

The Original Internist article

## ***Food Allergy and Food Intolerance: specific versus innate immunity***

*Roger Davis Deutsch*

### ***Nomenclature***

The concept of an allergy was fairly well understood when von Pirquet, an Austrian physician, first introduced the term in 1906. It was intended to denote an *altered reaction* to a normally innocuous substance. Two decades later allergists in Europe agreed to narrow the definition to apply only to such an altered reaction as may be characterized by an immediate onset of symptoms.

Contemporary physicians recognize a distinction between immediate and delayed-type altered reactions in their nomenclature by applying the terms, “intolerance” or “sensitivity” in the case of common reactions to foods and other chemicals, where symptom onset is delayed and typically of a less acute nature than that which has come to be known as a “true” allergy, classical allergy, or Type I hypersensitivity, according to the Gell and Coombs classification system.

Although both phenomena involve an aberrant immune response, the mechanisms underlying each are quite different. Broadly speaking, classical allergy is a function of the specific immune system, whilst intolerance involves activation of the innate branch of the immune system.

### ***Classical allergy is a function of the specific immune system***

The most prominent hallmark of specific immunity is memory; hence the rationale underlying immunization. It is termed, “specific” because it makes use of pathogen- or allergen-specific binding sites on Immunoglobulins or lymphocyte receptor molecules in the process of recognition. Prior exposure to the activating substance is therefore necessary in order to “prime” or elicit a subsequent response of the specific immune system.

Lymphocytes that initiate an allergic response first manufacture antibodies specific to the particular allergen. Although the European allergists were unaware of the causative agent, experimentation performed by allergists Praustnitz and Kustner in 1920 demonstrated that passive transfer of allergy could occur by injecting the serum of an allergic subject into the tissue of a non-allergic recipient. Subsequent scratch testing at the site with the specific allergen induced a classical wheal and flare reaction. Although the causative factor existing in the serum was unknown, it was referred to it as *regain*.

## ***IgE***

In 1967 two independent teams discovered that the reaginic antibody (*regain*) was IgE. One was a husband and wife team in Colorado, named, Ishizaka; the other a three member team at the Karolinska Institute in Sweden. The Karolinska team later developed an immunoassay for quantitation of allergen specific IgE. The test is called *RAST*, an acronym for *Radio Allergo Sorbent Test*. It is a sandwich immunoassay using a radiolabeled anti-IgE antibody tag. When radiation emitted from cloned antibodies bound to the allergen specific IgE antibodies is measured it provides a reliable indication of allergy. Variations of the technique using enzyme tags and optical densitometric readings (ELISA) are commonly used.

The role of IgE in the pathogenesis of allergy was later elucidated. Essentially, an antigen capturing and presenting cell (usually a macrophage or dendritic cell) takes up an allergen and then breaks it down internally. The broken down peptides of the allergen bind to a major histocompatibility complex molecule (MHC molecule) and the MHC/allergen complex then migrates to the surface membrane. A T-cell, in this case a T-Helper 2 cell with a conforming receptor molecule, will recognize the antigen peptide/MHC complex. Once the required interaction, i.e., binding of the allergen particles/MHC complex with the T-cell receptor; and, a co-stimulatory signal, usually involving a B7 molecule on the APC and a CD 28 receptor on the T-cell, occurs, the T-cell becomes activated. It then “instructs” contacted B-lymphocytes with a conforming receptor to also become active.

In this allergic pathway the chemical message is Interleukin 4 (*IL4*). The so activated B-cells transform into plasmacytes, commence manufacturing antibodies specific to the allergen peptides in question, multiply, and secrete soluble forms of the specific receptor molecule, in other words, allergen specific IgE antibodies conforming with the original allergen peptides, into the lymph and general circulation.

Once in circulation IgE antibodies will bind with *f<sub>c</sub>* receptors on the surfaces of mast cells occurring in the connective tissue of the skin, as well as other mucosal linings, and basophils in the blood. These white blood cells possess internal granules containing pre-formed mediators of inflammation, including histamine. Should two or more cell-bound IgE antibodies subsequently encounter the specific allergen, their binding and “cross-linking” causes aggregation of cell membrane receptors inducing various enzymes and kinases to initiate a process resulting in the release of these mediators. The process is known as degranulation, (figure 1) and will rapidly induce an inflammatory response; giving rise to increased blood vessel permeability, mucus secretion, irritation of nerve endings and smooth muscle constriction, all common traits of “true” allergy.

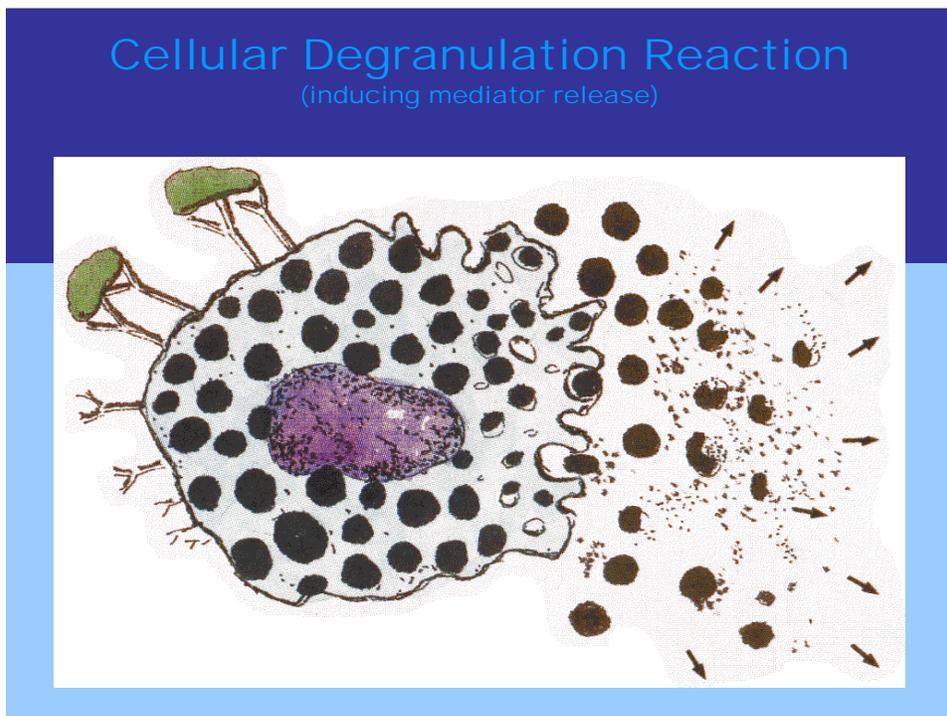
In addition to the release of pre-formed mediators, of which histamine is most common, the cells will also synthesize lipid mediators known as prostaglandins and leucotrienes,

which augment and prolong the reaction. Some lipid mediators can exert a constrictive effect on smooth muscles surrounding the bronchial tube which is 30 times more powerful than that of histamine. The substrates of these lipid mediators derive from  $\omega 6$  fats and thus dietary emphasis on the  $\omega 3$ 's, which will compete for the common enzymatic pathway, represents a sound dietary strategy for curbing inflammation.

Both pre-formed and newly synthesized lipid mediators, as well as other cytokines, like IL3, 5 and granulocyte macrophage-colony stimulating factor, will attract other inflammatory white cells -basophils and eosinophils, but not neutrophils- to the local site of the reaction, causing further and prolonged damage to the tissue. A chronic state of inflammation and allergic lesions may ensue. Although neutrophils are not directly involved in Type one allergy, as we'll see, they are the cells most involved in intolerance.

It is also worth noting that this pathway not only depends on the binding of the cell bound IgE antibodies and the specific allergen, but also on a secondary or co-stimulatory signal generated by the antigen presenting cell. In fact, in the absence of this secondary signal the T-cell will actually become anergic. In fact, this is the mechanism by which T-cells develop tolerance to self proteins whilst they are maturing in the thymus.

Therefore, clinicians should be circumspect regarding claims that an in vitro lab test will detect either allergy, or intolerance, when a specific condition of the assay calls for the isolation of the lymphocytes in autologous serum, because; by definition, the antigen presenting cells and the necessary co-stimulatory signal they provide, are absent.



(Fig. 1)

***IgE associated with parasitic infection: IgG associated with smaller micro-organisms (bacterial and viral)***

Since IgE is instrumental in this process, a therapeutic strategy of injecting antibodies targeted against the cell binding portion of the IgE molecules appear to block the interaction at a critical point and thus prevents mast cell and basophil activation. In some test subjects, allergic subjects appear to have achieved tolerance to peanut under experimental conditions. However, there can be an untoward side effect of down regulating IgE.

This T-Helper 2 pathway is activated by parasitic infections. The resulting explosive release of toxic inflammatory mediators, such as histamine, is a logical strategy for the immune system when confronting a pathogen of such relatively large size. Thus, indiscriminately blocking the IgE mechanism may render the organism more susceptible to parasitic infection.

***Modulation of the specific immune response to prevent allergy***

Fortunately, a subtler and more specific therapy has been researched which, theoretically, will block a specific allergen reaction while leaving the general protective function of the immune system intact. This more recent and promising approach to classical allergy lies with redirecting or modulation of this pathway to the non allergy provoking T Helper 1 pathway.

When the immune system is confronted with a virus or bacteria instead of a parasite, the same basic series of events occur, except that T Helper 1, as opposed to TH 2 cells, are activated, and the signals they transmit to B cells, notably, interferon  $\gamma$  (as opposed to IL 4) induce the B cells to produce antibodies of the IgG isotype, rather than the pathogenic IgE isotype. Instead of binding to mast cells and basophils and inducing them to release their deadly chemical arsenals, IgG antibodies, which are about 10,000 times more prevalent than IgE, will coat the virus or bacteria, thus enabling a phagocyte to dock onto it and degrade it, with the help of lysosomal enzymes. Whereas this process is effective against infection, it does not, notably, produce symptoms of allergy.

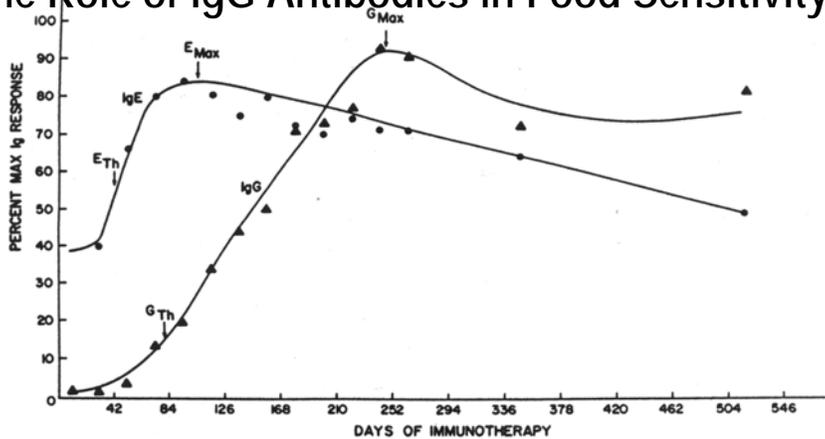
This therapeutic effect is achieved by the use of injections of “immunostimulatory sequences” (ISS) of bacterial or viral nucleotides, covalently bound to the specific antigenic epitope. The bacterial or viral nucleotides will attract a TH1 cell rather than the TH2 type. Promising clinical results have been obtained using the specific allergenic epitope of ragweed pollen, Amb a 1, which will activate a TH 1 cell with a receptor molecule specific to that antigenic epitope. In this way, the non-allergy provoking Th1 response to the specific allergen is up-regulated, and the allergenic TH2 pathway will be down-regulated.

Therefore, the reaction leads to the production of allergen specific IgG antibodies. In this case, ragweed allergen specific IgG antibodies, which are non allergy producing; as opposed to the reaginic allergy provoking IgE antibodies, are produced.

### *The Protective role of IgG*

It has long been observed that frequent and high exposure to an antigen favors an IgG response while low level and infrequent allergen exposure induces an IgE response. This is the rationale underlying classical immunotherapy, commonly known as “allergy shots”, used since 1911. The theory is born out by studies showing that as classical immunotherapy treatment progresses, allergen specific IgE titers decline, while titers of specific IgG increase. (Figure 2) As the IgG increases, symptoms also abate. (Figure 3) Once again it is seen that IgG is not an allergy provoking antibody. As in the case of viral or bacterial infection, it is protective, not allergy provoking.

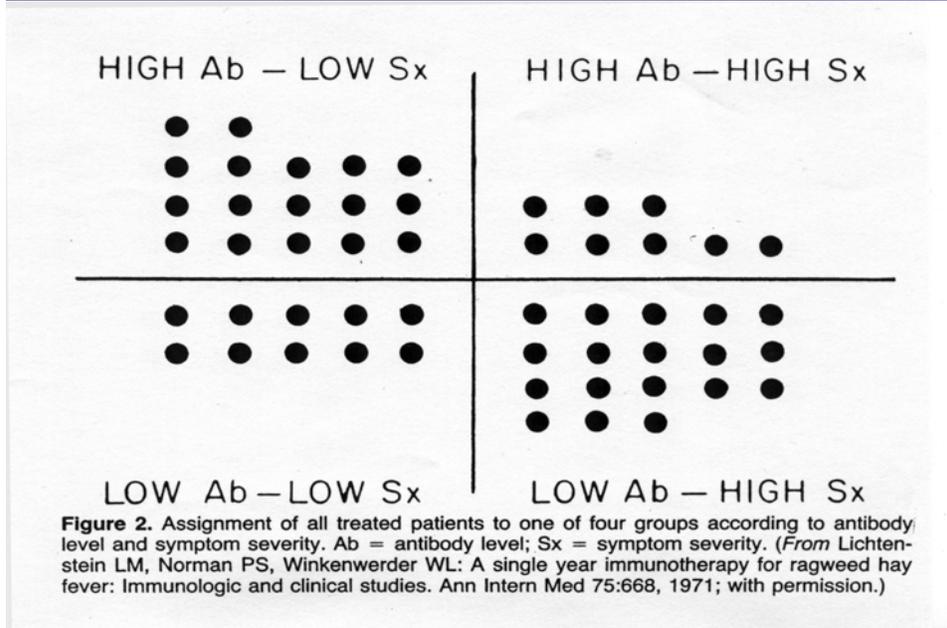
## The Role of IgG Antibodies in Food Sensitivity ?



**Figure 6.** Kinetics of RW-IgE and RW-IgG antibody responses in 51 patients undergoing RW immunotherapy. Each point is the median antibody response expressed as the percentage of maximum response for all patients who were treated during progressive 21-day intervals of treatment. Median threshold and maximal antibody responses are indicated for IgE and IgG. The kinetic drawing demonstrates that RW-IgE threshold and maximum levels occurred earlier than the corresponding RW-IgG threshold and maximum levels. After maximum, the RW-IgG curve plateaued and the RW-IgE fell (45%) to baseline. (From Creticos PS, van Metre TE, Mardiney MR, et al: Dose response of IgE and IgG antibodies during ragweed immunotherapy. J Allergy Clin Immunol 73:102, 1984; with permission.)

(Fig.2)

## The Role of IgG Antibodies in Food Sensitivity ?



(Fig 3)

Inasmuch as IgG does not play a pathogenic role with respect to classical or true allergy, the question remains, might it not play a role with respect to food sensitivities or intolerances. One must answer in the negative as evidenced by numerous clinical studies:

Dr. K.M. Keller et. al. from the Univ. of Bonn, in their 1999 paper, *Quality assurance in diagnostics: are their normal values for IgG-antibodies to cow's milk protein?* states, "the occurrence of IgG-cow's milk antibodies is a physiologic phenomenon without diagnostic significance". Another 1999 report published in the *British Medical Journal* (BMI 1999;318:1710-1) proclaims, "IgG anti gliadin antibodies have a high sensitivity not only for patients with celiac disease, but also for those with minimal or no damage...When the histological criteria of celiac disease are used as the gold standard IgG, anti gliadin antibody has low specificity."

Dr. S. I. Enganmann from the Dept of Pediatrics of the Geneva School of Medicine, in his paper, *Allergenicity of major cow's milk and peanut proteins determined by IgE and IgG immunoblotting*, writes, "The presence of IgG antibodies in nonallergics was related to regular ingestion of food".

Drs. Jenkins and Vickers from the London Royal Hosp. National Health Service Trust and Research Council for Complementary Medicine, report in *Clinical and Experimental Allergy*, 1998, Vol. 28, in a paper entitled, *Unreliability of IgE/IgG4 antibody testing as a diagnostic tool in food intolerance*, "We found no evidence that IgE/IgG4 antibody test...is a reliable diagnostic tool."

Drs. S. Zar, D. Kumar & M. I. Benson from St. Georges Hospital Medical School, London, sum up the situation in their paper, *Food hypersensitivity and Irritable bowel Syndrome (IBS)* thusly, “In fact, several studies have suggested that IgG and IgG4 production may be a normal immunological response to dietary antigens. It is probable that food hypersensitivity is a heterogeneous condition, and that more than one immunological abnormality may exist.” *Aliment. Pharmaco. Ther.* 2001;15

IgG maintains its protective role with respect to excess food antigens in the circulation by complexing with them and assisting the monocyte-macrophage system in their elimination; without, just as in the case of other allergens, inducing pathology. High IgG titers correlate with exposure, but not sensitivity.

Thus, the specific branch of the immune system provides protection against specific foreign pathogens. It requires prior exposure to the pathogen in order to mount a targeted and specific response. Misidentification of normally non-pathogenic substances, such as pollens, mite feces, drugs, epidermals, occasionally foods and others, may induce an altered reaction, or allergy. Allergic reaction is very much a function of the specific immune system; it produces distinct symptomatology and it follows a well defined and clearly understood pathway. Food intolerance, on the other hand, is induced by multiple pathogenic pathways, some immune and some non-immune, induces chronic and less acute symptomatology, is not IgG related, is both genetically determined yet exposure related; and therefore is far less well understood and consequently, under-treated.

### ***Innate immunity***

Given the confusion regarding the role of IgG in the pathology of food intolerance it is not surprising that many clinicians believe prior exposure to a food is necessary in order to develop a sensitivity, as indeed it would if in fact food intolerance were a function of specific immunity. However, this is not the case.

One prominent alternative medical practitioner complained that all of his kosher pediatric patients were testing positive to pork on my laboratory's cellular food intolerance assay; and, since by definition, none of these patients had any prior exposure to pork, the test must be inaccurate. But this is not correct.

With respect to activation of the innate immune system, the situation is different. It may be activated by various factors and priming, or previous exposure, is not a pre-requisite. As Dr. Charles A. Janeway, Jr., Professor of Immunobiology at Yale states, “..the innate immune system is born with the ability to recognize certain microbes....(and) can destroy

many pathogens on first encounter.” (*How the immune system recognizes invaders, Scientific American, Sept. 1993*)

Although there is interplay between the specific and the innate branches of the immune system, so far as food intolerance is concerned, when an immune mechanism is involved, it is primarily that of the innate branch.

A major component of the innate immunity is the complement system, a cascade of serum proteins first described by the Belgian bacteriologist, Jules Bordet in 1900. These proteins “complement” the activity of antibodies by binding to the membranes of microorganisms, a process termed *opsonization*, thus rendering them more susceptible to phagocytosis. These proteins are non-specific, meaning, they will bind indiscriminately. However, host cells contain enzymes that normally inactivate them, an example of self vs. non-self discrimination.

Another way in which the complement system protects us from detrimental microorganisms is by attaching to their lipid membranes and assembling various components of the cascade called the *membrane attack complex*. Once activated they are capable of punching a hole in the membrane, thereby causing the inward rush of surrounding fluid and resultant destruction of the invader.

Sometimes, as in the case of bacteria which cause pneumonia or strep, the bacteria wears a polysaccharide coat in an attempt to foil the attachment of the complement proteins. Nonetheless, the human innate immune system can deal with this obstacle in one of two ways: either the tissue macrophages, which have receptors for these sugars, can bind directly to the bacteria, and, as their name implies, devour them; or, the activated macrophage will signal the liver through interleukin 6 to synthesize a special protein, called *mannose binding protein*, which will bind the bacterium, activate the complement cascade and then attract the phagocytes in to finish the job.

As mentioned, excess antigen is cleared from the circulation by complexing with IgG antibodies. Sometimes, a Gell and Coombs Type III immune, also known as immune complex disease, may occur wherein immune complexes are deposited in tissue or joints and attract inflammatory cells to the site, as in RA and glomerulonephritis. But, these are almost exclusively of the IgM class rather than IgG. In examining 1012 renal biopsies from patients with glomerulonephritis through electron microscopy, Dr. M. Haas from the Dept. of Pathology at Johns Hopkins School of Medicine, observed that when immune complexes were identified to contain antibodies they were almost entirely comprised of IgM and rarely of IgG isotypes. However the predominant component was C3, the initiator of the complement cascade via the classical pathway.

These findings are consistent with what our lab found while investigating the various mechanisms involved in food induced asthmatic reactions. (**Figures 4, 5**)

## Multiple Pathogenic Mechanisms in Food Sensitivity Reactions In-Vitro

Mark I. Pasula, Ph.D., Research Director, AMIL Corp., Mari, FL  
 Samy G Puccio, Research Assistant, AMIL Corp., Mari, FL

Presented at the 4th International Symposium on Immunological and Clinical Problems of  
 Food Allergy, Milan, Italy November 5-9, 1989. Published in the Proceedings.

### RESULTS SUMMARY

	IgA <sup>1</sup>	IgM <sup>1</sup>	IgG <sup>1</sup>	IgG4 <sup>1</sup>	C3 <sup>2</sup>	C4 <sup>2</sup>	Spect <sup>3</sup>
BEEF	0	1	0	0	2	0	1
CORN	1	0	1	0	0	0	1
EGG	0	2	1	0	0	1	1
MILK	0	2	0	0	2	0	0
ORANGE	0	1	2	0	1	0	0
PEANUT	1	3	0	3	2	0	2
SOYBEAN	0	0	0	0	3	0	1
TOMATO	2	1	0	0	3	0	0
WHEAT	0	0	1	0	4	0	1
YEAST	0	2	0	0	2	0	0
<b>TOTAL</b>	<b>4</b>	<b>12</b>	<b>5</b>	<b>3</b>	<b>19</b>	<b>1</b>	<b>7</b>

1. Frequency of immunoglobulin level change exceeded S.D. 2 for that food.
2. Frequency of complement activation for that food as measured by the height difference of the rocket peaks.
3. Frequency of spectrophotometry reading of hemolysis exceeded S.D. 2 for that food.

(Fig. 4)

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The objective of this study was to investigate various pathogenic mechanisms that might operate when the whole blood of 9 food sensitive asthmatic patients was incubated with individual food extracts. Scores falling outside the range of 2 standard deviations were: IgA = 4, IgM = 12, IgG = 5, IgG4 = 3. Marked hemolysis occurred in 7 tests and complement activation was seen in 19 for C3 and in 3 for C4. Significant changes in one or more immunoglobulin and complement component occurred in every patient to one or more foods.

(Fig. 5)

The main phagocytic cells of the innate immune system are the neutrophils. These are the one class of granulocytes that are not involved in the late phase reaction of type I allergy; however, they comprise about 60 to 70% of the granulocytes in the circulation. The overall system is an effective first line of defense in acute infection but chronic activation leads to disease.

As professor William R. Clark, Prof. Emeritus, Immunology (UCLA) states in his book, *A Means to an End: The Biological Basis of Aging*, Oxford University Press, 1999, "One of the more common sources of reactive oxygen species in the body as a whole is from cells that use the destructive power of these molecules as a natural defense against microbial infection. Phagocytes (literally, "eaters of cells") such as macrophages and neutrophils purposely generate high levels of oxygen radicals, which they store in tightly sealed intracellular compartments.... Oxygen radicals released in this fashion can be taken up by adjacent cells, and once inside they cause the same sort of damage as radicals produced internally....in the case of prolonged infections a chronic inflammatory state may develop, and the repeated engorging and death of phagocytes can cause serious oxidative damage to nearby healthy cells. This is also a major source of damage in chronic inflammatory autoimmune reactions such as rheumatoid arthritis, and can lead to serious tissue loss.

The damage done by reactive oxygen molecules needed to operate living cells can be enormous. No molecular species is immune. Oxygen radicals can attack and deform proteins molecules, disrupting structural complexes and inhibiting important enzymatic functions....Oxygen radicals also attack the individual nucleotide bases that make up both nuclear and mitochondrial DNA."

### ***Chronic inflammation and degenerative disease***

Atherosclerosis is the result of an inflammatory process that occurs in the intima of the arteries. Cells of the innate immune system are involved. Cholesterol itself is not the cause. It is only when the cholesterol is oxidized by the immune system-generated free radicals that it becomes a factor in the formation of plaque. As the oxidized cholesterol is consumed by macrophages they convert to *foam cells*. The result is stenosis of the artery, laying the basis for a stroke following a thrombotic event.

Recently, Dr. R Zhang and co-investigators from the Dept. of Cell Biology, Cleveland Clinic Foundation, reported in JAMA in Nov. 2001, *Association between myeloperoxidase levels and risk of coronary artery disease*, a significant association between both blood and leukocyte levels of the neutrophil produced inflammatory mediator, myeloperoxidase (MPO) and the presence of cardiovascular disease (CAD). According to the investigators, "These findings support a potential role for MPO as an inflammatory marker in CAD and may have implications for atherosclerosis diagnosis and risk assessment."

In 2001, Doctors Duncan and Schmidt from the School of Medicine at the Univ. Fed. do Rio Grande do Sul, in Sao Paulo, Brazil performed a careful analysis of the association of inflammatory markers of the innate immune system and diabetes, cardiovascular disease and obesity, reporting in a paper entitled, *Chronic activation of the innate immune system may underlie metabolic syndrome*, "...evidence to suggest that chronic activation of the innate immune system may underlie the metabolic syndrome, characterizing the common soil for the causality of type 2 diabetes mellitus and cardiovascular disease." They conclude, "Better understanding of the role of the innate immune system in these diseases may lead to important advances in the prediction and management of diabetes and cardiovascular disease." (Sao Paulo Med. J. 2001 May 3;119(3):122-7).

Similarly, obesity is a complicated and frustrating problem involving neurological and endocrine as well as immunologic components. In a study performed at Baylor Medical College, Sports Medicine and Performance Institute in Houston, reported in *The Bariatrician, Spring 1996*, entitled, *The Short term efficacy of the Alcat Test of food sensitivities to facilitate changes in body composition and self-reported disease symptoms: a randomized controlled study*, it was found that overweight subjects following an eating plan eliminating foods suspected of activating innate immunity, based on laboratory analysis of whole blood samples, experienced a significant improvement in body composition and scale weight.

The effect of immune activating foods was distinct from that of caloric restriction, as a well matched control group that followed a calorie restricted diet was included in the study. The report, by Gilbert Kaats, Ph.D. and co-workers states that "80 percent of the subjects in the experimental group lowered their body fat during the study compared to 34 percent in the control group. 78 percent of the experimental group achieved an improvement in their body composition compared to 29 percent in the control group...(and) 98 percent of the subjects following the ALCAT plan either lost scale weight or improved their body composition."

Professor Cabo-Soler, Chief of the Biochemistry Dept. at the Univ. of Valencia reported in 1995 that isocaloric food elimination diets, based on Alcat test results, enabled dieters to enhance their weight loss; emphasizing a reduction of fat coupled while maintaining or even increasing lean tissue.

These data lend support to the notion that the increase in metabolic syndrome and chronic degenerative disorders seen in industrial societies is a function of chronic inflammatory processes brought on by altered reactions to the preponderance of artificial and genetically unfamiliar foods, and other environmental challenges, which overwhelm the body's detoxification capabilities and trigger chronic innate immune reactivity.

### ***Causes of food intolerance***

It appears that multiple mechanisms are involved in adverse reactions to foods. An enzyme deficiency, such as a lactase deficiency will manifest lactose intolerance. Prof. Brostoff, from the Middlesex Hospital Medical School of the University of London

explains that azo dyes, used extensively in prepared foods, will inhibit the activity of phenyl-sulpanotransferase-P, which will breakdown cresol-P in the gut. If cresol-P is not broken down it becomes neurotoxic.

Benjam Feingold warned about food colorings in the 60's with respect to hyperactivity in children. We have found in a multi-disciplinary study of autistic children that all of the subjects had at least some reactivity to food colorings, as determined by our in vitro cellular assay. (ref. Kotsanis study).

Similarly, many foods contain chemicals, or have chemicals added to them, which are intolerogenic. Salicylates, for example, occur in many fruits and vegetables, and can induce a pharmacologically mediated adverse reaction in susceptible individuals.

Dietary lectins, which may be resistant to degradation through cooking and digestion, occur in a numerous vegetables, fruits, grains and some meats. All mammalian blood and tissue cells have membrane carbohydrate molecules that bind lectins and may cause reactivity. Some lectins can even bind multiple fc receptors on mast cells which triggers histamine release, similar to that which is seen in classical allergic reactions. However, some lectin activity is actually beneficial, in that it may augment the normal immune response. This, as well as some other lectin activity, is not blood type specific.

Recently, Dr. Lu Shan and co-investigators from multiple departments at Stanford University and the Institute of Immunology from the Rikshospitalet in Oslo, reported in a paper entitled, *Structural basis for gluten intolerance in celiac sprue*, identifying a 33 mer peptide, rich in proline and glutamine, which was highly resistant to gastric, pancreatic and small intestinal brush border membrane proteases. They also found that it occurs in all grains that are toxic to celiacs sprue patients (wheat, rye and barley) but absent in other grains. Additionally, the peptide was shown to be a potent stimulator of T cells (CD+, or helper type) in 14 out of 14 celiac sprue patients. However, in both in vitro and in vivo assays the peptide could be broken down by a bacteria derived prolyl endopeptidase thus suggesting a possible treatment strategy.

### ***Synergism***

This model illustrates an adverse reaction to foods, in this case gliadan fractions occurring in grains, that involves activation of specific immunity; the T cells of celiac patients with a specific leukocyte antigen which then release potent cytokines, attracting inflammatory cells of the innate immune system which cause damage to local tissue through the release of their toxic mediators.

An additional feed back loop from innate immune reactivity to specific immune function is observed when activation of the innate immune system up-regulates the expression of B7 molecules on antigen presenting cells, which, as seen in classical allergy, for example,

provide the secondary signal necessary to turn on T helper cells. Thus, the co-ordination of the two branches of the immune system suggest a complex synergistic function and it is often seen that treatment of allergy decreases food intolerance; and, conversely, the effective management of food intolerance, improves allergic states.

Nonetheless, classical allergy is mediated by the specific branch of the immune system and the broad category of adverse reactions to foods are mediated, primarily, by the innate branch of the immune system, secondary to gastrointestinal dysfunction and/or detoxification insufficiency. Although several factors can induce histamine release, usually it is IgE. Symptom onset is immediate and it requires a small dose of allergen to trigger symptoms.

### ***Food intolerance is multi-factorial***

Multiple pathogenic mechanisms are involved in adverse reactions to foods, some of which are immunologic; others, toxic or pharmacologic. Symptoms are typically dose dependent, and symptom onset is delayed. Adverse reactions to foods are hard wired in our genes but susceptibility is dependant upon many factors; such as, the integrity of the natural barrier of the gut wall; the viability of phase I and phase II detoxification pathways and the presence or absence of other co-factors. A combination of these conditions could push one over their level of tolerance at any given time. It should be born in mind that the human lymphocyte possesses all of the enzymes and substrates that are involved in hepatic detoxification and therefore serves as a back up system, albeit, one that may provoke unwanted symptoms.

It is sometimes seen that reactions to apple do not occur unless airborne birch pollen, which cross reacts with apple, is high. A food which contains an intolerogenic chemical is tolerated in moderation; but over consumption of it, or it in combination with other food(s) dependent on the same detoxification pathway may overwhelm that pathway and produce symptoms when consumed on a more frequent basis. Therefore, nutritional status which supports detoxification can exert a significant impact on food intolerance states. Therefore, rotational eating plans are usually encouraged for food intolerants.

In exercised induced asthma, increased body temperature serves as a co-factor with antigen to induce the degranulation of basophils, and histamine release, which will not occur at normal body temperature.

Stress produced cortisol will destroy secretory IgA antibodies in the gut (and at the site of other mucus membranes as well) allowing for the perfusion of undigested food macromolecules that may activate the immune system. Intestinal disbioses, Type I allergy in the gut, prescribed cortisone, and other variables may also contribute to a leaky gut.

Given the complexity of food intolerance it is easy to appreciate the need for a rapid, cost effective and accurate laboratory test to substitute for the laborious process of elimination

and challenge, which, if properly performed, would take months, and try the patience of even the most patient of patients, not to mention their health care provider.

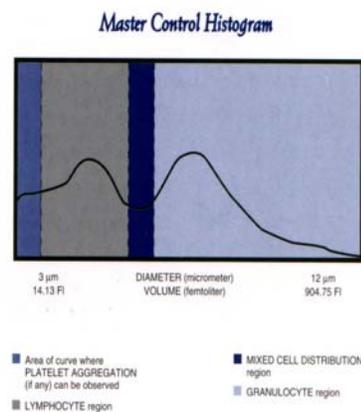
### ***Laboratory testing for food intolerance***

We began our development of a reliable test for food intolerance in 1984. Previously, during the 1930's, allergists Cooke and Vaughn focused on changes in WBC counts following an in vivo challenge with a battery of foods. Initial successes encouraged others to continue this line of research utilizing microscopic observations of white cells following antigenic challenge in vitro. These methods offered some tantalizing results but were crude and results were not reproducible.

Our efforts focused on the utilization of electronic methods of cell measurement and computer analysis of the results following an ex vivo challenge of whole blood with food extracts and other substances suspected of association with non-IgE mediated hypersensitivity. (Figure 6)

## The ALCAT Diagnostic System

**R**ecognizing that patients' reactions to foods, molds, chemicals, and drugs follow various pathways, a technologically simple method of measuring the effects of multiple pathogenic mechanisms on cellular populations provides the most logical and cost-efficient approach to testing such sensitivities. It appears that most, if not all, of the various mediator pathways involved in these sensitivities affect reactions in associated blood cells. The ALCAT Diagnostic System is designed to measure these blood cell reactions. The methodology includes using innovative laboratory reagents allowing for accurate cell measurement in their native form. Individually processed test samples, when compared with the Master Control graph, will show cellular reactivity (cell count and size) if it has occurred. Scores are generated by relating these effective volumetric changes to the control curve.



**(Fig. 6)**

Analysis of whole blood offers a significant advantage in that it contains all of the immune factors, cellular elements and serum proteins that might be involved in an adverse reaction of this type, regardless of the underlying biological mechanism. Regardless of the various pathways that may underlie an adverse reaction to a food the final common pathway will involve some mediator release, and in the process, immune cells will alter in some fashion measurable through this technique.

The method of measurement is the same as that which is used in routine hematology. It has demonstrated a high degree of correlation with clinical manifestations as confirmed

through a rigorous double blind trial. Drs. Peter Fell and Jonathon reported an 83.4% correlation with Alcat test results and double blind oral challenges with foods. (45th Annual Congress of the American College of Allergy and Immunology). Dr. Lene Hoj reported a 96% correlation with Alcat test results and double blind placebo controlled oral challenges with food additives. (*Journal of Allergy and Clinical Immunology*, Vol. 97 part 1, Jan., 1996).

Dr. Hoj also reported a random sampling of clinical outcomes across a range of conditions suggesting the test results are accurate and useful in treating these conditions. (Figure 7)

Outcome-study in 353 consecutive patients following the ALCAT diet plan

Main Complaints	Perennial Rhinitis / Sinusitis (n=37)	Atopic Eczema (N=72)	Urticaria (n=24)	Irritable Colon (n=46)	Migraine / Headache (n=21)	Polyarthrosis (n=20)	Asthma (n=27)	Angio-edema (n=27)	Multio-organic syndrome (n=40)
Syptoms greatly improved	30	63	19	32	20	14	19	19	21
Improved	5	5	1	8		3	7	2	9
Little or no improvement	1	2	2	5	1	2	1		5
Worsening		2	2	1					3
No follow up	1					1			2
Total improved %	95	94	83	87	95	85	96	100	75

L. Høj et al - 1998

(Fig. 7)

These results have been instrumental in convincing the government of Greater Copenhagen and some insurance companies that a well designed elimination diet can save considerable health care costs. It is our hope that this precedent is followed by those responsible for the health of employees, public health officials and especially health care practitioners and patients, who are ultimately responsible for their own well being.

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