance. Challenges may require several days to weeks before clinical symptoms become evident. Loss of reactivity is reported to occur, but the natural history of this disorder has not been well studied.

Celiac disease (gluten-sensitive enteropathy) is a more extensive enteropathy leading to malabsorption. Total villous atrophy and extensive cellular infiltrate are associated with sensitivity to gliadin, the alcohol-soluble portion of gluten found in wheat, oat, rye, and barley. Patients often present with diarrhea or frank steatorrhea, abdominal distention and flatulence, weight loss, and occasionally nausea and vomiting. Oral ulcers and other extraintestinal symptoms secondary to malabsorption are not uncommon. Approximately 90% of patients with celiac disease are HLA-B8 positive and nearly 80% have the HLA-DR17 antigen, supporting a genetic predisposition.[52] Diagnosis depends on demonstrating biopsy evidence of villous atrophy and inflammatory infiltrate, resolution of biopsy findings after 6 to 12 weeks of gluten elimination, and recurrence of biopsy changes following gluten challenge.[53] Quantitation of IgA antigliadin and IgA antiendomysial

antibodies are excellent screening tests for celiac disease, but diagnosis requires intestinal biopsy.[54] Once the diagnosis of celiac disease is established, lifelong elimination of gluten-containing foods is necessary to control symptoms and to avoid the increased risk of malignancy.

Allergic eosinophilic gastroenteritis is characterized by intolerance to multiple foods, eosinophilic infiltrates of the stomach and small intestines, peripheral eosinophilia, elevated IgE levels, and multiple food allergies due to IgE- or non-IgE-mediated mechanisms. In about 50% of adults with this disorder, the disease is believed to be the result of multiple food allergies that result in repeated degranulation of the mast cells within the GI mucosa. The prevalence of food-induced symptoms in children is unknown, but 42% of infants diagnosed as having infiltration of the esophagus with eosinophils and gastroesophageal reflux were found to be milk allergic.[55] The disorder presents as postprandial nausea and vomiting, gastroesophageal reflux, early satiety, and growth failure in children or weight loss in adults. Diagnosis is based on the demonstration of an infiltration of eosinophils in the GI wall, which may be sporadic and therefore requires multiple biopsy sites. Gastrointestinal biopsy specimens reveal a prominent eosinophilic infiltration of the lower esophagus, stomach or small intestinal mucosa, muscular layer, and/or serosa.[56,57] Most patients with food-induced symptoms have other signs of allergy, including asthma and allergic rhinitis. Foods potentially provoking symptoms may be suspected from history and skin testing or RASTs. Elimination of suspect foods for 6 to 12 weeks should lead to symptomatic resolution. Reintroduction of suspect food allergens should provoke recurrence of symptoms and eosinophilic infiltration in the GI wall on biopsy. In patients unresponsive to dietary elimination, periodic oral steroid treatment is generally required.

Other Non-IgE-Mediated Food Hypersensitivities.--Dermatitis herpetiformis is characterized by a chronic, intensely pruritic, papulovesicular rash symmetrically distributed over the extensor surfaces of the extremities and buttocks, and gluten-sensitive enteropathy in 85% of patients.[58] Deposits of IgA, neutrophils, and C3 accumulate in the dermoepidermal junction of both involved and uninvolved skin. The histology of the intestinal lesion is virtually identical to that seen in celiac disease, although generally milder and often clinically insignificant. The diagnosis of dermatitis herpetiformis depends on the presence of the characteristic skin lesions and the demonstration of IgA deposition in the skin. Elimination of gluten from the diet often leads to resolution of skin symptoms and normalization of intestinal findings over several months. Administration of sulfones, the mainstay of therapy, leads to rapid resolution of skin symptoms but has virtually no effect on intestinal symptoms.

Food-induced pulmonary hemosiderosis (Heiner syndrome) is a rare disorder characterized by recurrent episodes of pneumonia associated with pulmonary infiltrates, hemosiderosis, GI blood loss iron-deficiency anemia, and failure to thrive in infants.[59] Hemosiderin-laden macrophages may be found in morning aspirates of the stomach or seen in biopsy specimens of the lung. Although peripheral blood eosinophilia and multiple serum precipitins to cow milk (egg and pork also have been implicated) are a relatively constant feature, the immunologic mechanisms responsible for this disorder are not known. Resolution of symptoms on elimination of the implicated food from the diet is considered the hallmark of this disorder.

Exacerbation of arthritis has been established in a few cases associated with ingestion of a

specific food by double-blind, placebo-controlled food challenges.[30] Food intolerance has been associated with migraine headaches. A number of vasoactive substances within foods, including tyramine, phenylethylamine, ethanol, and caffeine, may precipitate migraine headaches. One double-blind, placebo-controlled study implicated food-induced symptoms in 15% of 104 adults with migraine headaches.[61] Although some studies have suggested an IgE-mediated mechanism, most studies have failed to link any obvious immunologic mechanisms with the provocation of food-induced migraines.

DIAGNOSING ADVERSE FOOD REACTIONS

Evaluation of patients with suspected adverse reactions to food involves a thorough history, physical examination, and diagnostic tests to eliminate other diseases in the differential diagnosis.[62] In obtaining the history, several points should be clarified to establish that a food allergic reaction occurred and to construct an appropriate blinded challenge at a later date: (1) the food presumed to have provoked the reaction, (2) the quantity of the suspected food ingested, (3) the length of time between ingestion and development of symptoms, (4) whether similar symptoms developed on other occasions when the food was eaten, (5) whether other factors (eg, exercise) are necessary, and (6) how long since the last reaction to the food occurred. Although any food may cause an allergic reaction, a few foods account for about 90% of reactions: in adults, these foods are peanuts, nuts, fish, and shellfish; and in children, egg, milk, peanuts, soy, and wheat.

Diet diaries are often used as an adjunct to history. Patients are instructed to keep a chronological record of all foods ingested over a specified period and record any symptoms experienced. The diary is then reviewed to determine whether there are any relationships between foods ingested and symptoms experienced. Occasionally this method detects an unrecognized association between a food and a patient's symptoms. As opposed to the medical history, it collects information on a prospective basis and is not as dependent on a patient's memory.

Elimination diets are used in both the diagnosis and the management of adverse food reactions. Foods suspected of provoking allergic disorders are completely eliminated from the diet. The success of these diets depends on the identification of the provoking allergen (s), the ability of the patient to maintain a diet completely free of all forms of the offending allergen, and the assumption that other factors do not provoke similar symptoms during the period of study, conditions that are difficult to fulfill. For example, in a young infant reacting to cow milk formula, resolution of symptoms following substitution of cow milk formula with a soy formula, casein hydrolysate, or amino acid derived formula is highly suggestive of cow milk allergy, but would be found in an infant with lactose intolerance. A beneficial outcome following the introduction of an elimination diet should not be considered diagnostic of food allergy, especially in chronic disorders such as atopic dermatitis, asthma, or various GI hypersensitivities.

There are no screening laboratory tests, such as an elevated serum IgE concentration or abnormal D-xylose absorption, that can differentiate food hypersensitivities from nonimmunologic disorders.[63] When the patient history suggests a food hypersensitivity disorder (Table 10-2), an IgE-mediated mechanism may be suspected in the presence of positive skin test results (prick or puncture techniques) or in vitro tests (eg, RAST), both of which simply establish the presence of IgE antibodies to specific foods. Overall, about 60% of positive skin prick test results do not reflect symptomatic food allergy (poor positive

predictive value). However, skin prick test results are rarely negative in patients with IgE-mediated allergic reactions (excellent negative predictive value). Intradermal skin testing is not recommended because of the even greater frequency of "false-positive" reactions and increased risk of systemic reactions. Food extracts are usually applied in a weight to volume concentration of 1 to 20 and evaluated in 10 to 20 minutes. Wheal diameters 3 mm greater than the negative control wheel are considered positive. In cases of the oral allergy syndrome, the "prick+prick"[64] technique with fresh fruits and vegetables is often necessary to exclude IgE-mediated food hypersensitivity.

In vitro diagnostic tests (eg, RAST) also are useful for demonstrating food allergen-specific IgE. Many modifications of the RAST procedure have become available over the years, including enzyme-linked immunosorbent assays, but all involve allergens coupled to a solid phase (eg, paper disk). Patient serum samples are reacted with the solid phase, and after proper washing, the amount of bound IgE antibodies is calculated by adding labeled antihuman IgE antibodies. In general, in vitro measurements of serum food-specific IgE antibodies performed in high-quality laboratories provide information similar to skin prick tests and are recommended in several clinical situations: patients with significant dermographism, patients with severe skin disease and limited surface area for testing, patients with suspected exquisite sensitivity to certain foods, and patients who have difficulty discontinuing use of antihistamines. Basophil degranulation tests have generally been reserved for research settings. However, semiautomated methods using small amounts of whole blood have been developed that are being promoted for screening multiple food allergens. Heparinized venous blood or separated blood leukocytes are incubated with extracts of suspected food allergens. If there is allergen-specific IgE present on the basophils, histamine will be released into the supernatant fluid and may be measured as an index of reactivity. Basophil degranulation tests appear comparable in their outcome with the RAST.[65]

The double-blind, placebo-controlled food challenge is considered the criterion standard ("gold standard") for diagnosing food allergies[66,67] and has been used successfully in both children and adults for examining a variety of food-related complaints.[68] The selection of foods to be tested in double-blind, placebo-controlled food challenges is based on patient history, RAST results, or both. Open or single-blind challenges may be used to screen suspected food allergens, but positive challenges should be confirmed by food challenge, except in very young infants or when only a single food was found to provoke classic allergic symptoms. Multiple food allergies are rare (except in allergic eosinophilic gastroenteritis) and, if suspected, must be confirmed by double-blind, placebo-controlled food challenge. Prior to performing the food challenge, suspect foods should be eliminated for 10 to 14 days or for up to 12 weeks in some GI disorders, such as allergic eosinophilic gastroenteritis and food-induced enteropathy.[69] If no improvement is noted, it is unlikely that food allergy is involved. Use of antihistamines should be discontinued long enough to establish a normal histamine skin test, and other medications should be minimized to levels sufficient to prevent breakthrough of acute symptoms. Patients with a positive skin test result and a clear history of severe anaphylaxis following an isolated ingestion of a specific food should not be challenged.

Most foods for challenges can be obtained in dehydrated or powdered forms from grocery stores, health food stores, or camping outlets. The food challenge is administered in the fasting state, starting with a dose unlikely to provoke symptoms (125-500 mg of dry powdered food). The dose is then doubled every 15 to 60 minutes, depending on the type

of reaction suspected. Once the patient has tolerated 10 g of dry powdered food blinded in capsules or liquid, IgE-mediated reactivity is generally ruled out (0.6 g/kg of body weight for most non-IgE-mediated hypersensitivities). If the blinded challenge is negative, the food must be given openly in usual quantities under observation to rule out the rare false-negative challenge.

To control for a variety of potential confounding factors, an equal number of placebo and food antigen challenges are necessary[66,69]; the order of administration should be randomized. The length of observation following a challenge depends on the type of reaction suspected, eg, generally up to 2 hours for IgE-mediated reactions, up to 4 to 8 hours for cow milk-induced enterocolitis, and so forth. Double-blind, placebo-controlled food challenges are the best means of controlling for the variability of chronic disorders (eg, chronic urticaria, atopic dermatitis), any potential temporal effects, and acute exacerbations secondary to reducing or discontinuing use of medications. Other precipitating factors are controlled or at least neutralized, and psychogenic factors and patient or observer bias are eliminated. Although the diagnostic accuracy is excellent, rare false-negative challenges may occur. In general, blinded, controlled food challenges should be conducted in a clinic or hospital setting, especially if an IgE-mediated reaction is suspected and only if trained personnel and equipment for treating systemic anaphylaxis are present. However, evaluation of "delayed" reactions can be conducted safely on an outpatient basis, provided there is no concern about a patient's breaking the blinding. In cases where a patient's symptoms are largely subjective, 3 cross-over trials with reactions developing only during the allergen challenge are necessary to conclude that a cause-and-effect relationship exists.

The diagnosis of food allergy remains a clinical exercise dependent on a careful history, selective skin tests or RASTs if an IgE-mediated disorder is suspected, appropriate exclusion diet, and blinded provocation. At the present time, there is no evidence of any diagnostic value for food-specific IgG or IgG4 antibody levels, food antigen-antibody complexes, evidence of lymphocyte activation (tritium [[sup.3]H] uptake, interleukin 2 production, leukocyte inhibitory factor production, etc), or sublingual or intracutaneous provocation. In GI disorders where prechallenge and postchallenge biopsy studies are required for diagnosis (eg, celiac disease), blinded challenge is not necessary.

THERAPY OF FOOD ALLERGIC DISORDERS

Strict elimination of the offending allergen is the only proven therapy once the diagnosis of food hypersensitivity is established. However, prescribing an elimination diet is no different than prescribing a medication; both may have unwanted adverse effects. Elimination diets may lead to malnutrition and/or eating disorders, especially if they include a large number of foods and/or are used for extended periods. Patients must be taught to scrutinize food labels to detect potential sources of hidden food allergens.[70,71] Symptomatic reactivity to food allergens is generally very specific, and patients rarely react to more than 1 member of a botanical family or animal species.[72] Patient information regarding appropriate food allergen avoidance and preparing for emergency management can be obtained through the Food Allergy Network in Fairfax, Va (telephone [800] 929-4040).

Several medications have been used in an attempt to protect patients with food hypersensitivity, including [H.sub.1] and [H.sub.2] antihistamines, ketotifin, oral cromolyn, and corticosteroids. These drugs may modify symptoms to food allergens, but overall they

have minimal efficacy or their adverse effects are unacceptable. No appropriately designed trial has demonstrated efficacy for the use of injection immunotherapy, oral desensitization, or subcutaneous provocation and neutralization.

Even the most careful patient may inadvertently ingest sufficient amounts of a food to which he or she is sensitive. In IgE-mediated disorders, the treatment is the same as that used when other factors provoke symptoms. Laryngeal or pulmonary symptoms following an inadvertent food exposure should be treated immediately with epinephrine.[40] The treatment of food-induced anaphylaxis is essentially the same as that for any cause of systemic anaphylaxis. Patients with a history of a previous severe anaphylactic reaction or a history of asthma and IgE-mediated food allergy should be taught how to self-administer epinephrine. The patient should have injectable epinephrine (Epi-Pen, Ana Guard, or Ana Kit) and an antihistamine (preferably liquid) available at all times. For children, day care centers and schools should have a list of emergency numbers with backups to be called. It should be recognized that a patient may experience only mild symptoms in the first few minutes after ingesting a food to which he or she is allergic, but this may be followed 10 to 60 minutes later with the onset of hypotension and other severe problems. Following self-medication for systemic reactions, the patient should immediately seek medical attention in an emergency setting and be observed for at least 4 hours following a major reaction. All patients with IgE-mediated food allergy should be warned about the possibility of developing a severe anaphylactic reaction and should be educated in the appropriate treatment measures to be taken in case of an accidental ingestion.

NATURAL HISTORY OF FOOD HYPERSENSITIVITY

It is generally believed that most young infants "outgrow" (become tolerant of) their food hypersensitivity. In prospective studies of adverse food reactions in infants, 85% of confirmed symptoms were gone by 3 years of age.[3,19] Although young infants appear more likely to outgrow their food hypersensitivity,[73] older children[73,74] and adults[75] also will lose their sensitivity if the responsible food allergen can be identified and completely eliminated from the diet. Approximately one third of children and adults lose their clinical reactivity after 1 to 2 years of allergen avoidance, although skin test (or RAST) positivity may persist for years.[74,75] The degree of compliance with the allergen avoidance diet and the allergen responsible for the reaction were directly associated with outcome; ie, patients with peanut, nut, fish, or shellfish sensitivity rarely lose clinical reactivity.

The majority of infants with non-IgE mediated food hypersensitivities also appear to outgrow their food reactivity (except celiac disease). Celiac disease is a lifelong sensitivity, and gluten-containing cereals must be avoided for life. The role of food hypersensitivity and allergen elimination diets in the natural history of disorders such as inflammatory bowel disease and irritable bowel syndrome remains controversial.

As reviewed recently,[29] exclusive breast-feeding has been promoted as a means of preventing food allergy and atopic disease, but considerable controversy remains regarding the effectiveness of this practice. Some studies suggest that lactating mothers should eliminate from their diets highly allergenic foods that may induce "lifelong" sensitization (eg, peanuts, nuts, seafood), but further studies are necessary to clarify the prophylactic role of early elimination diets and breast-feeding.

FUTURE DIRECTIONS

Many questions remain to be answered in the field of food allergic disorders, including the most appropriate means of diagnosis, natural history of various disorders, identification of individuals at risk, and suitable means of therapy. Basic information on the development of oral tolerance induction in humans must be elucidated. The immunopathogenic mechanisms responsible for many food allergic disorders require clear delineation to facilitate accurate classification, diagnosis, and development of more effective diagnostic tests. Much research has focused on the identification and characterization of allergenic proteins, which should aid in the development of diagnostic studies and novel forms of therapy, eg, mutated allergens and plasmid DNA for immunotherapy. With increased understanding of the basic immunopathogenic mechanisms responsible for food hypersensitivity disorders and of the structural characteristics of food allergens, proper identification and management of these disorders should soon follow.

References

[1.] Bruijnzeel-Koomen C, Ortolani C, Aas K, et al. Adverse reactions to food: position paper. Allergy. 1995;50:623-635.

[2.] Sampson HA, Metcalfe DD. Food allergies. JAMA. 1992;268:2840-2844.

[3.] Bock SA. Prospective appraisal of complaints of adverse reactions to foods in children during the first 3 years of life. Pediatrics. 1987;79:683-688.

[4.] Young E, Stoneham MD, Petruckevitch A, Barton J, Rona R. A population study of food intolerance. Lancet. 1994;343:1127-1130.

[5.] Host A, Halken S. A prospective study of cow milk allergy in Danish infants during the first 3 years of life. Allergy. 1990;45:587-596.

[6.] Schrander JJP, van den Bogart JPH, Forget PP, Schrander-Stumpel CTRM, Kuijten RH, Kester ADM. Cow's milk protein intolerance in infants under 1 year of age: a prospective epidemiological study. Eur J Pediatr. 1993;152:640-644.

[7.] Hide DW, Guyer BM. Cow milk intolerance in Isle of Wight infants. Br J Clin Pract. 1983;37:285-287.

[8.] Burks AW, Mallory SB, Williams LW, Shirrell MA. Atopic dermatitis: clinical relevance of food hypersensitivity reactions. J Pediatr. 1988;113:447-451.

[9.] Novembre E, de Martino M, Vierucci A. Foods and respiratory allergy. J Allergy Clin Immunol. 1988;81:1059-1065.

[10.] Fuglsang G, Madsen C, Saval P, Osterballe O. Prevalence of intolerance to food additives among Danish school children. Pediatr Allergy Immunol. 1993;4:123-129.

[11.] Niestijl Jansen JJ, Kardinaal AFM, Huijbers GH, Vlieg-Boerstra BJ, Martens BPM, Ockhuizen T. Prevalence of food allergy and intolerance in the adult Dutch population. J

Allergy Clin Immunol. 1994;93:446-456.

[12.] Young E, Patel S, Stoneham MD, Rona R, Wilkinson JD. The prevalence of reactions to food additives in a survey population. J R Coll Physicians Lond. 1987;21:241-211.

[13.] Bernhisel-Broadbent J, Taylor S, Sampson HA. Cross-allergenieity in the legume botanical family in children with food hypersensitivity, II: laboratory correlates. J Allergy Clin Immunol. 1989;84:701-709.

[14.] Bernhisel-Broadbent J, Scanlon SM, Sampson HA. Fish hypersensitivity, I: in vitro and oral challenge results in fish-allergce patients. J Allergy Clin Immunol. 1992;89:730-737.

[15.] Jones SM, Magnolfi CF, Cooke SK, Sampson HA. Immunologic cross-reactivity among cereal grains and grasses in children with food hypersensitivity. J Allergy Clin Immunol. 1995;96:341-351.

[16.] Ahlroth M, Alenius H, Turjanmaa K, Makinen-Kiljunen S, Reunala T, Palosuo T. Cross-reacting allergens in natural rubber latex and avocado. J Allergy Clin Immunol. 1995;96:167-173.

[17.] Walzer M. Allergy of the abdominal organs. J Lab Clin Med. 1941;26:1867-1877.

[18.] Brunner M, Walzer M. Absorption of undigested proteins in human beings: the absorption of unaltered fish protein in adults. Arch Intern Med. 1928;42:173-179.

[19.] Host A. Cow's milk protein allergy and intolerance in infancy. Pediatr Allergy Immunol. 1994;5:5-36.

[20.] Hanson DG, Vaz N, Maia L, Hornbrook M, Lynch J, Roy C. Inhibition of specific immune responses by feeding protein antigen. Int Arch Allergy Appl Immunol. 1977;55:1518-1524.

[21.] Husby S, Mestecky J, Moldoveanu Z, Holland S, Elson CO. Oral tolerance in humans: T cell but not B cell tolerance after antigen feeding. J Immunol. 1994;152:4663-4670.

[22.] Ramsdell F, Fowlkes B. Clonal deletion versus clonal energy: the role of the thymus in inducing self-tolerance. Science. 1991;248:1342-1348.

[23.] Mowat AM. The regulation of immune responses to dietary protein antigens. Immunol Today. 1987;8:93-98.

[24.] Bruce MG, Strobel S, Hanson DG, et al. Irradiated mice lose the capacity to 'process' fed antigen for systemic tolerance of delayed-type hypersensitivity. Clin Exp Immunol. 1987;70:611-618.

[25.] Furrie E, Turner M, Strobel S. Failure of SCID mice to generate an oral tolerogen after a feed of ovalbumin: a role for a functioning gut-associated lymphoid system. Immunology. 1994;83:562-567.

[26.] Miller A, Lider O, Roberts A, Sporn M, Weiner H. Suppressor T cells generated by oral tolerization to myelin basic protein suppress both in vitro and in vivo immune responses by the release of transforming growth factor beta after antigen-specific triggering. Proc Natl Acad Sci U S A. 1992;89:421-423.

[27.] Sigurs N, Hattevig G, Kjellman B. Maternal avoidance of eggs, cow's milk, and fish during lactation: effect on allergic manifestation, skin-prick tests, and specific IgE antibodies in children at age 4 years. Pediatrics. 1992;89:735-739.

[28.] Zeiger R, Heller S. The development and prediction of atopy in high-risk children: follow-up at seven years in a prospective randomized study of combined maternal and infant food allergen avoidance. J Allergy Clin Immunol. 1995-95:1179-1190.

[29.] Zeiger R. Breast-feeding and dietary avoidance. In: de Week A, Sampson H, eds. Intestinal Immunology and Food Allergy. New York, NY: Raven Press; 1995;203-222.

[30.] Hide D, Matthews S, Matthews L, et al. Effect of allergen avoidance in infancy on allergic manifestations at age two years. J Allergy Clin Immunol. 1994;93:842-846.

[31.] Hoffinan K, Ho D, Sampson H. Evaluation of the usefulness of lymphocyte proliferation assays in the diagnosis of cow milk allergy. J Allergy Clin Immunol. 1997;99:360-366.

[32.] Sampson HA, MacDonald SM. IgE-dependent histamine-releasing factors. Springer Semin Immunopathol. 1993;15:89-98.

[33.] Mudde G, Bheekha R, Bruijnzeel-Koomen C. Consequences of IgE/CD23-mediated antigen presentation in allergy. Immunol Today. 1995;16:380-383.

[34.] Mudde G, van Reijsen F, Boland G, de Gast G, Bruijnzeel P, Bruijnzeel-Koomen C. Allergen presentation by epidermal Langerhan's cells from patients with atopic dermatitis is mediated by IgE. Immunology. 1990;69:335-341.

[35.] Abernathy-Carver K, Sampson H, Picker L, Leung D. Milk-indueed eczema is associated with the expansion of T cells expressing cutaneous lymphocyte antigen. J Clin Invest. 1995;95:913-918.

[36.] Jones SM, Sampson HA. The role of allergens in atopic dermatitis. In: Leung DYM, ed. Atopic Dermatitis: From Pathogenesis to Treatment. Georgetown, Tex: RG Landes Co; 1996:41-112.

[37.] James JM, Eigenmann PA, Eggleston PA, Sampson HA. Airway reactivity changes in food-allergic, asthmatic children undergoing double-blind placebo-controlled food challenges. Am J Respir Crit Care Med. 1996;153:597-603.

[38.] Sampson H, Eigenmann PA. Allergic and nonallergic rhinitis: food allergy and intolerance. In: Myrgaand N, Naclerio R, eds. Allergic and Nonallergic Rhinitis. Copenhagen, Denmark: Munksgaard, 1996.

[39.] Yunginger JW, Sweeney KG, Sturner WQ. et al. Fatal food-induced anaphylaxis. JAMA. 1988;260:1450-1452.

[40.] Sampson HA, Mendelson LM, Rosen JP. Fatal and near-fatal anaphylactic reactions to food in children and adolescents. N Engl J Med. 1992;327:380-384.

[41.] Yocum MW, Khan DA. Assessment of patients who have experienced anaphylaxis: a3-year survey. Mayo Clin Proc. 1994;69:16-23.

[42.] Kemp SF, Lockey RF, Wolf BL, et al. Anaphylaxis: a review of 266 cases. Arch Intern Med. 1995; 155:1749-1754.

[43.] Romano A, Fonso M, Giuffreda F, et al. Diagnostic work-up for food-dependent, exercise-induced anaphylaxis. Allergy. 1995;50:817-824.

[44.] Dohi M, Suko M, Sugiyama H, et al. Food-dependent exercise-induced anaphylaxis: a study on 11 Japanese eases. J Allergy Ciin Immunol. 1991;87:34-40.

[45.] Ortolani C, Ispano M, Pastorello EA, Ansaloni R, Magri GC. Comparison of results of skin prick tests (with fresh foods and commercial food extracts) and RAST in 100 patients with oral allergy syndrome. J Allergy Clin Immunol. 1989;83:683-690.

[46.] Champion R, Roberts S, Carpenter R, Roger J. Urticaria and angioedema: a review of 554 patients. Br J Dermatol. 1969;81:588-597.

[47.] Sampson HA. Atopic dermatitis. Ann Allergy. 1992;69:469-479.

[48.] Sampson HA. The role of food allergy and mediator release in atopic dermatitis. J Allergy Clin Immunol. 1988;81:635-645.

[49.] Powell GK. Milk- and soy-induced enterocolitis of infancy. J Pediatr. 1978;93:553-560.

[50.] Odze R, Wershil B, Leichtner A. Allergic colitis in infants. J Pediatr. 1995;126:163-170.

[51.] Kuitunen P, Visakorpi J, Savilahti E, Pelkonen P. Malabsorption syndrome with cow's milk intolerance: clinical findings and course in 54 cases. Arch Dis Child. 1975;50:351-356.

[52.] Trier J. Celiac sprue. In: Sleisenger M, Fordtran J, Scharschmidt B, Feldman M, eds. Gastrointestinal Disease: Pathophysiology/Diagnosis/Management. Philadelphia, Pa: WB Saunders Co; 1993:1078-1096.

[53.] McNeish AS, Harms HK, Rey T, Shmerling D, Visakorpi J, Walker-Smith J. Re-evaluation of diagnostic criteria for coeliac disease. Arch Dis Child. 1979;54:783-786.

[54.] Walker-Smith J, Guandalini S, Schmitz J, Schmerling D, Viskorpi J. Revised criteria for diagnosis of coeliac disease. Arch Dis Child. 1990;65:909-911.

[55.] Iacono G, Carroccio A, Cavataio F, et al. Gastroesophageal reflux and cow's milk allergy in infants: a prospective study. J Allergy Clin Immunol. 1996;97:822-827.

[56.] Lee C, Changchien C, Chen P, et al. Eosinophilic gastroenteritis: 10 years experience. Am J Gastroenterol. 1993;88:70-74.

[57.] Kelly KJ, Lazenby AJ, Rowe PC Yardley JH, Perman JA, Sampson HA. Eosinophilic esophagitis attributed to gastroesophageal reflux: improvement with an amino-acid based formula. Gastroenterology. 1995;109:1503-1512.

[58.] Hall RP. The pathogenesis of dermatitis herpetiformis: recent advances. J Am Acad Dermatol. 1987;16:1129-1144.

[59.] Heiner DC, Sears JW. Chronic respiratory disease associated with multiple circulating precipitins to cow's milk. AJDC. 1960;100:500-502.

[60.] Panush RS. Food induced ('allergic') arthritis: clinical and serologic studies. J Rheumatol. 1990;17:291-294.

[61.] Weber RW, Vaughan TR. Food and migraine headache. Immunol Allergy Clin North Am. 1991;11:831-841.

[62.] Sampson HA. Differential diagnosis in adverse reactions to foods. J Allergy Clin Immunol. 1986; 78:212-219.

[63.] Hoffman KM, Ho DG, Sampson HA. Evaluation of the usefulness of lymphocyte proliferation assays in the diagnosis of cow's milk allergy. J Allergy Clin Immunol. 1996;99:360-366.

[64.] Dreborg S, Foucard T. Allergy to apple, carrot, and potato in children with birch-pollen allergy. Allergy. 1983;38:167-172.

[65.] Sampson H. In vitro diagnosis and mediator assays for food allergies. Allergy Proc. 1993;14:259-261.

[66.] Sampson H. Immunologically mediated food allergy: the importance of food challenge procedures. Ann Allergy. 1988;60:262-269.

[67.] Sampson HA. Diagnosing food allergy. In: Spector SL, ed. Provocation Testing in Clinical Practice. New York, NY: Marcel Dekker Inc; 1995:623-646.

[68.] Bock SA, Sampson HA, Atkins FM, et al. Double-blind, placebo-controlled food challenge (DBPCFC) as an office procedure: a manual. J Allergy Clin Immunol. 1988;82:986-997.

[69.] Metcalfe D, Sampson H. Workshop on experimental methodology for clinical studies of adverse reactions to foods and food additives. J Allergy Clin Immunol. 1990;86:421-442.

[70.] Barnes Koerner C, Sampson HA. Diets and nutrition. In: Metcalfe DD, Sampson HA, Simon RA, eds. Food Allergy:Adverse Reactions to Foods and Food Additives. Boston, Mass: Blackwell Scientific Publications; 1991:332-354.

[71.] Steinman HA. 'Hidden' allergens in foods. J Allergy Clin Immunol. 1996;98:241-250.

[72.] Bernhisel-Broadbent J. Allergenic cross-reactivity of foods and characterization of food allergens and extracts. Ann Allergy Asthma Immunol. 1995;75:295-303.

[73.] Bock SA. The natural history of food sensitivity. J Allergy Clin Immunol. 1982;69:173-177.

[74.] Sampson HA, Scanlon SM. Natural history of food hypersensitivity in children with atopic dermatitis. J Pediatr. 1989;115:23-27.

[75.] Pastorello E, Stocchi L, Pravetonni, V, et al. Role of the food elimination diet in adults with food allergy. J Allergy Clin Immunol. 1989;84:475-483.

EXHIBIT 4

Peanut allergy: where do we stand?

Oct 2nd, 1998

Updates, comments: *

John Weisnagel, M.D.

NEW * A little more than a year ago, the idea of looking into the complicated problem of peanut allergy came about following a great deal of attention given to the subject in the media

at that particular time. This followed many publications in the medical literature as cited in the references seen below in the opening paragraphs, conclusions of the authors considered as "alarming, frightening", according to comments of some visitors scanning this article. There were articles in magazines, like Time, Newsweek, as well as in local papers on what seems an increase in peanut allergy, on banning peanuts in schools or on commercial flights, etc.[22,25] (see also table of contents, above). Some of the articles, and reactions to them, were posted and appear in the article, and may still be accessible (at times, they're removed without any warning). The effect of all this attention to peanut allergy resulted in a panic situation, both in the minds of the public as well as the medical community, an attitude that seems to persist.

Today, things have quieted somewhat in both the medical literature and media, although peanut allergy is still there as it always was -- the reactions are not all anaphylactic, very benign in many cases, still occuring mostly in the very young, but very often regarded as potentially severe and treated as such. However, there are encouraging indications, contrary to previous publications, that **allergy to peanuts can disappear**. (see recently posted reports, the last one on outgrowing peanut allergy posted following the American College of Allergists Annual meeting held in Chicago in Nov. 1999) There are studies in progress in various centers evaluating the duration of this allergy. This ongoing article is being updated regularly, as developments occur, hopefully not only to make everyone aware of this unpredictable allergy, but also to help ease the fear that was generated. (posted Dec. 20th, 1999)

(text possibly too technical in references that follow has been altered, and comments added for general public access)

Background

The natural history of food allergy involves the development of the sensitivity and eventual loss of it, as observed in children as well as adults. Very young children with allergy to milk proteins, soya, or eggs, tend to lose their allergies as they grow older[7, 26] even in the case of anaphylactic reactions (severe allergic reactions requiring emergency treatment; detailed further in the article)[27]. However, with certain foods such as tree nuts, shellfish and peanuts, things are different. According to Bock and Atkins, children with allergy to peanuts tend to keep their allergy for many years[19].

In 1995, at the Annual Meeting of the American Academy of Allergy, Asthma and Immunology, Bock and collaborators presented their findings in the follow-up of 60 children with confirmed allergy to peanuts, aged between 3 months and 17 years. They concluded that:

1) Peanut allergy occurs with surprising frequency in young children: 17 before age one; 30 between one and two years of age; 19 between two and three years of age; and 3 between three and four years of age;

2) children do not seem to lose peanut allergy very often; 3) accidental reactions are common; 4) reactions in young children may require emergency Rx.

Characteristics pertaining to peanut allergy

-Peanut allergy is characterized by **more severe symptoms than other food allergies** and by **high rates of symptoms on minimal contact**. In a questionnaire study of 622 self-reported allergic subjects, a total of 406 patients (66%) reported symptoms on contact with peanut. Only 121 (19%) had been knowingly exposed to peanut before the first documented reaction **implying a high frequency of occult sensitization**.[2](see "Important facts" further in this article re early sensitization).

* -Skin-prick testing and peanut-specific IgE (immunoglobulin E) antibody levels done by the RAST [radio-allergo-sorbent test] blood test) **do not predict clinical severity** [2]. (skin tests and blood tests identifying peanut-specific antibody are not good predictors of the intensity of the allergy)

* -Zimmerman and coll. reported in 1989 a positive RAST test to peanut in 64 % of children **who gave no history of having eaten peanuts** [37].

NEW* re predictive value of prick skin tests to peanuts in children who have never previously eaten peanuts

At the annual meeting of the AAAA&I held Mar 3-8th, 2000 in San Diego, Hayami and Kagan presented a retrospective study to assess the use of **prick skin tests** (PST) **as a diagnostic tool for peanut allergy** in children who have never knowingly ingested peanuts, also specificity, sensitivity, and positive and negative predictive values of PSTs to peanuts in children who have undergone a blinded, placebo controlled challenge. PSTs were considered positive if the wheal was 3mm > negative control. All subjects had a positive skin test to peanut despite no prior history of peanut ingestion, and all have practised strict avoidance of peanuts. The testing was done because of family history of peanut allergy, parental request, atopic dermatitis, or as part of other allergy tests. Food challenges were offered to patients to determine if the PST was indicative of true allergy. The mean age of children undergoing food challenge was 5.5 yrs. **Of the 20 subjects, 6 had positive challenges**. The mean wheal diameter of children with negative challenges was 7.57 mm (range 3-15mm). The mean wheal diameter of children with positive challenges was 10.66 mm (range 7-14mm). **The positive predictive value of a peanut skin test > 3mm was 33.3%. The positive predictive value increased to 46.1% when only skin tests > 6mm were considered**. All of the subjects with a positive challenge had wheals > 6mm. There was a trend to larger mean wheal diameters in children with positive challenges. No correlation was found between the presence of asthma, atopic dermatitis, or other food allergy. **The poor predictive value of the PST in children without a clinical history of peanut allergy reaffirms the need to conduct oral challenges prior to the designation of peanut allergy.** There is a suggestion that PST < 6mm may predict negative (posted Mar 9th, 2000)

* -Alt, Ramesh, and Reisman presented a paper at the 1997 American Academy of Allergy, Asthma and Immunology (AAAA&I) Annual Meeting on anaphylaxis in a 6 month old infant, after eating a portion of a cracker containing peanut. **No previous exposure** to peanuts, but a RAST test showed a very high sensitivity to peanut!

-Immediate hypersensitivity to peanuts is a **frequent cause of anaphylactic reactions and deaths** in children and adults [3].

-Approximately **one third of emergency-room visits for anaphylaxis may be due to peanut sensitivity** [8,15]

-Severe allergic reactions caused by foodstuffs have been reported in Sweden since 1993, 60 cases, five of them fatal, occurring during the first 3-year period. **More than 70 % of all reactions reported were caused by peanuts, soya beans, nuts or almonds.** In only 13% of reported cases were the patients over 17 years of age...with extremely severe reactions including asthma[4].

-Peanut anaphylaxis is a potentially near-fatal or fatal disease **complicated by the fact that peanuts as well as other food items are commonly used as an adulterant in the preparation of foods, often hidden.** [6,14]. Peanuts are frequently added to Chinese foods, oriental cuisine generally, snacks, soups, cereals, and baked goods [20]

> * At the Feb. 1997 annual meeting of the AAAA&I, using an ELISA test ('enzyme-linked immunosorbent assay') Nordlee et al reported their findings on the**analysis of commercially produced food products labeled** either a) listing peanut as the last ingredient, b) 'may contain peanut' and c) label not listing peanuts. Their results: for a): ND (not detectable) to 5000 ppm; for b) ND to 1200 ppm; and for c) ND to 4000 ppm.
>
> (this means that food preparations may contain peanut if not mentioned on the label!!!)
>
> * Brett GM, Bull VJ, Morgan MR report a study on peanut and sesame allergy, using the ELISA test. . . "the problem of the **detection of "hidden" allergens in food** is a major concern for both the industry and consumers at present. **Who might use such assays for maximum benefit**, and in what format they should be provided, are key questions for food analysts, and the issues are discussed." (posted jan.3d, 1999)

* In the Oct. 1998 issue of *Allergy*, Hourihane notes... due to the severity of reactions induced by peanuts and tree nuts... **Justifiable demands are being made for better medical guidance of the practice of food labeling for industry and catering businesses** [38].

* Food allergies, particularly to peanuts, are a common cause of anaphylaxis. Approximately 125 people die each year in the USA secondary to food-induced anaphylaxis. . . **Anaphylaxis is recognized by cutaneous, respiratory, cardiovascular, and gatrointestinal signs and symptoms occuring singly or in combination.** [80] (posted Aug. 12th, 1999)

-The minimum dose of food protein to which subjects with food allergy have reacted in **double-blind, placebo-controlled food challenges** is between 50 and 100 mg. (double-blind and placebo-controlled signify that neither the patient nor physician know whether the food or a placebo [substitute] is being used [food evaluated and a substitute both appear the same], and a control non allergic individual also participates in the challenge) However, subjects with peanut allergy often report severe reactions after minimal contact with peanuts, even through intact skin. In a group of well-characterized , highly sensitive subjects with peanut allergy, the threshold dose of peanut varies. As little as 100 microg. of peanut provokes symptoms in some subjects with peanut allergy[10] Dr. Michael Goldman refers to this publication as well as to two others underlining this in *Peanut Allergy: How much peanut is too much?* which is accessible at the Calgary Allergy Network.

-In the Sept 1998 issue of *Clinical and Experimental Allergy*, Moneret-Vautrin, and coll. reported an **evaluation of 142 observations of allergy to peanuts in France [23]. The clinical features were**:

- atopic dermatitis [eczema] (40%)
- angioedema (37%)
- asthma (14%)
- anaphylactic shock (6%)
- digestive symptoms (1.4%)

* Rance F and Dutau G, who were co-authors of the Sept 1998 article above, just published (April, 1999) "Peanut hypersensitiviy in children" in *Pediatr Pulmonol Suppl.* reporting the following:

- of 132 pediatric cases of peanut hypersensitiviy, aged between 6 months and 15 years, confirmed by food challenge, **more than half were diagnosed before age three.**
- **the most common symptom was atopic dermatitis (43.1% of cases).** Others were: hoarseness (34.8%), **asthma (13.6%), anaphylaxis (6%), gastro-intestinal symptoms (1.5%),** and **oral syndrome [ithchy mouth, lips, throat] (0.7%).**
- all patients had positive skin tests, with a mean wheal diameter of 8mm (range: 2 to 25mm); **wheal diameter was significantly smaller in the youngest children (mean 4.5mm for children < 1 yr of age).**
- peanut-specific IgE concentration was < 0.75 IU/ml in 16 cases (14.3%), the mean for the entire group being 30.9IU/ml (range: 0.75 to 100 IU/ml).
- food challenges were not performed in three of the children with a history of anaphylaxis.
- **labial food challenge [simple contact of food with lips] was positive in 85 cases (64.8%)**
- an oral food challenge was carried out in 45 children (34.3%) and the **mean reactive dose was 850 mg (range: 1 mg to 7gm).**
- labial food challenge with **peanut oil was positive in 2 cases of 50 tested (4%)** and **17 of 63 children (29.9%) tested by oral food challenge were also found to be sensitive to peanut oil.**
- **half the children were also allergic to other foods, as demonstrated by food challenge (53.7%) or to airbone allergens (62.8%).**

The authors conclude: **Hypersensitiviy in the very youngest children raises questions about how sensitization occurs.** Diagnosis was confirmed by food challenge. **Peanut products are very difficult to eliminate from the diet because of inadequate labeling of food products.** An ELISA test, available in a number of countries, can be used to detect peanut in foods (as reported above). [61] (posted April 5th, 1999)

* In the December 99 issue of the *Anaphylaxis Network Newsletter*, there was an article by Dr. Wesley Burks,
University of Arkansas, on food anaphylaxis. It mentioned partway through that **"It is not rare, particularly for
peanut-allergic children who had minimal cutaneous (skin) and gastrointestinal symptoms as young children, to experience significant systematic anaphylactic symptoms following the ingestion of peanuts in their adolescent years."** (brought to my attention by Nancy Wiebe of the Calgary Allergy Network and posted Jan 23d, 2000)

Link between peanuts and tree nuts, and soy

-A questionnaire survey, examination, and blood levels of peanut-specific IgE antibody of a **total of 122 patients** (63% males; median age 8 years at time of study) with convincing histories of at least one acute reaction (and at least one organ system involved within 60 minutes of ingestion) reported in July 1998 by Sicherer, Burks and Sampson, showed the following:

- 68 had reactions only to peanuts
- 20 only to nuts
- **34 to both peanuts and nuts**
- of those reacting to nuts, 34 had reactions to one, 12 to two, and 8 to three or more different tree nuts, the most common being walnut, almond and pecan.
- initial reactions usually occurred at home (median age, 24 months for peanuts, and 62 months for nuts.)
- it was the result of **first exposure to peanut in 72% of cases**
- 89% of reactions involved the skin (urticaria [hives], angioedema [swelling of throat, difficulty swallowing])
- 52% the respiratory tract (wheezing, throat tightness, repetitive coughing, dyspnea [shortness of breath])
- 32% the gastrointestinal tract (vomiting, diarrhea)
- two organ systems were affected in 31% of initial reactions
- all three systems in 21% of the reactions
- **38 of the 190 first reactions to peanuts or nuts were treated with injection of epinephrine (adrenaline).**
- accidental ingestion occurred in 55% of peanut allergic children (average of two accidents per patient with an accidental ingestion) and in 30% of tree nut allergic children over a median period of 5.5 years.
- **symptoms after accidental exposure were generally similar to those at initial exposure.** Accidents occurred commonly in school but also at home and in restaurants. Modes of

accidental ingestion included **sharing food, hidden ingredients, cross-contamination and school craft projects using peanut butter.**

- **83% of the children were breast-fed, with > 90% of the mothers ingesting peanuts and at least one tree nut during lactation.**
- among patients reporting no history of exposure (>60% of patients for each tree nut), **IgE antibodies were found to a particular nut in 50% to 82% of patients and to peanuts in 100% of patients.**

Conclusions:

- **acute allergic reactions to peanuts occur early in life**
- **peanut and tree nut allergic reactions coexist in one third of peanut allergic patients,**
- **reactions frequently occur on first known exposure** and may be life-threatening requiring emergency treatment
- accidental ingestion is common, occurring frequently outside the home and often requiring emergency treatment
- consequently, **early diagnosis followed by education on avoidance and treatment measures (including self-administered epinephrine) is imperative** [13].

* Comments:

Dr. H. Blumer, we seem to encounter more allergy to hazelnuts than to the other tree nuts in Quebec. (oct. 1998)

See also: **"Prevalence of peanut and tree nut (TN) allergy in the US determined by a random digit dial telephone survey."**[65](further down)

* Pumphrey and coll. in the Sept 1999 issue of Clin Exp Allergy, **"explored the pattern of specific IgE to three distantly related nuts in patients of all ages with nut allergy (peanut, hazelnut and brazil nut).** From 1994 to 1998: **731 patients** (age 7 months to 65 years, median 6.6 yrs) **had specific IgE** (> 0.35kUA/L) **to at least one of these three nuts**: 282 had IgE to one nut, 130 to two nuts, and 319 to all three nuts. . . **very similar patterns were found in all subgroups**. . Conclusion: **the probability of a patient with nut allergy having specific IgE to a particular combination of peanut, hazelnut and brazil nut is similar, whatever their age or sex.** The apparent increase in multiple nut reactivity with increasing age may therefore be due to exposure of previously unchallenged sensitivity. **The frequency of multiple-nut specificity is sufficiently high that patients should always be tested for allergy to a range of nuts if they have a history of reacting to any nut. "** [83] (posted Sept 6th, 1999)

* Re **Macademia nuts** :

At the Annual AAAA&I meeting in San Diego, Mar 3-8th, 2000, RM Harris,MD reported on a case

of **macademia nut induced anaphylaxis** (macademia nut is an Australian tree nut, originating from macademia intergrifolia, tetraphylla, and their hybrids). Macademia nut oil is reportedly used as a dietary sutbstitute for its health benefits. No testing extracts of macademia were available and skin tests were done using fresh food. A 4+ positive result was obtained not from the outer surface of the nut but from the pulp of the nut. This is the first reported case of macademia nut anaphylaxis, and it points out the need to consider "fresh food testing" when prepared testing resources are not available. (posted March 9th, 2000)

At the same meeting, Sutherland M. et al, also reported on **anaphylaxis in an 18 year old female after eating a flourless orange cake made with macademia meal**. Skin test to raw macademia nut was very positive (wheal of 30mm) one month later and immunolgic immunoblot experiments showed the presence of a protein related partly to hazelnut. **The authors recommend that macademia allergic patients should also avoid hazelnuts**. (posted March 9th, 2000)

* From Sweden, a survey on severe food allergies, by Foucard T, and Malmheden Yman I: **A study on severe food reactions in Sweden--is soy protein an underestimated cause of food anaphylaxis?** [68] The abstract reads as follows:
"Because of a fatal case of soy anaphylaxis occurring in Sweden in 1992, a study was started the following year in which all physicians were asked to report fatal and life-threatening reactions caused by food. The results of the first 3 years of the study are reported here, including results from another ongoing study on deaths from asthma during the same period.
RESULTS: In 1993-6, 61 cases of severe reactions to food were reported, five of them fatal. Peanut, soy, and tree nuts seemed to have caused 45 of the 61 reactions, and four of them were fatal. If two cases occurring less than a year before our study started are included, we are aware of two deaths caused by peanuts and **four deaths caused by soy. All four youngsters who died from soy anaphylaxis with asthma were severely allergic to peanuts but had no previously known allergy to soy**. In most cases, there was a rather symptom-free period for 30-90 min between early mild symptoms and severe and rapidly deteriorating asthma.

CONCLUSIONS: Soy has probably been underestimated as a cause of food anaphylaxis. Those at risk seem to be young people with asthma and peanut allergy so severe that they notice symptoms after indirect contact. " (posted May 13th, 1999)

* **Link with lupine**

-At the annual AAAA&I meeting held in San Diego, Mar 3-8,2000, Kanny reported on **acute asthma due to lupine (lupinus albus, a légume) in a patient allergic to peanuts.** The patient has a severe allergy to peanuts, presenting as acute asthma. **Lupine flour is present in certain foods**, authorized in France in 1997. Skin tests to raw and cooked lupine flour were positive as well as a high specific IgE titre to lupine flour. An oral challenge test was also positive with 965 mg of lupine flour (this quantity is present in 100 grams of bread.) Also published in *Rev Med Interne* [94]. (posted April 2nd, 2000)

A search of Medline resulted in a **few publications re the association of lupine and peanut allergy**:

-Hefle, Lemanske, and Bush reported an "Adverse reaction to lupine-fortified pasta" in 1994 in a **5-year-old girl with peanut allergy, in the form of urticaria and angioedema after ingesting a spaghetti-like pasta fortified with sweet lupine seed flour**. The pasta was extracted and used in immunologic studies in patients with peanut sensitivity to determine whether such individuals are at similar risk. Skin prick tests done with lupine pasta extract were positive in 5 of 7 peanut-allergic subjects, also reporting adverse reactions to green peas; RAST tests were also highly positive, and immunologic studies corroborated this allergy in peanut sensitive individuals. [91] (posted Mar 12th, 2000)

-Toxicity to lupine was also reported.

-In Oct 1999, in the *Journal of Allergy and Clinical Immunology*, Moneret-Vautrin et al **studied the risk of cross-allergy to lupine in patients allergic to peanut and lupine allergenicity**. Results: the skin prick test responses with lupine flour were positive in 11 of 24 subjects (44%); challenges positive in 7 of 8 sujects; the major lupine flour allergen (mol. wt, 43kd) is present in peanuts. **Conclusion: the risk of peanut-lupine allergy is high, contrary to the risk with other legumes**.The inclusion of 10% lupine flour in wheat flour without mandatory labeling makes lupine a hidden allergen, presenting a major risk of cross-reaction in subjects already allergic to peanut products. A high sensitizing potential can also be postulated for this legume. [92] (posted March 12th, 2000)

-In Nov 1999, a group from Spain (Matheu et al) published in the *Annals of Allergy, Asthma and Immunology*, a case of **lupine-induced anaphylaxis**. Skin tests and immunological work-up showed a positive skin prick test to lupine and cross-reactivity with other legumes, yet the patient tolerated a peanut challenge as well a a green bean challenge, but not with pea.The authors conclude that "**discrepancies were found between the clinical aspect and in vitro study of peanut allergy. Factors determining the wide variability in cross-reactivity among individuals are still obscure.**" [93](posted March 11th, 2000)

Sensitization to peanuts

possible during pregnancy, probable during breast feeding:

- * The *British Medical Journal*, June 27th, 1998 published a letter entitled **"Women warned to avoid peanuts during pregnancy and lactation."** that came from the Department of Health, Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment, Wetherby, North Yorkshire. According to **John Warner**, professor of child health at Southampton University and a member of the government's working group on peanut allergy, there appears to be a "**link between maternal consumption of peanuts and peanut products and earlier onset and increasing prevalence of allergy**. Evidence from aborted fetal samples shows that from the second trimester onwards fetuses are capable of producing an

allergic reaction. There are several theories on how sensitization occurs. Some research shows that antigens from the mother can cross the placenta, whereas other work suggests fetuses can swallow IgE from the amniotic fluid, causing sensitization [31].

- * Following the June 27th, 1998, article in the *British Medical Journal*, a comment was published in *The Lancet* by Pamela W Ewan, July 4th, 1998, entitled "Prevention of peanut allergy" in which she notes that the Committee's report said that pregnant women "may wish" to avoid eating peanuts...she stresses the importance of peanut allergy as a common cause of anaphylaxis...its prevalence having increased substantially[32] ...regarding in utero (during pregnancy) sensitization, **there is a lack of convincing evidence from prospective studies that manipulation of the maternal diet during pregnancy has a lasting effect on the development of food allergy. Indirect data suggest that lactation is a more likely route of primary sensitization, but this point remains to be established**[34].
- * In the Aug 29th, 1998 issue of *The Lancet*, Deborah E Fox, Gideon Lack, as well as Richard S H Pumphrey, Phillip B Wilson, and Amolak S Bansai, respond to Pamela Ewan's commentary. The first letter agrees with Ewan's**call for further studies 'so that these public health measures can be soundly based'...the UK guidelines ..have caused distress to mothers with peanut-allergic children**. The second letter authors **suggest that the advice of the Committee be extended to all nuts** [35].
- * -In a Feb 1999 study done in Cape Town, South Africa[79], it was shown that:
  - **mothers who consumed peanuts more than once a week during pregnancy were more likely to give birth to a peanut-allergic child than mothers who consumed peanuts less than once a week.**
  - **Peanuts or peanut butter was introduced into the child's diet from a significantly younger age in the peanut-allergic subjects.**
  - **There was a positive correlation in the peanut-allergic subjects between age of introduction of peanuts and age at the onset of symptoms.**
  - **Exclusive breast feeding did not protect against the development of peanut sensitization.**
  - **Peanut allergy is associated with an increased risk of sensitization to other foods.** (posted Aug. 6th, 1999)

 * In the June 2000 of the *Anaphylaxis Network Newsletter*, **Dr Peter Vadas**, past President of the Anaphylaxis Foundation of Canada, and the Medical Director of the Regional Anaphylaxis Clinic at St Michael's Hospital in Toronto, writes in his article on 'The Process of Sensitization', "A study just completed in my laboratory has shown that peanut protein does, in fact, pass from the maternal diet via the bloodstream into breast milk. Using a very sensitive assay for peanut allergens, we tested samples of breast milk for the presence of peanut protein at various times after consumption of dry, roasted peanuts by a group of volunteers. The two major peanut allergens associated with anaphylaxis were detected in breast milk within one to three hours after ingestion in approximately 50% of the volunteers. **These data confirm the previously unproven notion that some infants may become sensitized by exposure to peanut protein through breastfeeding.**"

Dr Vadas continues, "However, the story is not quite so simple. The concentration of peanut protein, timing of exposure and frequency of **exposure may lead to either allergic sensitization or to tolerization.** The latter process actually protects against

allergies. In some cases, exposure to peanut protein in breast milk may actually protect against later development of peanut allergy. At this stage, it would be overly simplistic to suggest that all lactating women avoid peanut products during breastfeeding. While this may protect some children from peanut sensitization, it may predispose other children to acquiring peanut allergy by preventing the process of tolerization. Instead, **it may be more prudent for lactating mothers to avoid peanut products while breastfeeding hight risk infants, namely those who have a strong family history of allergies or those who already have a first degree relative with peanut allergy.** (posted July 26th, 2000)

-The concept of **tolerization, or tolerance**, was touched upon by Drs Gideon Lack and Jean Golding, in their comments regarding Pamela W. Ewing's article entitled 'Clinical study of peanut and nut allergy in 62 consecutive patients: new features and associations.' *BMJ 1996;312:1074-8 (27 April)*...."**exposure to peanuts and other food allergens during lactation and childhood may be important in the development of immunological tolerance and may prevent allergic sensitisation to these foods...avoidance measures would serve only to reduce exposure to peanuts to low levels, and this could pardoxically increase allergic sensitisation to peanuts**; low dose exposure to allergens (rather than high dose exposure) favours production of IgE, and as little as 2 μg of inhaled allergen a year may be sufficient to induce allergic sensitisation via the airways." (posted July 26th, 2000)[96]

Other possible sources of sensitization:

- *-How about peanut oil in vitamin A and D preparations? According to a Feb 1999 Swedish study, **sensitization to peanut during childhood through consumption of vitamin A and D in oil-based solution seems unlikely.**[78] (posted Aug. 6th, 1999)
- Another suggestion is that **sensitization might occur by contact with the skin**, through the application of **creams containing arachis (peanut) oil for eczema, or nipple ointments in mothers during breast feeding** as reported by Lack G, Fox DES, Golding J, at the AAAA&I Annual meeting in Washington, DC, March 1998. (posted Aug 6th, 1999)

Prevalence of food allergies

-the exact prevalence of food allergy, specifically peanut sensitivity, is not known. Reports vary:

-The incidence of food allergy in children is approximately 1.3% and among adults 0.3% [5].

-True food allergies are much less prevalent than is generally believed. **They are more common in infants and children under age three than in older children and adults.** Infant colic generally is not caused by a food allergy. In infants, urticaria, eczema or gastrointestinal bleeding may be due to foods such as milk and eggs, but clinical tolerance usually develops within a few years. Peanuts, tree nuts, seafood and seeds, as well as milk and eggs, can cause anaphylaxis in highly allergic children, and re-exposure to such foods presents the risk of life-threatening reactions[7].

-Approximately 5% of children younger than 3 years and 1.5% of the general population experience food allergic disorders, indicating that about 4 million Americans suffer from food allergies[11].

-A dichotomy exists between perceived food allergy and that confirmed by appropriate challenge procedures. Only 40% of suspected food allergy has been confirmed by double-blind, placebo-controlled food challenges. . .In a recent survey of 5000 American homes, the percentage of individuals reporting peanut allergy was 7.2% [16].

-Allergy to peanuts represents **28% of food allergies** and occurs under 1 year of age in 46% of cases, under 15 years of age in 93% [23].

-Ewan reported on 62 cases of peanut and/or nut allrergy evaluated in a one year period. **Peanuts accounted for nearly half of the allergies, with 55% of the allergies presenting by age 2 years and 92% by age 7 years.** [33].

New* -Here's a publication that just may change our perception of peanut and nut allergy somewhat. The April 1999 issue of the *Journal of Allergy and Clinical Immunology* contains an article by Sicherer, Munoz-Furlong, Burks and Sampson entitled **"Prevalence of peanut and tree nut (TN) allergy in the US determined by a random digit dial telephone survey."** [65] The title may sound nondescript, but read on- the findings are very significant:

- A total of 4374 households contacted by telephone participated (participant rate, 67%), representing 12,032 individuals.)
- Peanut or TN allergy was self-reported in 164 individuals (1.4%). . . **the prevalence of reported allergy in adults (1.6%) was higher than that found in children under 18 years of age (0.6%).**
- In 131 individuals, details of the reactions were obtained. When applying criteria requiring reactions to be typical of IgE-mediated (allergic) reactions (hives, angioedema, wheezing, throat tightness, vomiting, and diarrhea) within an hour of ingestion, 10% of these subjects were excluded.
- Among the remaining 118 subjects, reactions related to: **peanut (58), walnut (24), cashew (8), Brazil nut (8), almond (7), pecan (7), hazelnut (3), Macadamia nut (2), unspecified mixed nuts (6)** (Only four [all adults] reported both peanut and TN allergy, and 5 reported reactions to more than one TN). Allergic reactions involved:
  - **1 organ system (skin, respiratory, or gastrointestinal systems) in 50 subjects (42%),**
  - **2 in 45 subjects (38%),**
  - **and all 3 in 23 subjects (20%).**
  - Forty-five percent of these 118 respondents reported more than 5 lifetime reactions. . .
  - 51% had other food allergies
  - 35% had atopic dermatitis (eczema)
  - 34% had asthma
  - 33% had allergic rhinitis. . . [94% of the subjects reported at least one of these atopic diseases (eczema, asthma or rhinitis.]

Conclusions: Peanut and/or tree nut allergy affects approximately 1.1% of the general population, or about 3 million Americans, representing a significant health concern. Despite the severity of reactions, about half of the subjects never sought an evaluation by a physician, and only a few had epinephrine available for emergency use.

Two observations of this study were novel:

- First, only 4 subjects (all adults) reported allergy to both peanut and at least one tree nut. Previous studies in patients referred for allergy evaluations reported reactivity to tree nuts in 20% [33] and 34 % [13] of patients with peanut allergy.
- The second novel finding was that these allergies were more common in adults than in children because the general prevalence of food allergy is usually greater in children (7%) than in adults (1% to 2%) [11]. Because peanut and tree nut allergies are usually not outgrown[17] [12], there may be a greater representation among adults, a population that has accumulated affected individuals.

Additional comment:

While the study was only a random telephone survey, done by a standardized questionnaire, by a professional group (Innovative Medical Research, Inc (Towson, Maryland), **the findings are different than previously reported, and seem less alarming.** (posted April 12th, 1999)

Comment on Doctor's Guide on Internet, by Anne Munoz-Furlong(posted May 6th, 1999)

* **"Up to 8% of children less than 3 years of age and approximately 2% of the adult population experience food-induced allergic disorders**. A limited number of foods are responsible for the vast majority of food-induced allergic reactions: **milk, egg, peanuts, fish, and tree nuts in children** and **peanuts, tree nuts, fish, and shellfish in adults**. Food-induced allergic reactions are responsible for a variety of symptoms involving the skin, gastrointestinal tract, and respiratory tract and may be caused by IgE-mediated (allergic) and non-IgE-mediated (or non-allergic) mechanisms. . **the skin and respiratory tract are most often affected by IgE-mediated food-induced allergic reactions**, whereas gastrointestinal disorders are most often caused by non-IgE reactions. . . The initial history and physical examination are essentially identical for one or the other, but the subsequent evaluation differs substantially. Proper diagnoses often require screening tests for evidence of food-specific IgE and proof of reactivity through elimination diets and oral food challenges. Once diagnosed, strict avoidance of the implicated food or foods is the only form of treatment. Clinical tolerance to food allergens will develop in many patients over time, and therefore follow-up food challenges are often indicated." [71, 72] (posted June 23d, 1999)

Diagnosis of food allergies

-**the double-blind, placebo-controlled food challenge (DBPCFC)** is the 'gold standard' for diagnosis of food hypersensitivity. **Skin prick tests and RASTs [allergy tests done on blood sample of patient] are sensitive indicators of food-specific IgE antibodies but poor predictors of clinical reactivity**. In other words, challenges are the only sure way of appropriately diagnosing food allergies, especially in cases of suspected food allergy [8].

-the evaluation of adverse reactions to foods depends on a careful clinical history, diagnostic studies

including appropriate skin testing or in vitro testing with food extracts. . . [11]

 * Regarding "a careful clinical history", two observations:

> **-refusal or dislike of a food** right from its first introduction in the child's diet **could be a sign of allergy to that particular food.**
>
> **-the food that may contain the allergen**, either hidden or non-identified, **is usually immediately spat out or vomitted if any amount was swallowed,** as if by a **"defense mechanism" in the allergic child**. Nevertheless, **in the severely allergic child, even if the food was not swallowed, a certain degree of absorption has taken place, and a reaction may occur (not in all cases)**: vomiting, angioedema (swelling of throat, tongue, or lips), itchiness, or hives, fortunately of short duration because of this characteristic.
>
> We occasionally see children in our practice that **have always disliked and refused peanut butter** or foods containing peanut, **but had never had any allergic reaction; skin tests, however, to peanut are sometimes very positive**. (personal comment, posted Jan 13th, 2000)

* Comments:

> **Dr. Rhoda Sheryl Kagan**: Stating that positive skin prick tests are "poor predictors of clinical reactivity" in the words of the authors, one should not forget that negative tests may also be poor predictors of sensitivity. (Oct. 1998)

-the skin prick test is the most widely used test for detecting food hypersensitivity. . . using **fresh foods** may be more effective for detecting the sensitivity to food allergens. Fresh foods should be used for primary testing for egg, peanut, and cow's milk sensitivity, according to some authors [9,28]. (see cases reported of anaphylaxis to macademia nuts, above)

* Comments:

> **Dr. H. Blumer:** (and I agree, based on personal experience) Allergy to eggs, cow's milk and peanut, will be detected by available allergy extracts, and fresh foods are not usually necessary. In cases of suspected allergy to these foods, fresh foods could be used if the tests are negative using the regular extracts. (Oct. 1998)

* Food extracts for diagnostic purposes often lack sufficient activity and consistency...divergent allergenic activities are found at times...heating of some foods remarkably reduce the activity...variations in extracting conditions...and storage stability..[41].

* Eigenmann and Sampson evaluated a more sophisticated method of interpreting skin tests while the results of double-blind, placebo-controlled challenges were considered the 'gold-standard' for diagnosis, and found that **skin prick tests are a useful procedure for evaluating clinical reactivity to egg, milk, peanut and wheat....and the usual grading method of a positive skin test recorded**

as a wheal diameter 3 mm greater than the negative control remains just as good a predictive value [43]. (posted Feb 2, 1999)

* Armstrong and Rylance, in the Feb. 1999 issue of *Archives of Diseases of Children*, report their findings in their study entitled "Defininte diagnosis of nut allergy." Out of 96 children referred over a 27 month period (1994-1996) for nut allergies presenting with urticaria, facial swelling, anaphylactic shock, vomiting... 16 children from a sample of 51 who were tested for nut allergy had no reaction to an oral challenge. Positive IgE against peanuts was found in 9 of these 16 children. Their conclusions were: **skin prick testing and IgE measured by RAST tests are inadequate tests for nut allergy. The definitive diagnosis test for nut allergy in the hospital setting is direct oral challenge** [69] (posted May 25th, 1999)

* Bock, at *Allergy Update 1999* in Toronto, stressed that **skin tests detect antibody-hypersensitiviy is demonstrated by double-blind placebo-controlled food challenges. Unfortunately, reliance on positive food skin tests is much lower than on the negative skin tests in regard to predictive accuracy or value.** (posted July 11th, 1999)

Increase (?) in the frequency and severity of reactions to peanuts

-The current increase in the prevalence of food allergies appears to have several causes including **better screening, improved diagnosis and changes in both the techniques used by food manufacturers and eating habits**[1].

-Experience over the past decade suggests that the **ready availability and early introduction of highly allergenic foods (e.g. peanuts and nuts) into the diet** will only increase the number of individuals suffering from hypersensitivity reactions to foods [11].

-Peanut and tree nut allergies are potentially life-threatening. . . and appear to be **increasing in prevalence** [13].

-**Increase in frequency** of peanut allergy **and fatal cases** have been reported [23].

* -The prevalence has increased substantially, **one in two-hundred 4-year-olds**[32] ...related probably to the doubling and trebling of the prevalence of allergic asthma, rhinitis and eczema in certain, mainly "westernized," populations, according to Pamela W. Ewan[33].

New * -Drs Gideon Lack, and Jean Golding, in a letter published in the British Medical Journal of Aug 1996, made the following comments about her article, " **Pamela W. Ewan makes the important statement that the incidence of peanut and nut allergy is rising and that sensitisation seems to occur early in life. Regrettably, she does not provide any evidence to back her recommendation that "young allergic children should avoid peanuts and nuts to prevent the development of this allergy" and her**

extraordinary suggestion that avoidance should be practised until the age of 7. There is no evidence that avoiding foods during lactation or early childhood prevents allergic sensitisation to these foods. [96] (posted July 26th, 2000)

* Comments:

Dr. Rhoda Sheryl Kagan: The known prevalence of the frequency and severity of reactions to peanuts is 0.6%-1.0%. The medical literature suggests an increase, but no figures are given. **Bock, in a talk given in Montreal last June (1998) said that the prevalence has not changed.** (posted Oct. 1998)

* According to Emmett, Angus, Fry. et Lee, from Surrey, UK . . . Peanut allergy is reported by 1 in 200 of the population and is commoner in those reporting other allergies. **The fact of similar rates in children and adults argues against a recent marked rise in prevalence.. . . .** [73] (posted July 12th, 1999)

New * Zeiger, in the Jan issue of J Pediatr Gastroenterol Nutr writes. . ."**food allergy has increased in prevalence during the past decade**, and thus represents a major burden to our young. . . Identifying and developing effective strategies to prevent food and other allergic diseases represents a high priority for medicine at this time because of the **unbridled increase in the prevalence and morbidity** attributed to them." [90] (posted Jan 23d, 2000)

* **The impact of peanut allergy on children and adults**

At a poster session during the Annual Meeting of the AAAA&I Feb 26-March 3, 1999 in Orlando, **MN Primeau, RS Kagan, C. Dufresne, Y. St-Pierre, H. Lim, and A. Clarke** presented their evaluation of the impairment in quality of life and family relations experienced by individuals with a confirmed diagnosis of peanut allergy (PA) based on history and skin test or RAST , compared with the impairment experienced by patients with a chronic musculoskeletal disease (MSD). Impairment of quality of life was assessed by the vertical visual analogue scale (VVAS) [anchored from 0 (no disruption of daily activities) to 100 (most disruption imaginable) and the Impact on Family Questionnaire [0 (no impact) to 24 (maximum impact)]. One hundred and thirty eight PA children with disease duration of 4 years were compared with 61 MSD children and 37 PA adults and 41 MSD adults. . . **Peanut allergic children compared to MSD children with little physical disability have much more impairment in their quality of life and family relations. More importantly, even when compared with MSD children overall, the impairment of peanut-allergic children is greater, attesting to the substantial impact of peanut allergy.**

A second element of this aspect was to evaluate **which factors were involved**. Their conclusions were: **Younger age of the children, closeness to the first reaction, past history of anaphylactic reaction and presence of other atopic conditions were all associated with increased impairment of quality of life or family relations.** Age at the first allergic reaction, severity of the first allergic reaction, presence of asthma and presence of other food allergies were not associated with the severity of impairment of quality of life and family relations. (posted March 13th, 1999)

* Dr. **Marie-Noël Primeau** asked to make the following changes to the work cited above, i.e. that the patients in their control group of musculoskeletal disease did not have MSD. The adults (>80%) had disseminated lupus erythematosus (LED or SLE) and the children, (>70%), juvenile rheumatoid arthritis.(posted March 24th, 1999)

* This study has now been published in *Clin Exp Allergy, in Aug. 2000*: **The psychological burden of peanut allergy as perceived by adults with peanut allergy and the parents of peanut-allergic children.** The authors conclude: "Given the considerable disruption in daily activities and family relations reported by the parents of peanut-allergic children, accurate diagnosis of peanut allergy is essential. Our work should make health care professionals dealing with children with confimed peanut allergy more aware of the support that these families may require. Furthermore, we hope to motivate food industries to offer more 'peanut free' products to decrease the dietary restrictions of these patients while minimizing their potential for accidental ingestion. " [97] (posted Aug. 23d, 2000)

Is it a lifelong allergy?

-to determine whether there are any differences between children who remain mildly or moderately allergic to peanut (15 subjects) and **children with similar histories but a negative reaction on challenge with peanut** (also 15 subjects) Hourihane and coll. found that of the children that had lost their allergy , 13 had allergy tests and 8 showed no allergy, **the other 5 still showed a positive test** but reactions were not > than 5 mm. IgE levels were the same in both groups. The group still allergic showed allergies to other foods more so than the negative group. The conclusion was: appropriately trained clinicians must be prepared to challenge preschool children with peanut as some will be tolerant despite a history of reactions to peanut and a positive skin prick test to peanut [12].

* See complete article

* Electronic responses to this article:

* Comments:

- **Dr. Rhoda Sheryl Kagan, and Dr. Anne Des Roches**: There's doubt as to the diagnosis of true peanut allergy in the fifteen patients that have lost their allergy, which was based on history only from the referring doctors. They don't seem to get to the central allergy clinics until approx. 3 years later for confirmation +/- challenge. One has to wonder. Also, there is worry that the airplay this article will get will lead to a degree of unrealistic optimism, until it is duplicated by others or its methods clarified. (posted Oct. 1998)

* In a letter to the Editor of the *British Journal of Medicine* Nov 7h, 1998, by **T. David**, professor of Child Health, Manchester. Eng. entitled **"Patients have not been proved to grow out of peanut allergy,"** he too questions the allergy histories of the patients in Hourihane's study - were they really allergic in the first place? He refers to two studies, one being Bock's 1987 article "Prospective appraisal of complaints of adverse reactions to foods in children during the first three years of life" where parents' reports could be confirmed in only 28% of 133 children with reported food intolerances[29]. In the author's reply, referring to the "unresolved question" he states that "our results suggest with some caution that some children grow out of peanut allergy, and we accept that absolute proof of resolution is absent."[30].

-*L'Actualité* (Vol: 23 No: 10 15 juin 1998 62) in their section on Health and Medicine, had a short paragraph entitled: "Une allergie reversible?" (A reversible allergy?) The translation reads as follows: "Is your child allergic to peanuts? Do not despair: he/she has a 40% chance of not being allergic to peanuts at age four. British researchers followed 14,210 children from birth to four years of age. One out of 200 infants becomes allergic to peanuts by 20 months of age.

Nevertheless, at age four, two out of five spontaneously outgrew the allergy.[25] (their source: *New Scientist*) . A search of Medline did not reveal any mention of this study. But:

* the study (ALSPAC or Avon Longitudinal Study of Pregnancy and Childhood birth cohort study) was presented at the annual AAAA&I meeting in Washington, DC, in March, 1998 by Golding, Fox and Lack on
14,210 children born over 21 months collated via questionnaires. Peanut allergy was identified on the basis of questionnaires, skin testing and/or anti-IgE to peanut, and confirmed by double-blind placebo-controlled food challenges (DBPCFC).

- The cumulative prevalence of peanut allergy at 24 months was 0.21% and at 48 months was +/- 0.31%.
- **The mean age at first reaction was 20.5 months.**
- **All allergic children reacted upon first known exposure to peanuts.**
- 75% of reactions were due to eating and 25% to touching peanut.
- Peanut butter was responsible for 40% of reactions, whole nut for 41% and peanut containing foods for 19%.
- 11% of the group had siblings with peanut allergy.
- Allergy to other foods was reported by 50% and 38% of children had egg allergy.
- The most common symptoms on DBPCFC were:
    - nasal symptoms (62%),
    - urticaria (hives) (54%),
    - vomiting (31%).
    - wheeze (15%)
    - and stridor (difficult breathing) (7%).
- Two patients required intramuscular epinephrine and one patient had a late-phase reaction.
- **41% (9/22) of children challenged were demonstrated to have outgrown their allergy.**
- Children who outgrew their allergy tended to present earlier than those with

persistent peanut allergy.

- The ones not having outgrown their allergy were significantly more allergic with
  - higher rates of eczema (100% vs 44%)
  - asthma (85% vs 11%) and
  - other food allergies (70% vs 33%) and they were more sensitive on allergy tests.

Conclusions:

Peanut allergy represents a significant problem by 2 years of age and that by 5 years nearly half of these children will lose their allergy. (posted March 13th, 1999)

This is not quite what was reported in an earlier study, Bock and Atkins in 1989 published their evaluation of 32 patients that had a positive DBPCFC as well as a positive skin test to peanuts. Follow-up challenges, conducted 2 to 14 years after the original challenge, showed that all retained their sensitivity, confirming the peanut sensitivity can be quite long-lasting [17]

-Peanut and tree nut allergies are potentially life-threatening, **rarely outgrown** . . [13] [56].

* -An interesting feature of food allergy in general, although unusual, **"worsening of reaction after prolonged avoidance has been described.**[27] . .David reported 4 children with atopic dermatitis (eczema) who had foods to which they were allergic reintroduced into their diets, and they experienced anaphylactic reactions[74]. . ." These are comments made by the authors (Oppenheimer JJ, and Bock, SA) in a report about an 8 year-old child with a history of milk-induced exacerbation of atopic dermatitis who, after 18 months of avoidance, experienced significant increase in her reactivity. The communication is titled"The ice cream parlor challenge could be a killer" published in the *J Allergy Clin Immunol* 1998;102:325-6. [75] (posted July 8th, 1999)

New* At the 1999 American College of Allergy, Asthma & Immunology Annual Meeting held in Chicago, Nov 11-17th, among the New Findings in Food Allergy Research presentations, Dr Sami Bahna reported on:

"Outgrowing" Peanut Allergy
Recent studies indicate that peanut allergies, which afflict approximately 1% of the US population, can be "outgrown" by adolescence[12]. Indeed, findings presented by J.M. Spergel, MD, PhD, suggest that resolution is more likely to occur in patients with smaller skin test reactions and clinical reactions limited to the epidermis. Spergel's group subjected 38 patients with a clinical history of reaction prior to evaluation and with a positive skin test to peanut challenge. Twenty-one patients persisted with positive challenge (PC) and **18 patients had a negative challenge (NC) despite positive skin tests.** One patient became tolerant by challenge while another patient's reaction went from positive to

negative.
Both PC and NC groups had equivalent medical backgrounds although none of the patients with anaphylaxis became tolerant within the follow-up period of 2 to 6 years. The most significant difference occurred, however, in the size of the skin test -- the PC group experienced larger wheal and flare ($P < .005$).**This study confirms the findings of a few other recent reports demonstrating that peanut sensitization can be outgrown.** Favorable factors include onset during childhood, low degree of reactivity, and clinical manifestations other than systemic anaphylaxis. (posted Nov 18th, 1999)

New!* "The natural history of food allergy documents that allergy to cow's milk, egg and soy frequently remit whereas **allergy to peanut, nuts and fish typically persist to adulthood, although exceptions exist.** Food allergen avoidance subsequent to sensitization and manifestation of symptoms appears to hasten tolerance; however, the immunologic mechanism responsible for tolerance to one food group and not another is poorly understood.[90] (posted Jan 23d, 2000)

New!* **"Natural hx of peanut allergy in young children and its association with peanut-specific IgE."**

At the annual meeting of the AAAA&I held in San Diego, Mar 3-8th, 2000, Vander, Leek, Liu and Brock state : "Previous studies have shown that peanut allergy is rarely outgrown, although recent observations suggest that younger children with milder reactions may lose their reactivity." The objectives of the study they report on, were to "observe the frequency and nature of adverse reactions due to accidental peanut exposure in young children with previous clinical hypersensitivity , and to determine the potential value of serum peanut-specific IgE antibody levels for ongoing follow-up." Eight-two (82) children were identified with clinical peanut hypersensitivity diagnosed before their 4th birthday. All had positive skin tests. They were followed over a median 5.6 yrs (range 1.2 to 22.1 yrs), contacted yearly to track adverse reactions due to accidental peanut exposure. IgE antibody levels were obtained in 42/82 subjects.
The majority of young children with clinical peanut hypersensitivity will have **adverse reactions due to accidental peanut exposure within 3 yrs of their initial evaluation**. In addition, it appears that young children who present with only skin reactions are at risk for respiratory and/or gastrointestinal involvement with subsequent peanut exposure. **Children who have had only cutaneous reactions to peanut have lower peanut-IgE levels** than those who have respiratory and/or gastrointestinal involvement. (posted Mar 9th,2000)

New!* **"The natural history of peanut allergy."**

A joint group from Johns Hopkins (Skolnik et al) with H. Sampson from Mont Sinai, at the annual AAAA&I meeting in San Diego, Mar 3-8th, 2000, also reported on the **duration of peanut allergy in a study whose purpose was to determine the number of children diagnosed with peanut allergy who became tolerant later in life.** Peanut-specific IgE (PN-IgE) quantification was done and the ones with a titre of < 20 kU/L and no history of reaction in the past year were asked to participate in a double-blind placebo-controlled peanut challenge (DBPCPC) (unless the previous reaction was

severe, in which case a cut-off of < 10 kU/L was used.) Some patients had open challenges. To date, 103 patients, age range 4-17.5 yrs (median 6.5) have participated in the study. These patients were diagnosed with peanut allergy from age 2 months to 10 yrs (median 1.5 yrs). Forty-four patients (43%) were identified as definitely peanut allergic since their PNIgE was > 20kU/L. Twenty-one patients with a PN-IgE < 20 kU/L refused the challenge. The remaining 38 patients participated in either a DBPCFC or an open challenge. **Skin tests were repeated before the challenge in 13/38 patients and four had turned negative.** The median range of PN-IgE of the patients challenged was 0.75 kU/L (range < 0.35 (undetectable) to 20.4 kU/L). **Overall, 26 patients had a negative challenge and are believed to have outgrown their peanut allergy** (ages 4-11.5 yrs (median 6), PN-IgE < 0.35 to 20.4kU/L (median 0.54). The remaining 12 experienced a positive challenge (ages 4-9.5 yrs ; median 5), PN-IgE < 0.35 to 11.6 (median 1.24 kU/L). 71% of patients with a PN-IgE < 2 kU/L had a negative challenge. Of those challenged, PN-IgE level for those who passed versus those who failed were not different at the time of diagnosis or challenge. The severity of the initial reactions were also similar, with both groups including patients with moderate to severe anaphylaxis.

Conclusion : **This study demonstrates that peanut allergy is not necessarily life long. Patients with very low PN-IgE levels should be challenged in a medical setting to determine whether they can now tolerate peanuts.** (posted Mar 9th, 2000)

 * Rommy Koetzler, M.D. and Alexander C. Ferguson, M.D. published their study entitled **Outcome of Peanut Allergy in Infancy: An Oral Challenge Study in School Age Children**, in the Canadian Journal of Allergy & Clincal Immunology, July 2000, Vol. 5 No.6. Fifteen children with documented peanut reactions, and positve skin tests as infants were challenged with increasing doses of emulsified peanut butter in serial doses of 10 μg to 5 g. increasing until symptoms or signs developed, or the maximum dose reached. *Results*: : 8 children had a mild reaction, 3 moderate, and none severe. Reactivity was unrelated to age at first peanut contact or to current age. Current skin test size (wheal diameter) was smaller in those with negative challenges, and anti-peanut IgE was lower. Symptoms were elicited by doses of 10μg or greater (abdominal pain, tingling tongue, itchy throat, nausea, itchy lips) whereas objective signs (vomiting, urticaria, pruritis, facial oedema, and cough) required 100mg or more of peanut butter. One subject had no reaction, and three had symptoms but no objective signs with a 5 gm dose. If objective signs are taken as evidence of persistent peanut allergy, 4/15 (27%) subjects appeared to be tolerant to peanut. They conclude that **"whereas allergy to peanut tends to persist, the severity of reactions decreases - more than trace amounts may be required to elicit a significant reaction and a substantial proportion of children may be tolerant.** A much larger cohort of children and repeated challenge testing will be required to confirm and validat theses findings. " (posted July 27th, 2000)

Immunotherapy (hyposensitization or desensitization)

-the question of desensitization (immunotherapy) has been brought up many times because of the increasing problem of peanut allergy, to try and help the patients diminish their allergy to peanuts, one reason being the large number of accidental ingestions. Over the years,trials have been published, the last one by Nelson, Bock et al, in June 1997. They recruited 12 patients with immediate hypersensitivity to ingestion of peanuts. Half were treated with injections of peanut extract: a

maintenance level of tolerance was first achieved by a rush protocol, then maintained with weekly injections for at least a year. The other six were untreated control subjects. All patients underwent double-blind, placebo-controlled, oral peanut challenges initially, after approximately 6 weeks, and after 1 year. Only three patients remained tolerant of the full maintenance dose. The increased tolerance to oral peanut challenge was maintained in the three subjects who received full maintenance doses, but there was partial or complete loss of protection in the patients who required dose reduction because of **systemic reactions (allergic symptoms following desensitization injections).** The authors conclude that injections of peanut extract increase the tolerance of patients with peanut allergy to oral ingestion of peanuts. **Injections result in repeated systemic reactions in most patients, even during maintenance injections. For clinical application of this method of treatment, a modified peanut extract is needed[3].**

In summary: at this point in time, desensitization for peanut allergy, although promising, is not recommended because of the dangers involved during treatment in the form of severe reactions. More research is needed before such treatment can be considered.

* -In a communication in the Nov 1998 issue of the *Canadian Journal of Allergy & Clinical Immunology*, Dr. Joseph Greenbaum recounts his experience with food immunotherapy, including one case of peanut immunotherapy. Although the author was encouraged with the results, the editor of the journal, Dr. Gordon Sussman, warns in his note, that "although well tolerated and appearing efficacious in this report, **several pitfalls and possible dangers of this type of treatment need to be addressed...**It is impossible to assess efficacy without a control population...**The major concern is patient safety.** Food immunotherapy may be an **extremely dangerous procedure and can create a false sense of security**. Several severe reactions and deaths have been reported using food immunotherapy, even in well-designed studies. Food immunotherapy, as outlined in these case studies sets a **dangerous precedent which could have disastrous consequences**. We agree that the treatment of food anaphylaxis using **avoidance is not ideal -- but it is presently the only proven treatment we have**. Let's work together to develop a better treatment through properly designed research protocols that give us reliable and reproducible information." [40]. (posted Dec 8th, 1998)

* **"Scientists develop vaccine strategy for peanut allergy"** is a commentary by Scott Gottlieb, from New York, published in the April 3d issue of the *British Medical Journal* [60], referring to the work of Dr Kam Leong, and associates at the Johns Hopkins School of Medicine in Baltimore, reported in *Nature Medicine* [66] "Researchers believe that they may be close to developing a new strategy to combat anaphylactic allergies - such as the increasingly common allergy to peanuts- in which doctors induce tolerance using an oral formulation containing a gene from the offending allergen. . .the DNA from peanut was administered orally to mice. . . the severity of anaphylaxis was blunted. . .**the findings are a long way from being used in clinical applications**." . . "The immune system of mice is also quite different from that of man. . . One can envision that this model would be an interesting approach to generate mucosal immunity for a variety of allergens" said Dr Leong. (posted April 5th and 18th, 1999)

* To see an example how such research could be interpreted differently:

BBC News on line, April 1st, 1999
Also, relevant news stories: Food producers play safe with nuts(20 Jul 98 |

Health

Food allergy clinic opens for mums-to-be (29 Jun 98 | Health
Woman can 'pass peanut allergy to their children' (01 Apr 99 | Health

(posted April 6th, 1999)

*-In the Aug. 1999 issue of the *Journal of Allergy and Clinical Immunology* Hong, Michael, Fehringer and Leung report on their experience with a **pepsin-digested peanut extract** that **could eventually be used in desensitization**. Previous immunotherapy (desensitization) studies of peanut-allergic patients (one of which is summarized above) showed a high incidence of systemic allergic reactions during treatment, making such treatment very dangerous, and not practical at this point in time. Researchers are constantly looking for a modified peanut extract to lower allergenic properties (in other words, resulting in much less systemic reactions.) Laboratory evaluation of this extract suggests that it may be useful in peanut immunotherapy because "pepsin digestion eliminates IgE reactivity but maintains T-cell reactivity" (less systemic reactions yet still effective)[81] (posted Aug 23d, 1999)

***Link between asthma and peanut allergy**

Is there a link between having asthma and the intensity of the allergic reaction caused by peanut? According to the medical publications on this aspect, **particularly regarding anaphylactic reactions reported to peanuts, the severity of the reaction seems to be directly related to the atopy the patient has (presence of total allergies), in other words, the most severe reactions reported occurred in patients that had other food allergies and environmental allergies, the latter ones responsible in great part for the asthma.**

- In 1988, Yunginger et al, of the Dept of Pediatrics, Mayo Medical School, Clinic and Foundation, published their findings on fatal food-induced anaphylaxis (rarely reported at that time.) . . . in 16 months, they identified 7 such cases (5 males and two females, aged 11 to 43 years). **All victims were atopic** with multiple prior anaphylactic episodes after ingestion of the incriminated food (**peanut (4);** pecan (1); crab (1); fish (1). Factors contributing to the severity of individual reactions included denial of symptoms, concomitant intake of alcohol, reliance on oral antihistamines alone to treat symptoms, and **adrenal suppression by chronic glucocorticoid therapy for coexisting asthma** (reduction of immune defense due to long-term use of inhaled cortisone preparations). . . each case showed elevated levels of IgE antibodies to the incriminated foods.[62]
- In 1992, Sampson, Mendelson and Rosen, of the Division of Pediatric allergy, Johns Hopkins University School of Medicine, identified 6 children and adolescents who died of anaphylactic reactions to foods and seven others who nearly died and required intensive care. . . Of the 13 children and adolescents (age range, 2 to 17 years) **12 had asthma that was well controlled**. All had known food allergies, but had unknowingly ingested the foods responsible for the reactions. The reactions were to **peanuts (four patients), nuts (six patients)**, eggs (one patient) and milk (two patients), all of which were contained in candy, cookies, and pastry.[63]

- Hourihane, Kilburn, Dean and Warner, in their 1997 publication: "Clinical characterisitcs of peanut allergy" [2] support this. There is no figure or table in the paper, but in a personal communication Dr Hourihane sent the following information: **in 525 subjects who have had more than one reaction to peanuts:** mild reactions occurred in 47 non-asthmatics versus 45 in asthmatics; moderate reactions in 65 asthmatics versus 168 in non-asthmatics, but **severe reactions occurred in 187 asthmatics versus 78 in non-asthmatics!!**. In total, reactions occurred in 335 asthmatics versus 190 in non asthmatics.
- Pumphrey en 1996 also showed an association between atopy including asthma with reactions to foods and with younger age in a series of anaphylactic reactions.[64]
- Sicherer, Burks et Sampson, in 1998, in *Pediatrics*, showed 74% of subjects had asthma but the link with severity of reaction was not reported. [13]
- "I think the link between asthma and severe reactions is convincing and is widely supported by those in the field (admittedly anecdotally). It is certainly taken seriously by all the leaders as an index of the need for adrenaline rescue medication supply and training." (Hourihane, personal communication) (posted April 8th, 1999)
- See also the study from Sweden in the chapter on "prevalence" of peanut allergy (above) posted May 13th, 1999

New * **What about reactions occurring by simply being in the presence of peanuts or exposed to the odor of peanuts?**

There's no mention in the above references regarding contact with peanuts other than by ingestion and by contact with intact skin[10] , although Hourihane refers to "**anecdotal reports (not supported by challenge studies) of subjects reacting strongly to the smell of peanuts or to being in the vicinity of an open jar of peanut butter** [58, 59]**.** The dose of presumably airborne peanut protein involved in these reactions must be very low. The **more common scenario is an allergic reaction after a minimal contact with peanuts** [2] , through intact skin (e.g., being touched by someone who has handled peanuts, accidental ingestion of small amounts of peanut protein, or eating bread buttered with a knife previously used to make a peanut butter sandwich for someone else)."

* **Commercial airlines and peanuts**

* At the recent annual meeting of the AAAA&I (Feb. 1999 in Orlando) Sicherer, Furlong, DeSimone, and Sampson presented a paper entitled: **"Peanut Allergic Reactions on Commercial Airlines."** the purpose of the study was to describe the clinical characteristics of allergic reactions to peanut (PN) on airplanes. Participants in the National Peanut and Tree Nut Allergy Registry (PAR) who indicated an allergic reaction were interviewed by telephone.

- 62 of 3,704 PAR registrants indicated a reaction on an airplane
- 42 patients or parental surrogates consented to further questioning (median age of affected: 2 yrs, range 6 mo-50yrs)
- of these, 31 reacted to PN, 3 to tree nuts, and 8 to uncertain exposures, suspected PN
- exposures occurred by mouth (20), skin (8), and inhalation (14)

- reactions generally occurred within 10 minutes of exposure (32/42);
- reaction severity correlated with exposure route (mouth > inhalation > skin)
- the causal food was generally served by the airline (37/42)
- medications were given in flight to 20 patients (epinephrine to 6) and to an additional 14 on landing/gate return (including IV to 2, one forcing a return to the gate), totaling 81% treated.
- flight crews were notified in 33% of reactions.
- during 10 PN allergic inhalation reactions, > 25 passengers were estimated to be eating PN at the time of reaction.
- initial symptoms generally involved the upper airway with progression to skin or further lower respiratory reactions (no gastrointestinal symptoms).
- 2 subjects were given epinephrine in flight.
- asthma was previously diagnosed in 6 patients.

Conclusion: Food (peanut and nut) allergic reactions occurred during commercial flights but airline personnel were notified in only 33% of cases. Reactions were frequently severe, requiring medication including epinephrine. **Severe reactions were primarily due to accidental ingestion, but respiratory reactions occurred from inhalation** when many passengers were consuming PN. (posted April 2nd, 1999)

> *I e-mailed Dr. Hourihane, asking his opinion on the importance of peanut odor, and this was his response: "I am not personally aware of proven anaphylaxis associated with the smell but it is often related by parents that the child has become lethargic and clingy after entering a room with peanuts open in the room. **This cannot be called anaphylaxis with any confidence**. My feeling is that some people really do degranulate on inhaled exposure (Dr. Hourihane is referring to degranulation of cells involved in allergic reactions, specifically mastocytes, meaning they have a typical allergic reaction) but**the reactions are minor - usually upper airway and eyes with some urticaria (hives) maybe**. The major problem when exposed like this is **panic** especially on planes and in other confined spaces." (posted April 8th, 1999)

* The paper presented at the Orlando Meeting of the AAAA&I (summarized above) has now been published in the *Journal of Allergy and Clinical Immunology*, July 1999, vol 104, 186-9.

Further comments from the authors: Allergic reactions to peanuts and tree nuts caused by accidental ingestion, skin contact, or inhalation occur during commercial flights. . . **most of the inhalation reactions described were not life-threatening**. However, when one considers the whole group experiencing acute allergic reactions by ingestion and inhalation to peanuts or tree nuts while on commercial airliners, the imporance of exercising caution and having emergency medication available becomes apparent. [76](posted Aug. 1st, 1999)

* In the same issue of the journal, John M. James, M.D. summarizes the 'airline-peanut allergy' problem in an artilcle entitled, **Airline snack foods: Tension in the peanut gallery.** Here are some of his remarks:

> -. . . "there has been increasing concern and debate about the potential for individuals

with peanut allergy to experience an allergic reaction while on a commercial airplane that is serving peanuts and/or peanut-containing food. . . .The cabin of a plane in flight is certainly a less than ideal environment in which to recognize and properly manage a potentially severe allergic reaction. . . In mid-1998, the Department of Transportation (DOT) issued a proposal that would have mandated that the 10 major US commercial airlines must provide "peanut-free zones" for passengers with allergic reactions to peanuts. . . This met great resistance from the Air Transportation Association. . . the US Congress. . .the mandate was never implemented, one of the reasons cited by members of the Congress was the lack of published, scientific data describing passengers with peanut allergy who had experienced allergic reactions caused by airborne peanut allergen on commercial airliners."

-Citing the paper by Sicherer and co-workers summarized above, Dr James underlines that this paper "represents the first published investigation describing the clinical characteristics of allergic reactions to peanuts on commercial airliners in subjects with peanut allergy. . . the self-reported allergic reactions, however, were very consistent with allergy. . .this investigation does not provide all the data needed to resolve this ongoing debate, but it certainly provides a solid foundation to better address these potentially life-threatening exposures and allergic reactions."

-"There are some disturbing findings in this investigation. First, why was there such a low level of notification of flight crews and airline personnel?. . .Second, could other potential irritants (eg. strong perfumes, passive tobacco smoke on clothing of smokers, and cleaning agents) have contributed to the inhalation reactions in some of the subjects, especially those with asthma? . . Finally, 5 subjects received epinephrine while in flight to manage severe allergic reactions. This observation relates to another relevant debate focusing on the availability of injectable epinephrine on board commercial airliners and the availability of trained flight personnel to administer this medication."

-"Two things are very clear to me as this debate continues to develop: education and preparedness should prevail. . . In the final analysis, more objective data and proper education will help guide us in the ultimate resolution of this important debate and lower the tension in the peanut gallery." [77] (posted Aug. 1st, 1999)

Peanut oil

-refined peanut oil (heat processed) is not allergenic (in other words, it will not cause an allergic reaction in the peanut-allergic individual). Of 10 peanut-allergic patients challenged with peanut oil, none reacted to the protein-free oils. Subsequent reports have indicated that **oils contaminated with peanut protein** may indeed produce significant allergic reactions in peanut-sensitive individuals. **Cold-pressed oils are more likely to contain peanut proteins than hot-pressed oils [15].**

*  -In a 1994 *J Allergy Clin Immunol* paper, Hoffman and Collins-Williams studied various makes of peanut oil, and found that refined, hot-pressed peanut oils are free of protein but cold-processed peanut oils could cause reactions in peanut allergic individuals. They concluded that: **"Highly reactive individuals should avoid foods prepared in or with peanut oils, especially**

"health foods," which may be prepared with cold-pressed or unrefined peanut oil that may be contaminated with peanut protein." [95] (posted June 10th, 2000)

-Hourihane and co-workers evaluated two grades of peanut oil for a large group of subjects with proven allergy to peanuts, in a double-blind, crossover food challenge with crude peanut oil and refined peanut oil. **None of the 60 subjects reacted to the refined oil**; six (10%) reacted to the crude oil. They concluded that crude peanut oil should continue to be avoided. Refined peanut oil did not pose a risk to any of the subjects. Change in labeling to distinguish the two grades are recommended [18].

-Another recent study confirms these findings, and examined several brands of walnut, almond, hazelnut, pistachio, and macadamia nut oils. The oil extracts known to be from oils that had undergone less processing at lower temperatures tended to demonstrate qualitatively greater IgE binding (blood test proof of peanut-specific antibody) and higher protein concentrations, posing a threat to patients with allergy [19].

-On the other hand, Olszewski and coll. reported an allergy to peanut oil by skin test, and by double-blind placebo controlled challenges, concluding the **presence of residual allergenic proteins in crude and refined peanut oil**, and that the increase consumption of allergens in the form of peanut oil and fats **can contribute to the occurrence or persistence of symptoms and may be suspected to increase the risk of sensitization** [23,24].

* Comments:

> **Dr. Rhoda Sheryl Kagan:** Sesame oil (although sesame is not a nut), an oil commonly used, contains considerable levels of peanut protein. (Oct. 1998)
>
> See also: Peanut Oil (at the Anaphylaxis Campaign UK website)

* -How about peanut oil in vitamin A and D preparations: according to a Feb 1999 Swedish study, **sensitization to peanut during childhood through consumption of vit A adn D in oil-based solution seems unlikely**.[78]

* **What about sesame seeds and oil?**

> * Birnaum and coll. presented a case of a 52 year old woman presenting **hives** on several occasions **after eating sesame seeds, Indian bread, Chinese, Greek or Indian meals in restaurants, and facial swelling after local application of creams which were found to contain sesame oil.** She tested positive to sesame on skin tests but not by RAST. (AAAA&I Annual Meeting, 1997) (posted Feb 13th, 1999)
>
> * Levy and coll. made a survey of **sesame allergy in Israel** by doing RAST tests and skin

tests on 234 patients referred for food allergy evaluation during 1995-1996. RAST test results: 13 (5.5%) were positive to sesame. Of patients referred to a food allergy clinic with a history of angioedema, 15 of 61 were found to be skin test positive. Six patients from this group, aged 14 months to 26 years,were open challenged with sesame. Five were positive: urticaria (5), rhinitis/conjunctivitis (3), nausea and tachycardia (1). (AAAA&I Annual Meeeting, 1998) (posted Feb 13th, 1999)

* **Sesame allergy**, although less common than peanut allergy, **can be** every bit as **severe**. Sesame is used extensively in the food industry, and the seeds present a danger because of their versatility[51]. With the increasing demand for vegetarian food, the consumption of vegetable burgers as an alternative to beef burgers has now become widespread[52].**Sesame seed and sesame seed oil contain masked allergens of growing importance** [53]and a cause of occupational asthma[54]. (posted Feb 13th, 1999)

NB. There was no mention of sesame being related to peanut in any of these papers, but:

- **allergy to kiwi, poppy seeds, and/or sesame seeds often occurs in patients with a simultaneous sensitization to nuts and flour** [45].
- A review of the database of results of allergen skin tests by the dept of Allergy, Royal Children's Hospital, Melbourne, Australia**during 1990-96, sensitization to peanut was found in 1601 infants and children, to a tree nut (almond, brazil, cashew, hazelnut, or walnut) in 590; 491 to both: representing a combined prevalence of sensitization of at least 0.2%**. Sensitization occurred early: 920 children aged under 24 months were sensitized to peanut and 270 to a tree nut. But 531 children were found allergic to sesame seed, higher than the number sensitized to any tree nut; sensitivity occurred in 60% of the children (317) before age 2. [55] (posted Feb 13th, 1999)

* **What about sunflower seeds and oil?**

- Sunflower seeds have been reported causing severe allergic reactions in sensitive individuals[48] **Sunflower oil is not allergenic to sunflower seed-sensitive patients** [49].
- Hefle et al at the AAAA&I Annual Meeting in 1997 presented a paper about their experience in the identification and characterization of sunflower seed allergens: scant knowledge so far. Relationship of sunflower pollen and other pollens of the Compositae family, including short ragweed[50](posted Feb 13th, 1999)

* **What about coconut?**

In the *Journal of Allergy and Clinical Immunology,* June 1999 issue, Teuber et Peterson report a **"Systemic allergic reaction to coconut (Cocos nucifera) in 2 subjects with hypersensitivity to tree nut** and demonstration of cross-reactivity to legumin-like seed storage proteins: new coconut and walnut food allergens.". . . The reduced coconut protein. . . was previously shown to be

immunologically similar to soy glycinin.They conclude that **coconut allergy in patients with tree nut allergy is rare**; these are the first two patients ever reported, and therefore there is no general indication to advise patients eith tree nut allergy to avoid coconuts. [70]. (posted June 14th, 1999))

* **Identification of the allergenic peanut proteins**

According to Clarke and coll., in the Oct. 1998 issue of *Clinical Experimental Allergy*, there are **19 peanut proteins**. . . the major ones being Ara h 1 and Ara h 2 to which 70% of subjects reacted. Their study, however, highlights the **diversity of the peanut allergens**, and because the percentage of cases with sensitivity to a **15kDa protein was found to be higher in patient groups with severe reactions to peanut**, they conclude that **diagnostic extracts containing a high proportion of this 15kDa component may aid in diagnosis**[39].

* ". . . following our characterization of the two peanut allergens Ara h 1 and Ara h 2, we have isolated a cDNA clone encoding a third peanut allergen, Ara h 3. . . recognized . . .by serum IgE from approximately 45% of our peanut-allergic patient population . . . " [57] (posted March 12th, 1999)

* -Kleber-Janke, and coll. report in Int Arch Allergy Immunol Aug 1999, that sera of 40 peanut-allergic individuals detected **at least one of six identified recombinant allergens** which can be used to establish individual patients' reactivity profiles. A comparison of these profiles with the clinical data will possibly allow a further insight into the **relationship between clinical severity of the symptoms and specific IgE levels toward the six peanut allergens**. [82] (posted Sept 6th, 1999)

Dealing with peanut allergy:

Faced with the serious problem of peanut allergy, the following associations have come up with **position statements.**

- The **American Academy of Allergy, Asthma & Immunology:**
  - ***Anaphylaxis in Schools and other childcare settings***
  - * ***Anaphylaxis: Topic of the month - Nov. 1999*** (posted Nov 7th, 1999)
- The **Canadian Society of Allergy and Clinical Immunology:**
  - ***Anaphylaxis in schools and other childcare services***
- **Allergy, Asthma and Immunology Society of Ontario:**
  - ***Peanut Allergy - What You Need To Know***
- **The Canadian Pediatric Society - Allergy Section:**
  - ***Fatal anaphylactic reactions to food in children***

and the **highlights and recommendations** underlined by information groups such as:

- The **Canadian Association of Information on Allergies and Asthma**
  - ***Anaphylaxis: The fatal allergic reaction***
- **L'Association Québecoise des Allergies Alimentaires** (e.g.sept 1998 special issue of Les Mets Sages entitled:
  - ***Prévention des allergies alimentaires à l'école et en service de garde*** (Preventing food allergies at school and day-care centers) copy of which is accessible (in french) on the Quebec Social Services Web site
- **Calgary Allergy Network**
  - ***Living with anaphylaxis: Handling the Stress***
  - ***A Guide for parents/students with anaphylaxis., etc.***
- * **Peanut Allergy Network**
  - ***When a staple of kids' diet can be lethal***
  - ***Some tips for averting perils in food allergies***
- **Anaphylaxis Foundation of Canada**
- * **Anaphylaxis Campaign UK website** (posted April 6th, 1999)
- * **Peanut allergy-Allergies Net links** (posted May 28th, 1999)

* When should epinephrine (adrenaline) be administered?

This remains a difficult and touchy question.
There is no question that epinephrine administered by means of a subcutaneous or intramuscular injection is the treatment of choice for anaphylaxis;[84, 85, 62] Other medications such as antihistamines, inhaled asthma medications, or steroids, that subsequently may be given by physicians in treating anaphylaxis should not be regarded as first-line medications. (Position statement 34 of the AAAA&I (American Academy of Allergy, Asthma and Immunology) Board of Directors: ***Anaphylaxis in Schools and other childcare settings***) This position of the AAAA&I, an endorsement of a consensus statement originally drafted by the Canadian Society of Allergy and Clinical Immunology (CSACI) with its provincial affiliates and allergy organizations in 1996, further states "**epinephrine is the first drug that should be used in the emergency management of a child having a potentially life-threatening allergic reaction**. . . In patients who have had anaphylactic reactions, it is recommended that epinephrine be given at the start of any reaction occurring in conjunction with exposure to a known or suspected allergen. In situations where there has been a history of a severe cardiovascular collapse to an allergen, the physician may advocate that epinephrine be administered immediately after ingestion of the offending food **and before any reaction has begun** ***Anaphylaxis in schools and other childcare services*** (CSACI).

The CSACI consensus further states in the Appendix 2 section dealing with the Management of Specific Allergens, specifically peanut, re: "Suspected or actual contact with a known allergen": **The child should be under close and constant supervision for 4 hours after the suspected ingestion. Administer the epinephrine auto-injector as soon as the child develops any one of the following symptoms and take him or her immediately to hospital. If no serious reaction occurs within 4 hours it is unlikely to occur.**

Hives
Itching (of any part of the body)
Swelling (of any body parts)
Red watery eyes
Runny nose
Vomiting
Diarrhea
Stomach cramps
Change of voice
Coughing
Wheezing
Throat tightness or closing
Difficulty swallowing
Difficulty breathing
Sense of doom
Dizziness
Fainting or loss of consciousness
Change of colour

The Allergy Section of the Canadian Pediatric Society, in 1994 had published a similar position statement in the *Journal of the Canadian Medical Association*: ***Fatal anaphylactic reactions to food in children.*** Here is part of the statement:

> The goals of pharmacologic treatment are to maintain airway patency and systolic blood pressure. **An epinephrine injection is the initial treatment of choice for anaphylaxis**: it suppresses release of mediators of inflammation from mast cells and basophils, and it directly decreases vasodilation, edema and bronchoconstriction. **Epinephrine must be administered promptly at the first warning symptoms, such as itching or swelling of the lips or mouth, tightening of the throat or nausea, and before respiratory distress, stridor or wheezing occur.**

Dr Hugh Sampson in an editorial in the *British Medical Journal* in April 1996, entitled "Managing peanut allergy" and in his Dec. 1997 publication on Food Allergy in the *JAMA* suggests that "**food allergic individuals at increased risk for severe anaphylactic reactions --that is, patients with histories of previous severe anaphylactic reactions or asthma, or both -- should be provided with self injectable adrenaline** [11] (such as Ana-Kit or Epi-Pen) and an antihistamine (liquid diphenhydramine (Benadryl™) or hydroxyzine (Atarax™).[46] Dr Sampson further states "**Laryngeal or pulmonary symptoms following an inadvertent food exposure should be treated immediately with epinephrine.**[63] In the June 1999 issue of the *Journal of Allergy and Clinical Immunology,* Dr Sampson repeats this same indication for epinephrine, and adds that "it must be stressed to all caregivers that **treatment must be initiated without delay in high-risk patients, and they must be transported to an emergency facility for further evaluation and treatment**. . ." [72]

* In the Aug. 1999 issue of the Journal of Allergy and Clinical Immunology, Yocum and coll. report on "Epidemiology of anapyhylaxis in Olmstead County: A population-based study."[87] **To classify an event as anaphylaxis, they required:**

- **one symptom of generalized mediator release**, such as flushing, itchiness or numbness or tingling of lips, armpits, hands or feet, generalized itchiness, hives or angioedema (oral or throat swelling), and red, itchy eyes,
- **and at least one of the following additional symptoms**:
  - **oral and gastro-intestinal symptoms** such as: oral mucosal itchiness, oral swelling, swollen tongue, palate or throat, nausea, vomiting, difficulty swallowing, abdominal cramps or diarrhea.
  - **respiratory symptoms**: rhinitis (sneezing, runny nose) throat tightness, cough, wheezing, hoarseness, change in voice, shortness of breath, throat swelling, cyanosis
  - **cardiovascular symptoms**: chest pain, irregular pulse, lowered blood pressure, rapid pulse, fainting, slow pulse, orthostasis (unsteadiness or dizziness), seizures and shock.

(Only two exceptions to these criteria could classify an event as anaphylaxis: isolated laryngeal edema or immediate shock and a syncopal event after injection of medication or a radiocontrast agent.)

> **The conclusion from the above criteria is that there's a fine line between a mild allergic reaction and anaphylaxis, and at times quite difficult to diagnose an event as not being anaphylaxis! When in doubt, administer epinephrine.** (posted Sept 24th, 1999)

In Europe, the attitude is somewhat different. Dr Etienne Bidat, Paris and Boulogne, on the AllergieNet website, in ***Prise en charge du choc anaphylactique*** (Management of anaphylactic shock) suggests the following:

- "Anaphylaxis is a major emergency in allergy, there is no time to waste; intervention must be immediate. Anaphylactic shock is often preceded by signs that need immediate treatment. These signs may be discreet, and may begin during or soon after a meal, and treatment should be initiated immediately. . . rather that wait for progression towards anaphylaxis!

  These first signs can be: itchiness or swelling of lips, hives, sneezing or runny nose, red eyes or abdominal cramps. At this point, an antihistamine is advised taken orally and medical help sought.

  At times, the symptoms may be more dramatic as: cough, wheezing, or vomiting in addition to the above-mentioned signs. An antihistamine must be taken as well as a bronchodilator for the respiratory symptoms. In any case, if these signs are not rapidly ameliorated or stabilized by the treatment, cortisone taken orally is suggested and medical help sought immediately. **If the reaction is more severe, with general malaise, loss of consciousness associated with an asthmatic episode, injection of epinephrine is the first-line treatment."** (posted Sept 24th, 1999)

* According to Moneret-Vautrin and Kanny's article entitled "**Anaphylaxis in schools and other child-care settings --the situation in France**" in the May 1999 issue of *Allerg Immunol (Paris),*

things are changing. The "Projet d'Accueil Individualisé" an emergency health care form is being used by allergologists, and countersigned by the treating physician in charge of the School Health Department, with description of symptoms, directives and treatment to be used. They state that "epinephrine is the first drug to be used."[86]

- In England, treatment of an allergic reaction to food is similar. Inhaled epinephrine, now withdrawn in Europe, was often used. Antihistamines are recommended for mild, urticarial reactions. Epinephrine is reserved for large dose ingestion of the implicated food and reactions that are not settling after 5-10 minutes, with the patient taken to a medical facility. Reactions may settle with antihistamines but epinephrine should be administered if the reaction seems to progress. (posted Sept 24th, 1999)

---

* New! **Anti IgE drug: new treatment for peanut allergy?**

During the month of Dec. 1999, a new drug for asthma was reported in the media, an anti-IgE monoclonal antibody, described as acting directly on the allergic component of asthma, IgE, following a publication the the New England Journal of Medicine: Treatment of Allergic Asthma with Monoclonal Anti-IgE Antibody[89]. On Dec. 28th, the Peanut Allergy Site (PeanutAllergy.com) posted information about a clinical trial of the drug in severe peanut allergy: Tanox announces start fo anti-IgE clinical trial. In the same posted announcement, comments are reproduced from members as well as from Dr Donald Leung, and Dr Hugh Sampson, both involved in the trial. **"In this study we are attempting to determine whether or not anti-IgE therapy will be effective in preventing anaphylactic reactions to peanuts. If it is effective in peanut allergic patients, it is very likely that it will actually protect allergic patients from all food allergies. . . We are very optimistic about this medication. . . "** (posted Dec 31st, 1999)

The **important facts** about peanut allergy are, among others:

- that **traces of peanuts could be found in a large amount of processed foods**, without any mention on the label
- that **sensitization is possible during pregnancy, probable during breast feeding**
- **learn to recognize symptoms of anaphylaxis** that occur rapidly, not necessarily in this order (hives, swelling of lips or tongue, difficulty swallowing, tightness in the throat and chest, itchiness, drooling, wheezing, choking, coughing, voice change, sneezing, nausea, vomiting, cramps, diarrhea, dizziness, pallor, loss of consciousness, etc.)
- **anaphylaxis** can proceed rapidly, it **must be treated immediately** with an injection of **epinephrine** (adrenaline) and patient taken to the emergency room of the nearest hospital. Self-administering kits are available (**Epipen or Anakit**)
- **prevention:**
  - *"Cross-Contamination -- What isPeanut Free".*
- **education**: e.g. *A Teacher's Guide to Allergies and Anaphylaxis*

-solutions suggested for school:

- *Allergy Free Zone Protects Student*
- *Managing Food Allergies in Your Classroom*

- *Preparing Foods Safely*
- *Banning peanuts in schools?
  - * *Why don't we just ban peanuts (and nuts) at schools?* by Nancy Wiebe (Calgary Allergy Network)
  - * See TIME magazine article of Oct 5th, 1998: *Don't ban peanuts*
  - * See TIME magazine comment of Sept 28th, 1998: *The forbidden legume*
  - * See also Food Allergy Network article: *Banning peanuts in school - does it work?*
  - * *Anaphylaxis and schools* (UK) (posted April 6th, 1999)
  - * *Allergy spurs school peanut-butter ban* By Kate Zernike - *The Boston Globe* (posted July 3d, 1999)
  - * *One school's decision.* (posted Nov 6th,1999)
  - * **Some Schools Ban Peanut Butter As Allergy Threat: News Brief 9/28/98** New (posted June 11th, 2000)

There is also the legal aspect of the problem:

- *Peanut Allergies: A medicolegal perspective*
- *Life, Liberty & Peanut Butter?*

In summary:

-background of peanut allergy:

- staple **food** in north America, **often hidden in many foods**
- **early introduction in children's diet**
- **increase in frequency and severity of reactions to peanuts**, fatal reactions reported more frequently
- **over 70% of initial reactions occurred in children not having had any contact with peanut!**
- **allergy to peanuts may be lifelong**, although may disappear in some
- **skin and laboratory tests not a good predictor of severity of reactions,** and may remain positive in those that have lost their allergy
- **unpredictability of peanut allergy**

Follow-up of peanut allergic patients, following initial reaction:

- **avoidance of any food that may contain peanuts**

- * Consult food **"recalls"** at the following sites: Food Allergy Network-recalls or at Canadian Food Inspection Agency
- * Helpful Information About Food Companies and Food Allergies (posted Aug. 18th, 1999)

- **avoidance also of tree nuts**, especially mixed nuts, which may also contain peanuts. Because of peanuts being considered as nuts in the food industry, labeling a food as containing nuts, may also mean peanuts. Besides, one third of peanut allergics also are allergic to tree nuts [13].
- **reading all the labels,** remembering that traces of peanut are not always mentioned. **Avoidance of any food or new preparation if the ingredients are not known.**
- **peanut is a legume** along with peas, beans, soy, lentils, alfalfa. The very allergic individual may also react to one or more of the other legumes, mostly to peas. **Avoiding all the legumes in the peanut allergic individual is not warranted, and will not change the peanut sensitivity.**
- * **A peanut-allergic subject usually tolerates most members of the legume family** [36], * [67] (posted April 18th, 1999).
- **a peanut allergic individual may tolerate foods that contain tree nuts**, as almonds, hazelnuts, in cereals and chocolate bars and may normally continue eating these preparations, although sensitization can occur. Could we always be sure that they will never contain traces of peanuts?
- **if the initial reaction was an anaphylactic reaction, epinephrine should be given immediately if accidental ingestion occurs, even before evidence of any reaction,** and the patient taken to the emergency of the nearest hospital. If the initial reaction was hives only, accidental ingestion does not necessitate epinephrine at once, but an Epipen or Anakit should be on hand, and given if signs of anaphylaxis are observed.
- **once a skin test shows a positive reaction to peanuts, whatever the size, performed on a patient having had an allergic reaction after eating a food containing peanut, the patient is considered allergic and should avoid all foods that may contain peanut.** If an accidental ingestion should occur and there is no reaction, the patient should be reevaluated and if the test is negative, a challenge should be performed by an allergist in a hospital setting.

Questions:

* The question that everyone is asking, and to which there is no clear-cut answer is: **will all children that have reacted to peanuts by having urticaria only, usually on the face, of short duration that resolved without any treatment, that show a positive skin test to peanut, progress to life-threatening anaphylaxis, after accidental ingestion?**

* **Jan 28th, 1999.** When seeing **siblings of peanut allergic children** particularly, but not necessarily, allergists are often asked to check to see if they are allergic to peanuts, or nuts. They have **no history of reaction of any kind to peanuts, or nuts,** and in many cases, arising from fear, or for any other reason, they have **never eaten peanuts or nuts. Based on the recent medical literature, with initial reactions occurring in more than 70% of cases without previous contact, should they be tested for peanut allergy?**

If the **test is negative**, the sibling is considered not allergic, **what are the recommendations? Should she/he eat peanuts?**

* **Answer:** According to **Dr. Anne Des Roches:** if the sibling with a negative history of peanut or other food allergy, has a negative skin test, in the case of a very young child, introduction of peanuts not before age 5. (posted April 18th, 1999)

If on the other hand, the **test is positive**, and strongly positive perhaps, the child obviously is considered allergic, and continues not eating peanuts or nuts. **Can one conclude that the child would have had an allergic reaction, possible even anaphylactic, had he or she eaten peanut, and doing the test in such cases is a preventive measure?**

* To help answer these questions:

- * In a 1996 article in the *British Medical Journal,* Hourihane and coll. reported their findings in a **survey of people with self reported peanut allergy or referred by their physician for suspected peanut allergy, in relation to heredity, maternal diet, and other atopic diseases:**
  - all forms of atopy were both more common in successive generations and more common in maternal than paternal relatives
  - peanut allergy was reported by 0.1% (3/2409) of grandparents, 0.6% (7/1213) of aunts and uncles, 1.6% (19/1218) of parents, and **6.9% (42/610) of siblings**
  - consumption of peanuts while pregnant or breast feeding was more common among mothers of probands (children with positive histories of peanut allergy) younger than 5 yrs of age, than probands over the age of 5.
  - age of onset correlated inversely with year of birth
  - skin prick testing of 50 children with reported peanut allergy . . . 14% were negative. No parent and 13% (5/39) of siblings had a positive result on skin prick testing for peanut. Two of these siblings had a negative challenge with peanuts. **The prevalence of peanut allergy in siblings is therefore 7% (3/39).**

    Conclusions:

  - Peanut allergy is **more common in siblings** of people with peanut allergy (7%) than in the parents or the general population (1.3%).
  - Its apparently increasing prevalence may reflect a **general increase of atopy**, which is **inherited more commonly from the mother.**
  - Peanut allergy is **presenting earlier in life**, possibly reflecting increased consumption of peanut by pregnant and nursing mothers [44]. (posted Feb 13th, 1999)
- * According to Hugh Sampson, . . . "infants at increased risk for developing peanut or nut allergy should be identified. These are infants from atopic families or families with other food allergies or atopic disorders. Their parents should be advised to eliminate all peanut products from the child's diet for at least three years, and mothers who are breast feeding should eliminate peanut products from their own diet. **Children under 3 years of age who are being evaluated for other allergies should be tested for peanut allergy**, and any child with peanut specific IgE antibodies should avoid all peanut and nut products for three to five years. If no reactions to inadvertent ingestions have occurred in the interim, the child should be reevaluated for evidence of peanut and nut specific IgE antibodies and clinical reactivity to peanuts." [46]. (posted Feb 13th, 1999)

-
- See also: "Predictive value of skin tests"

* Some questions that were asked of Dr Pamela W. Ewan following her article: **Clinical study of peanut and nut allergy in 62 consecutive patients: new features and associations**, published in the *British Medical Journal* [33] in 1996, found on the Internet at Mediconsult.com are reproduced here:

1. Could eliminating exposure to peanuts and nuts in childhood prevent the development of allergies?

That's difficult to answer. We need much more data over a long period of time to be certain. One of our hypotheses is that the early introduction of peanuts is an important factor responsible for the increase in peanut allergy. If that's right, delaying introduction might lead to prevention of this allergy. It's known for certain in other allergies that small children, if exposed to a potent allergen, seem to be more likely to react. We have not seen this large number of young children with peanut allergy until recently, so something has changed, and one of a number of things that have changed is diet.

2. Have you seen cases of adults who have been eating peanuts all their lives, and suddenly get a reaction?

Very few. We do see that, but it's uncommon, although allergies can develop at any age.

3. Can skin tests be dangerous to young children?

Skin tests are very safe, but it's important that they be done in expert hands, because occasionally you get a reaction. We tested large numbers of nut-allergic people, including very young ones, and we saw no adverse reactions.

4. Do genetic factors predispose to nut allergy or other allergies?

That's certainly true of other allergies, and I presume that it will apply to nut allergy as well. It has been known for a very long time that if one parent is allergic, there's a good chance the child will be, and if both parents are, the chance is even greater. But it's not a direct inheritance. It's very complex trying to disentangle the link between genes and the development of allergic antibody responses. In this study, almost all of the patients who were nut-allergic also had other common allergies, so they were clearly of a background genetically predisposed to allergy.

5. Can an infant be sensitized through breast milk?

Probably. We know that proteins from the maternal diet can get into breast milk. This has been established with other foods, so there's no reason it couldn't happen with peanuts, although as far

as I know this hasn't been properly demonstrated. You must have been previously exposed in order to produce the antibody which causes the allergic reaction, so theoretically it couldn't occur on your first exposure. Cases where the mother is sure that a reaction occurred the very first time the baby was given peanut in any form raise issues like "Could it have been from breast milk?". It's postulated that tiny amounts of the protein in the mother's milk might be enough to sensitize the baby -- in other words, cause him to manufacture the harmful allergic antibody to the protein. Another possible way could be across the placenta, in utero. If the mother is eating a lot of peanuts during pregnancy, it's theoretically possible for the proteins to cross the placental barrier into the baby.

6. To what factors do you attribute the increase in allergies?

In the last 10 to 20 years, there has been a huge increase in the number of allergic disorders. Earlier or more frequent exposure to allergens is one important factor, but I don't think it's the only one. Another is atopy, the tendency to form allergic antibodies. An atopic child exposed to peanut butter is at much greater risk of developing peanut allergy than a normal child. We found atopy in 96% of the patients in the study by carrying out skin prick tests to other common allergens. The same number had other common allergic disease -- allergic asthma or rhinitis, or atopic eczema. One theory is that it's in part to do with modern living. The way we live now, in enclosed environments with central heating, carpets and double-glazed windows, favours the growth of the house dust mite, which is one of the commonest causes of asthma, rhinitis and eczema. That may be a very important factor, and there may be others that we don't yet have data on.

Comment from Dr. Ewan:

One thing our study suggests is that if you have a child with a common allergy, it's very unwise to give that child peanuts or nuts. It may well be that the same advice is valid even for children who aren't allergic, but we don't yet have data to support that. But if you have an allergic child, there are very strong reasons for at least delaying the introduction of peanuts and nuts, and certainly to not give them to very young children. It's a fearsome allergy -- it's a very dangerous thing to have. It can have such terrible consequences, so if there's any way of avoiding it, that would be sensible to do. (posted April 21st, 1999)

References:

1. Rance F, Dutau G.: Labial food challenge in children with food allergy. Pediatr Allergy Immunol 1997 Feb;8(1): 41-44.

2. Hourihane JO, Kilburn SA, Dean P, Warner JO: Clinical characteristics of peanut allergy. Clin Exp Allergy 1997 Jun;27(6):634-639.

3. Nelson HS, Lahr J, Rule R, Bock A, Leung D: Treatment of anaphylactic sensitivity to peanuts by immunotherapy with injections of aqueous peanut extract. J Allergy Clin Immunol 1997 Jun;99(6 Pt 1):744-751.

4. Foucard T, Edberg U, Malmheden Yman I.: [Fatal and severe food hypersensitivity. Peanut and soya underestimated allergens]. Lakartidningen 1997 Jul 23;94(30-31):2635-2638.

5. Chandra RK.: Food hypersensitivity and allergic disease: a selective review. Am J Clin Nutr 1997 Aug;66(2):526S-529S.

6. Cantani A.: Allergic reaction to inadvertent peanut contact in a child. Allergy Asthma Proc. 1997 Sep;18(5):323-326.

7. Anderson JA: Milk, eggs and peanuts: food allergies in children. Am Fam Physician 1997 Oct 1;56 (5):1365-1374.

8. Sampson HA, Ho DG.: Relationship between food-specific IgE concentrations and the risk of positive food challenges in children and adolescents. J Allergy Clin Immuno 1997 Oct;100(4):444-451.

9. Rance F, Juchet A, Bremont F, Dutau G.: Correlations between skin prick tests using commercial extracts and fresh foods, specific IgE, and food challenges. Allergy 1997 Oct;52(10):1031-1035.

10. Hourihane JO'B, Kilburn SA, Nordlee JA, Hefle SL, Taylor SL, Warner JO.: An evaluation of the sensitivity of subjects with peanut allergy to very low doses of peanut protein: a randomized, double-blind, placebo-controlled food challenge study. J Allergy Clin Immunol 1997 Nov;100(5):596-600.

11. Sampson HA.: Food Allergy. JAMA 1997 Dec 10;278(22):1888-1894.

12. Hourihane JO, Roberts SA, Warner JO: Resolution of peanut allergy: case-control study. BMJ 1998 Apr 25;316(7140):1271-1275. (complete article accessible)

13. Sicherer SH, Burks AW, Sampson HA.: Clinical features of acute allergic reactions to peanut and tree nuts in children. Pediatrics 1998 Jul;102(1):E6.

14. Hogendijk S, Eigenmann PA, Hauser C.: The problem of hidden food allergens: two cases of anaphylaxis to peanut proteins concealed in a pizza sauce]. Schweiz Med Wochenschr 1998 Jul 21;128(29-30):1134-1137.

15. Bush RK: Management of peanut allergy. Can J All & Clin Imm 1996 Nov;1(5):178-183.

16. Altman DR, Chiaramonte LT.: Public perception of food allergy. J. Allergy Clin Immunol 1996;97:1247-1251.

17. Bock SA, Atkins FM: The natural history of peanut allergy. J Allergy Clin Immunol 1989;83:900-904.

18. Hourihane JO, Bedwani SJ, Dean TP, Warner JO: Randomized, double-blind, crossover challenge study of allergenicity of peanut oils in subjects allergic to peanuts. BMJ 1997 Apr 12;314 (7087):1084-1088.

19. Teuber SS, Brown RL, Haapanen LA: Allergenicity of gourmet nut oils processed by different

methods. J Allergy Clin Immunol 1997 Apr;99(4):502-507.

20. Steinman, HA: "Hidden allergens in foods. J Allergy Clin Immunol 1996 Aug; 98(2):241-250.

21. Bock SA: Incidence of severe food reactions in Colorado (Abstract).J. Allergy Clin Immunol 1992;89:192

22. Peggy Curran, The Gazette, Peanut-butter blues: Lunch-bag staple fallen on hard times. Tuesday 15 September 1998.

23. Moneret-Vautrin DA, Rance F, Kanny G, Olsewski A, Gueant JL, Dutau G, Guerin L:Food allergy to peanuts in France--evaluation of 142 observations.Clin Exp Allergy 1998 Sep;28(9):1113-9

24. Olszewski A, Pons L, Moutete F, Aimone-Gastin I, Kanny G, Moneret-Vautrin DA, Gueant JL Isolation and characterization of proteic allergens in refined peanut oil. Clin Exp Allergy 1998 Jul;28 (7):850-9

25. Une allergie réversible? L'Actualité Vol: 23 No: 10 15 juin 1998 p 62

26. Bock, SA: The natural history of food sensitivity. J Allergy Clin Immunol, 69:173-177, 1982

27. Bock SA, The natural history of severe reactions to foods in young children. J Pediatr,107:676-680, 1985.

28. Rosen JP, Selcow JE, Mendelson LM, Grodofsky MP, Factor JM, Sampson HA: Skin testing with natural foods in patients suspected of having food allergies: is it a necessity? J Allergy Clin Immunol 1994 Jun;93(6):1068-70.

29. Bock SA: Prospective appraisal of complaints of adverse reactions to foods in children during the first three years of life. Pediatrics 1987;79:683-688.

30. David, T: Patients have not been proved to grow out of peanut allergy. BMJ 1998;317:1317 (7 nov.) (complete article accessible)

31. Kmietowicz, Z: Women warned to avoid peanuts during pregnancy and lactation. BMJ 1998;316:1926 (27 June.) (complete article accessible)

32. Tariq SM, Stevens M, Mathews S, Ridout S, Twiselton R, Hide DW. Cohort study of peanut and tree nut sensitization by age of 4 years. BMJ 1996;313:514-517 (complete article accessible)

33. Ewan PW. Clinical study of peanut and nut allergy in 62 consecutive patients: new features and associations. BMJ 1996;312:1074-78 (full text accessible)

34. Ewan PW. Prevention of peanut allergy. Commentary. Lancet 1998 Jul 4;352(9121):4-5

35. Fox, DE, Lack G. as well as Pumphrey RSH, Wilson PB, Bansal, AS: Peanut allergy. Lancet 1998 Aug 29;352(9129);741-2 (correspondence)

36. Bernhisel-Broadbent J, Sampson HA. Cross-reactivity in the legume botanical family in children

with food hypersensitivity. J Allergy Clin Immunol. 1989;83:435-440

37. Zimmerman B, Forsyth S, Gold M. Highly atopic children: formation of IgE antibody to food protein, especially peanut. J. Allergy Clin Immunol. 1989;83:764-770

38. Hourihane, JO: Prevalence and severity of food allergy -- need for control. Allergy 1998;53(46 Suppl):84-88.

39. Clarke MC, Kilburn SA, O'B Hourihane J, Dean KR, Warner JO, Dean TP.: Serological characteristics of peanut allergy. Clin Exp Allergy 1998 Oct;28(10):1251-1257.

40. Greenbaum, J.: Allergen immunotherapy - Communication. Can J of Allergy & Clin Immunol.3:6, Nov 1998.

41. Vieths S, Hoffmann A, Holzhauser T, Muller U, Reindl, J, Haustein D. Factors influencing the quality of food extracts for in vitro and in vivo diagnosis. Allergy 1998;53(46 suppl):65-71

42. Brett GM, Bull VJ, Morgan MR. Identification of hidden allergens within foods. Allergy 1998;53 (46 Suppl):109-10

43. Eigenmann PA, Sampson HA: Interpreting skin prick tests in the evaluation of food allergy in children. Pediatr Allergy Immunol 1998 Nov;9(4):186-91

44. Hourihane JO, Dean TP, Warner JO: Peanut allergy in relation to heredity, maternal diet, and other atopic diseases: Results of a questionnaire survey, skin prick testing, and food challenges. BMJ 313(7056):518-21, 1996 Aug 31 (full text)

45. Vocks E, Borga A, Szliska C, Seifert HU, Seifert B, Burow G, Borelli S. Common allergenic structures in hazelnut, rye grain, sesame seeds, kiwi, and poppy seeds. Allergy 1993 Apr;48(3):168-72

46. Sampson HA: Managing peanut allergy. Editorial. BMJ 1996;312:1050-1051 (27 April) (full text accessible)

47. Pamela W Ewan :Clinical study of peanut and nut allergy in 62 consecutive patients: new features and associations. BMJ 1996;312:1074-1078 (27 April) (full text accessible)

48. Axelsson IG, Ihre E, Zetterstrom O: Anaphylaxtic reactions to sunflower seed. Allergy 1994 Aug;49(7):517-20.)

49. Halsey AB, Martin ME, Ruff ME, Jacobs FO, Jacobs RE: Sunflower oil is not allergenic to sunflower seed-sensitive patients. J Allergy Clin Immunol 1986 Sep;78(3 Pt 1):408-10.

50. Fernandez C, Martin-Esteban M, Fiandor A, Pascual C, Lopez Serrano C, Martinez Alzamora F, Diaz Pena JM, Ojeda Casas JA: Analysis of cross-reactivity between sunflower pollen and other pollens of the Compositae family. J Allergy Clin Immunol 1993 Nov;92(5):660-7)

51. Perkins MS: Sesame allergy is also a problem. Letter. BMJ 1996; 313:330 (3 August) (full text accessible)

97. Primeau M, Kagan R, Joseph L, Lim H, Dufresne C, Duffy C, Prhcal I, Clarke A: The psychological burden of peanut allergy as perceived by adults with peanut allergy and the parents of peanut-allergic children. Clin Exp Allergy 2000 Aug;30(8):1135-43.

John Weisnagel, M.D. Allergy Service, Dept. of Pediatrics, Hôpital Ste Justine, Montreal, Qué. and in private practice since 1962, now at Polyclinique Médicale Concorde, 300 est boul. de la Concorde, Laval, Qué. H7G 2E6. Past president of the Association of Allergists and Immunologists of Quebec. Member of the Canadian Society of Allergy and Clinical Immunology, and of the American Academy of Allergy, Asthma and Immunology.

Related links:

Peanut Allergy by prof. P. Potter (Allergy Society of South Africa)
Understanding food allergy
Food Allergy Network
Peanut Allergy Network
Peanut allergy links
MedicAlert
Ident-Id

(Article posted Oct 2nd, 1998. Updated regularly. Any comments and modifications are welcome.)

Last update: Aug. 23d, 2000

J.W.

Association of Allergists and Immunologists of Quebec
CSACI: Canadian Society of Allergy and Clinical Immunology
Hôpital Ste Justine: Allergy Out-patient Clinic



jweis@mmic.net

ROUTING SLIP
GENERATED BY: HF-40
DATE: DEC 28, 2000

FDA CONTROL NUMBER: 00 7717 **TRACER #:** **OS #:**

DATE OF CORRESPONDENCE: 12/13/00 **DATE INTO FDA:** 12/28/00

TO: JANE E HENNEY HF-1

FROM: MIKE HATCH

SYNOPSIS: COMMENTS ON THE MULTISTATE CITIZEN PETITION FOR RULES REGARDING THE LABELING AND MANUFACTURE OF FOODS CONTAINING ALLERGENIC SUBSTANCES

LEAD OFFICE: HFA-305 **HOME OFFICE:** HF-40

CONTACT/PHONE#: KRISTINE M MORAN 301-827-4446

COPIES: GENERAL DISTRIBUTION
HF-1 JANE E HENNEY
HF-40 B. Malkin
HF-40 ANNE B CRAWFORD
HF-40 VICTORIA B WOLFHARD
HFS-1 JOSEPH A LEVITT
HF-22 WILLIAM K HUBBARD

COORDINATION:

SIGNATURE REQUIRED:

REFERRALS FROM HF-40

ASSIGNED TO	ACTION	DUE DATE
HFA-305 Dockets	NECESSARY ACTION	

REMARKS: DOCKET # 00P-1322 - ALLERGENIC SUBSTANCES

MIKE HATCH
ATTORNEY GENERAL
1400 NCL TOWER
445 MINNESOTA STREET
ST. PAUL, MINNESOTA 55101-2131

3.20

FIRST CLASS
SAINT PAUL MN DEC 19'06
U.S. POSTAGE
3.20

MIKE HATCH
ATTORNEY GENERAL
1400 NCL TOWER
445 MINNESOTA STREET
ST. PAUL, MINNESOTA 55101-2131

Commissioner Jane Henney
U.S. Food and Drug Administration
5600 Fishers Lane
PKLN 1471, Room HF-1
Rockville, MD 20857