DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR FOOD SAFETY AND APPLIED NUTRITION

FOOD ADVISORY COMMITTEE MEETING

Advice on CFSAN'S Draft Report: Approaches to Establish Thresholds for Major Food Allergens and for Gluten in Food

Thursday, July 14, 2005

8:30 A.M. to 5:20 P.M.

Greenbelt Marriott
6400 Ivy Lane
Grand Ballroom
Greenbelt, Maryland 20770

P A R T I C I P A N T S

FOOD ADVISORY COMMITTEE STANDING MEMBERS:

Richard A. Durst, Ph.D. - Acting Chairman
Jeffrey A. Barach, Ph.D. (Industry Representative)
Patrick S. Callery, Ph.D.
Dennis Gonsalves, Ph.D., M.S.
Jean M. Halloran (Consumer Representative)
Douglas C. Heimburger, M.D., M.S.
Margaret C. McBride, M.D.
Mark Nelson, Ph.D. (Industry Representative)
Carol I. Waslien Ghazaii, Ph.D., R.D.

TEMPORARY VOTING MEMBERS:

Petr Bocek, M.D., Ph.D. (Absent 7/14/05 Session)
Margaret Briley, Ph.D., R.D.
Erica Brittain, Ph.D.
Ciaran P. Kelly, M.D.
Soheila June Maleki, Ph.D.
David O. Oryang
Marc D. Silverstein, M.D.
Suzanne Teuber, M.D.

FOOD AND DRUG ADMINISTRATION:
Robert E. Brackett, Ph.D. - Director
Food and Drug Administration, CFSAN

Catherine Copp, J.D. - Senior Policy Advisor
Food and Drug Administration, CFSAN

Steven M. Gendel, Ph.D. - Senior Scientist
Food and Drug Administration
National Center for Food Safety and Technology

Rhonda Kane, M.S., R.D. - Consumer Officer
Food and Drug Administration, CFSAN

Marcia Moore, Food Advisory Committee, Executive Secretary

P A R T I C I P A N T S (Continued)

FOOD AND DRUG ADMINISTRATION STAFF:

Michael M. Landa, J.D. - Deputy Director for Regulatory Affairs
Food and Drug Administration, CFSAN

Stafano Luccioli, M.D. - Senior Medical Advisor
Food and Drug Administration, CFSAN

GUEST SPEAKERS:

Pekka Collin, M.D., M.P.H. - Professor
University of Tampere, Medical School, Finland

Catherine L. Copp, J.D.
Policy Advisor, CFSAN, FDA

Alessio Fasano, M.D. - Professor of Pediatrics
Medicine & Physiology and Director, the Mucosal
Biology Research Center, Center for Celiac
Research, University of Maryland School of
Medicine

Steven M. Gendel, Ph.D. - Senior Scientist
National Center for Food Safety and Technology, FDA

Rhonda R. Kane, M.S., R.D. - Consumer Safety
Officer CFSAN, FDA

Donald Kasarda, Ph.D. - Consultant and Retired
Senior Scientist, Agriculture Research Service,
USDA

Cynthia Kupper, R.D., C.D. - Executive Director
Gluten Intolerance Group of North America

Joseph A. Murray, M.D. - Professor of Medicine
The Mayo Clinic of Rochester, Minnesota

C O N T E N T S

C O N T E N T S

P R O C E E D I N G S

CALL TO ORDER AND WELCOME AND INTRODUCTIONS

CHAIRMAN DURST: Good morning. I would like to call the meeting to order. All right, I would like to welcome everyone back and also welcome new participants in our meeting this morning.

For those of you who weren't here yesterday, there is a "Conflict of Interest Statement" over on the table, if you want to refer to that at all, otherwise I would also ask again that maybe our participants or our members of the Food Advisory Committee would introduce themselves again for the benefit of those who were not here yesterday.

I am Dick Durst, professor [of]chemistry at Food Science and Technology Department at Cornell University.

Marc, would you start it off?

DR. SILVERSTEIN: Marc Silverstein, I'm a general internist and geriatrician at Baylor Health Care System in Dallas.

DR. TEUBER: Suzanne Teuber, I am an allergist at UC-Davis.

MR. ORYANG: I am David Oryang. I am a risk analyst and agricultural engineer at the United States Department of Agriculture, Animal and Plant Health Inspection Service.

DR. KELLY: Good morning. Ciaran Kelly, I am a gastroenterologist at Harvard Medical School in Boston.

DR. MALEKI: I am Soheila Maleki. I am a scientist with the USDA.

DR. BRITTAIN: Erica Brittain, I am a statistician at the National Institute of Allergy and Infectious Disease.

DR. BRILEY: Margaret Briley, University of Texas at Austin, nutritionist.

MRS. MOORE: Marcia Moore, I am the executive secretary for the Food Advisory Committee and the Food and Drug Administration.

DR. WASLIEN: I am Carol Waslien, nutritional epidemiologist at the School of Medicine, the University of Hawaii.

DR. BRILEY: I am Margaret McBride, child neurologist at Akron Children's Hospital.

DR. CALLERY: Pat Callery, West Virginia University, pharmaceutical scientist.

DR. GONSALVES: I am Dennis Gonsalves, a scientist at USDA.

DR. HEIMBURGER: I am Doug Heimburger, a physician and nutrition specialist at the University of Alabama at Birmingham.

DR. BARACH: Jeff Barach with Food Products Association here, in Washington, D.C., in regulatory affairs.

DR. NELSON: Mark Nelson with the Grocery Manufacturers Association here, in Washington, D.C., and I am responsible for scientific and regulatory policy.

MS. HALLORAN: Jean Halloran with Consumers Union located in Yonkers, New York, and I am director of food policy initiatives.

CHAIRMAN DURST: Thank you very much.

I would also like to remind everyone and also for our new people here at the meeting that

the "Charge" of the Committee is written out on the meeting document. The most important thing is that we are focusing on the "Threshold Working Group Draft Report on Approaches to Establish Thresholds for Major Food Allergens and for Gluten in Food."

We are not here to set any kind of thresholds or discuss the labeling of these foods for allergens, but strictly to make comments on the best approaches to use for setting these thresholds.

Did I cover everything that we need to?

(No verbal response.)

CHAIRMAN DURST: In that case, let's begin with our first presentation. This is Catherine Copp, the policy advisor for CFSAN, FDA, on the use of gluten thresholds.

USE OF GLUTEN THRESHOLDS

MS. COPP: I have been asked this morning to proceed with discussion on gluten and threshold levels for gluten or possible thresholds for gluten framework. It is similar to yesterday. I simply want to provide you with some context for the

evaluating the Draft Report portion that addresses gluten in food. This is the hazard of being first.

(Slide.)

MS. COPP: Yesterday, I mentioned the Food Allergen Labeling and Consumer Protection Act. This is a new law that Congress passed last August. Although it focuses primarily on allergens, food allergens, Congress also directed FDA to address the separate problem of gluten in food.

When I say directed, I mean that Congress has mandated that the Agency consider and then establish regulations according to a schedule to define "gluten-free" for use on food labels and also to identify the appropriate use of the term.

As with Allergens, for consumers with celiac disease, strict avoidance of gluten at levels that will elicit an adverse effect is the only means to prevent potentially serious reactions.

Accurate, complete and informative labeling on foods can help these consumers achieve their goal. We believe that understanding

thresholds for gluten and having a sound scientific framework for evaluating the existence of such thresholds will help FDA develop a definition of gluten-free and identify appropriate use of the term. That's it.

Thank you.

CHAIRMAN DURST: Does anyone have any comments or question on Catherine's presentation?

(No verbal response.)

CHAIRMAN DURST: Okay. We will move on then to the presentation from Dr. Joseph Murray, professor of medicine at the Mayo Clinic of Rochester, Minnesota, on the introduction to celiac disease.

INTRODUCTION TO CELIAC DISEASE

DR. MURRAY: Good morning, Committee Members. I will be providing a general overview to celiac disease.

(Slide.)

DR. MURRAY: First of all, we will discuss what is celiac disease. We will discuss, briefly, the pathogenesis of the disease; who gets it; what

the treatment is, at least in a very relatively superficial fashion. We will discuss some of the complications and compliance issues of celiac disease and a prognosis or future of celiac disease.

(Slide.)

DR. MURRAY: Obviously, yesterday was focused on food allergies. "Celiac disease" is one of the food intolerances that is immune-mediated, though it is not thought to be IgE-mediated; so, it comes into the non-IgE-mediated food intolerances that are mediated by an immune response.

(Slide.)

DR. MURRAY: Where does it happen? It happens within the smaller intestine, predominantly the proximal, smaller intestine is the workhorse of the digestive system. It is this surface of the intestinal lining that is maximally expanded by the development of circular folds and on top of these circular folds the so-called "villi," these villi, shown here in a histological picture, which maximize the digestive surface area.

It is on the surface entrocytes of these villi that most of the enzymes and in the layer immediately above that in the lumen where most digestion of the macromolecules from nutrition are broken down and then absorbed. This is just a picture. It looks like one of those shag-ply carpets from the 1970s. This is a normal appearance.

(Slide.)

DR. MURRAY: However, celiac disease is an inflammatory state of the small intestinal mucosa. It occurs in those who are genetically predisposed, and it resolves, the damage resolves, with exclusion of dietary gluten.

Here, on the left, is a normal intestine with a normal villus structure; and on the right, fully evolved celiac disease with complete destruction.

The villi are gone, not only are they gone but this entire intestinal mucosa is greatly thickened and filled with inflammatory cells. This is where the primary site of injury occurs in

celiac disease.

I didn't mention it, but it is a permanent condition. While it will heal most of the time with exclusion of gluten, the intolerance to gluten is permanent and will recur when the individual is reexposed to gluten.

(Slide.)

DR. MURRAY: Now, what causes celiac disease?

(Slide.)

DR. MURRAY: We know there are two major components to this disease: the first is the genetic background of predisposition.

Much of that predisposition revolves in the HLA type, which is part of our human leucocyte antigen-recognition system. It is how we determine self- and non-self and generate an immune response as appropriate and its interaction with environmental factors, primarily the environmental factor of gluten.

These two conspire together to produce an immune response that becomes out of control

resulting in inflammation, which we just showed to you, that occurs primarily in the proximal small intestine and then subsequently the consequences of this inflammation leading to malabsorption and symptoms.

(Slide.)

DR. MURRAY: What do we know about the genetics of the disease? For many years, we know there is a strong, familial predisposition to the disease.

If you are unlucky enough to be a monozygous twin of somebody affected with celiac disease, your concordance rate is 80 percent. It is not 100 percent, but it is about 80 percent. If you are a sibling of a celiac, your chance of having it is 10 percent. If you are a child of, about 5 to 10 percent.

There is a very strong association with certain HLA molecules. These are Class II MHC molecules but particularly two types. First, DQ2 is the predominant type that is required for celiac disease, and in some populations DQ2 is also an

enabling type.

These genes, however, while they are essentially required for the disease, are not sufficient alone to the development of the disease. Probably 30 to 40 percent of the Caucasian population carry one or both of these molecules, but most of them don't get celiac disease. There are other HLA genes that are likely involved, though they have not been well elucidated and certainly not confirmed in many populations.

There are other chromosomal disorders -- Down's syndrome, Turner's syndrome, and Williams syndrome -- that are associated with a greatly increased risk of developing celiac disease for reasons that are not entirely clear, but probably are associated with the increase risk of disease in those chromosomal disorders.

(Slide.)

DR. MURRAY: Looking at the primary environmental trigger for the disease -- that is, gluten -- it is basically the storage proteins that come from these particular cultivated grasses:

wheat, barley, rye, and other similar grains from within those families. Other grasses -- for example, rice, items such as corn, sorghum, millet, and probably not even oats -- are not involved in triggering the disease.

(Slide.)

DR. MURRAY: It is the storage proteins from the endosperm compartment of the wheat kernel particularly, and those are gliadins oar glutenins that are thought to contain the antigenic moieties that trigger the disease.

(Slide.)

DR. MURRAY: What is it about these wheat proteins? Well, if you take wheat, as an example of the others, these storage proteins are uniquely high in certain amino acids, especially glutamines and prolines.

Over 30 percent of the amino acids in gliadin are glutamines. The glutamines, of course, can be cross-linked to give the grain its resiliency. Really the cooking ability, the ability to use wheat as such an effective way of

making things that stick together like bread, for example, and maintain their shape, is largely a property of these particular combinations of amino acids.

The proline sequences that contain or proline residues contained within the wheat proteins also appear to form helices, and these helices are resistant to digestion within the mammalian gut.

(Slide.)

DR. MURRAY: This may be a key factor in what results in the likelihood of these peptides basically being maintained and becoming, then, still available for the immune system to recognize in a patient with celiac disease.

Now, gliadin molecules are presented by these HLA types to T-cells in the intestine, and T-cells that are specifically primed to respond to gluten. There are certain gliadin molecules that have a higher affinity than others for these Class II molecules and then the T-cell receptor.

These peptides may be processed or altered

within the gut, perhaps, to make them more antigenic. They may not start out very antigenic, but then they undergo some change within the gut that may make them more antigenic.

It turns out that some of these peptides that are particular immunodominant, these are the ones that are most likely to produce an immune response, that those immunodominant peptides may be digestion resistant because they contain those proline sequences that perform helix, making them relatively poorly digestible by peptidases within the gut.

(Slide.)

DR. MURRAY: Now, it turns out that there is a contribution to this antigenic nature from within the intestine itself, and this may well be because of this enzyme tissue transglutaminase.

This is an enzyme that is present within the gut mucosa. It is released by cells, especially fibroblasts when they become inflamed, and it cross-links cystine residues.

It turns out that it will also act on

gliadin by deamidating some of those glutamine residues, some specific glutamine residues, to glutamates, making it more antigenic by deamidating that gliadin peptide and making it fit more perfectly or with a tighter affinity into the binding groove of the DQ2-HLA molecule, and, hence, producing a more vigorous immune response within the gut.

(Slide.)

DR. MURRAY: This is a schema, a relatively simplified schema, of what I have just talked about. We start with wheat. You look at particularly the ethanol-soluble fraction, and gliadin is probably broken up into smaller peptides, but still of a sufficient size to produce an immune response.

It is taken up across the epithelium presented by antigen presenting cells to the T-cells. These are T-cells that will specifically respond to gluten then producing two types of responses: a cellular response, characterized by lymphocytes producing interferon gamma and possibly

other cytokines. It is probably the cellular response that leads to the "inflammatory cascade" that produces the damaged epithelium characteristic of celiac disease.

It also produces help to the B-cell side, to produce plasma cells that produce antibodies. These antibodies are directed both against the exogenous antigen gliadin and also antibodies against tissue transglutaminase or what was known as an the endomysial antibody. It is not known what the actual pathogenic role of this is, but it is a very useful serologic or blood marker for the disease.

I mentioned about the antigen getting changed by tissue transglutaminase. This is a little cartoon which shows the peptide derived from gluten. If you change one specific glutamine to a glutamic acid, which could be done by tissue transglutaminase, this then binds much more tightly. This is the HLA molecule here on the surface of the antigen presenting cell, and it fits more perfectly into the T-cell receptor, producing

a more potent T-cell response.

(Slide.)

DR. MURRAY: Now, there are other things that happen in the setting of celiac disease, and I am really touching just on the surface of many of these, but there are other things that result in this inflammation that damage the lining of the intestine.

For example, there are metallic proteases that damage the structural elements that maintain the structure that maintain villus structure. There is endothelial injury that occurs affecting the blood vessels in the villus. There are antibodies, autoantibodies, that are produced that affect actin that are involved in the site maintaining the structure of the entrocyte itself.

(Slide.)

DR. MURRAY: Recently, there has been work suggesting that there is a molecule called "zonulin" that may be released in the setting of celiac disease.

This is important because it opens up

tight junctions between entrocytes which may allow even more ready access of the antigen, the foreign antigens, between the cells into lamina propria where antigen-presenting cells can then present those peptides to the gluten-responsive T-cells, further accelerating the disease.

(Slide.)

DR. MURRAY: Now, I pointed out that many people, 30 percent or more of the Caucasian population, carry DQ2 or DQ8. Virtually, the entire population are exposed to gluten, but most people don't get the disease.

There must be triggers that produce the disease. There is evidence that suggests that gluten in the infant diet, specifically the age of introduction of gluten into the infant's diet, may be important in triggering or at least producing autoantibody markers suggestive of celiac disease early in life.

It is not clear, however, if that changes, whether you delay introduction or not whether that changes, the lifetime risk of celiac disease, but

it certainly seems to be important in triggering or producing evidence in childhood at least of celiac disease immune markers.

The amount of gluten in the child's diet may be important. There are other events such as pregnancy, infection, or surgeries that may bring previously asymptomatic celiac disease to clinical presentation.

(Slide.)

DR. MURRAY: One could speculate, and I think this is based on some data, putting data together, that one's risk for celiac disease starts with your HLA type. Only those who carry HLA types are at risk. You, then, are exposed to gluten. Perhaps the timing of exposure is important, developing in some individuals a sensitivity to gluten.

Then, with the interaction of other factors such as other genes other than HLA, other things that may predispose one to autoimmunity including gender and other events that may occur -- gastroenteritis, aging, postsurgical or postpartum

changes in the immune system that may occur -- may lead to a loss of tolerance, inflammation, and subsequent malabsorption.

(Slide.

DR. MURRAY: Don Kasarda, who is here once used the term or suggested that celiac disease was a collision between our evolution of our immune system and our ability to recognize self and non-self through the HLA system and our cultivation of wheat and these other grasses. This collision occurs in the intestine.

(Slide.)

DR. MURRAY: Now, when this collision occurs and results in damage, how does it present? And who gets the disease?

(Slide.)

DR. MURRAY: Well, this is classic celiac disease, and this is the way that I certainly learned about celiac disease. A severe malnourished child with evidence of malnutrition often associated with the large, swollen abdomen but great muscle, terrific muscle, wasting and

protein-calorie malnutrition with symptoms that would occur sometime after the onset of gluten introduction into the diet, sometime between the age of six months and seven years of age: with failure to thrive; abdominal distention; anorexia; diarrhea; steatorrhea, that is the passage of malabsorptive stools laden with fat; anemia; growth failure; and vitamin deficiencies. That was really the picture that we had of celiac disease 30 years ago.

(Slide.)

DR. MURRAY: However, we now see celiac disease in adulthood. In fact, celiac disease can present at any age. Symptoms can include things such as abdominal pain, even upper-GI symptoms: heartburn, nausea, vomiting, anemia, fatigue.

There are of course patients who have symptoms of malabsorption, though not necessarily the classic, fully evolved malabsorptive picture. Steatorrhea as a presenting symptom is relatively rare, even patients may have constipation.

(Slide.)

DR. MURRAY: It can mimic other disorders such as lactose intolerance. Indeed, lactose intolerance may be secondary to the damage caused by celiac disease. It may mimic the symptoms of irritable bowel syndrome or symptoms of inflammatory bowel disease.

(Slide.)

DR. MURRAY: There are specific deficiencies that can occur in celiac disease, especially the fat-soluble vitamins -- D, E, A, and K -- with their resultant syndromes from deficiencies.

Iron deficiency is especially common in celiac disease because iron is absorbed in the proximal small intestine; folate deficiency, again, because it is absorbed in the proximal small intestine; and, interestingly, B12 deficiency may be relatively common in celiac disease by a variety of mechanisms. Other trace elements -- zinc, B6, selenium, and others -- may also be deficient in celiac disease.

While in the past we would look for

combinations of these, often a patient would present with many of these deficiencies at the time of diagnosis, now it is relatively uncommon to see the entire spectrum of deficiencies. Indeed, you usually see one or two deficiencies that are clinically evident, and the others may not even be present.

(Slide.)

DR. MURRAY: How about non-intestinal? I have mentioned that the major site of injury is in the gut, but there are patients who will present with non-intestinal presentations which can involve into things such as the musculoskeletal system, joint pains and osteoporosis or osteomalacia; infertility or reproductive issues, delayed puberty, spontaneous recurrent abortions have been described; hematologic, which is predominantly anemia; hyposplenism is an unusual consequence but can present; and then dentition, enamel defects, can be a presenting feature.

(Slide.)

DR. MURRAY: To focus on iron deficiency

anemia, which is probably one of the most common reasons that I see celiac disease, about 5 to 8 percent of adults who present with unexplained iron deficiency in some studies have celiac disease.

It is especially common in those who are resistant to the use of oral iron. If you look at individuals who are coming to gastroenterologists for endoscopy, it may be 5 to 15 percent of those patients, depending on the study, who may have celiac disease if biopsies are taken from the small intestine.

However, many of those patients are even missed because the biopsies are still not taken during routine endoscopy in patients who have got anemia in about a third to a half of patients.

(Slide.)

DR. MURRAY: Osteomalacia or bone disease, this is an example of severe disease with pseudofractures in the pelvis of an individual, whose only presentation was osteomalacia with no GI symptoms, caused by celiac disease.

Other non-intestinal presentations include

neurologic or even neuropsychiatric syndromes such as neuropathy, ataxia, seizures, cognitive decline, or dementias; fibromyalgia-like syndromes or chronic fatigue syndrome-like presentations; individuals with skin and mucous membranes, there is a specific rash associated with celiac disease, a recurrent aphthous ulceration of the mouth; the dental enamel defects we mentioned.

(Slide.)

DR. MURRAY: And, then, dermatitis herpetiformis was specifically mentioned, because this very blistering, extremely itchy skin rash that affects the extensor surfaces is a direct manifestation of intestinal gluten sensitivity.

(Slide.)

DR. MURRAY: Now, what about other associated conditions? Celiac disease is associated with other autoimmune conditions. It may be seen in 3 to 7 percent of Type I diabetics, individuals with thyroid disease, individuals with inflammatory arthritis, primary biliary cirrhosis, as examples of others; and then the congenital

disorders, especially those associated with chromosomal abnormalities and also selective IgA deficiency. If you look at relatives of celiacs, it is anywhere between 5 to 20 percent, depending on how one is related to someone with celiac disease.

(Slide.)

DR. MURRAY: Now, beyond the symptomatic celiac disease, there are also individuals who have no symptoms, who already have fully evolved damage within their intestine, and there may be no symptom or there may not be occurring in someone with an associated disease.

This is frequent to find this in first- and second-degree relatives of patients with celiac disease.

(Slide.)

DR. MURRAY: There is also what is termed "latent" -- well, whether it is latent celiac disease or latent gluten sensitivity -- individuals who have a positive serologic response but have a negative small-bowel biopsy. Some of those

patients will go on to develop the full-blown disease, if followed, on a normal diet.

(Slide.)

DR. MURRAY: What about the epidemiology? To summarize, while it was first identified in Europe, it occurs essentially in all populations, which could be termed Caucasian. Its prevalence is probably somewhere between 1 in 90 to 1 in 300; however, the diagnosis rate is much lower, which would suggest a prevalence of about 1 in 2,000, if you just look at the diagnosed cases.

It is one of the most frequent genetically based diseases. If you look at other countries -- Latin America, or other areas; Africa, especially North Africa; if you look at Asian countries -- there is celiac disease present in those. The worldwide average prevalence is somewhere very close to 1 percent.

(Slide.)

DR. MURRAY: I'm coming a little closer to home. This is the data from Olmsted County, that we published a couple of years ago, which looked at

the new case identification or the incidence rate.

The solid yellow line is the new cases per 100,000 in the population, which is essentially quite low and stable over many decades until the 1990s and into 2000 to 2001, showing a greatly increased rate of detection of celiac disease.

If we looked at who were being diagnosed, this is the age of diagnosis by age category. This is the incidence per 100,000 of people in that age category in the community. You can see that the new cases being diagnosed are predominantly people between the age of 45 and 64.

The solid line indicates females; so, females are diagnosed at a rate about twice that of males of all ages.

There are a significant portion of individuals, almost a third, who were diagnosed for the first time over the age of 65.

(Slide.)

DR. MURRAY: One can term or consider celiac disease like an iceberg. These are a series of icebergs where the tip of the iceberg is the

part that has been detected, and the part underwater is the part that can be found if one screens the population. Of note, these are numbers per thousand not percent.

Obviously, there are some places like Ireland, for instance, which is quite a big iceberg with a lot above water but also a lot below water. Finland, which this iceberg is probably even more out of the water as they have got a very active program for finding celiac disease.

This is circa 1996. The U.S.A. iceberg is still close to a very low level of actually being diagnosed; but this number, the part underwater, has actually grown to be something very close to what you would find in Finland or Ireland, especially when one looks at, at least what we know about is really from a Caucasian population.

(Slide.)

DR. MURRAY: One miniature study, this is one we simply looked at, Natrona County in Wyoming. This is a very isolated community. Anybody who has been to Wyoming, there is lots of nothing for miles

and miles.

We were able to study about 4,000 individuals from a health fair, generally healthy, and found the numbers above just under 1 percent of people who had serologic evidence for celiac disease.

Only half of them had GI symptoms. Most of them did not have other risk factors for celiac disease, just two having family members with celiac disease.

However, these are numbers that would confirm basically the rest of the world's data that suggests that the prevalence of celiac disease, if you look for it, is probably slightly under 1 percent.

(Slide.)

DR. MURRAY: Now, how does one make the diagnosis? It starts with suspicion. Serologic tests may be very effective at detecting the disease. The intestinal biopsies are regarded as the gold standard. Then, one ultimately gets a response to a gluten-free diet to confirm the

diagnosis.

(Slide.)

DR. MURRAY: The pathology, as we have mentioned already, is a pathology of chronic inflammation within the intestine with features such as intraepithelial lymphocytes on the surface, villus atrophy or the loss of the villus surface, great crypt hyperplasia, and then characterized by being a lamina propria filled with lymphocytes, macrophages, plasma cells, and even eosinophils.

(Slide.)

DR. MURRAY: There is however a spectrum of damage that occurs, typified here by the Marsh classification. This is classic disease, but there are also milder forms of the disease that may be asymptomatic in most individuals.

(Slide.)

DR. MURRAY: Our algorithm for finding celiac disease, if we have a high clinical suspicion, an individual with malabsorption, we biopsy those individuals. If we have an individual who is at moderately increased risk, serology is

probably the most effective way of finding it. Though, we yet do not depend on the serology alone to detect this, there are other circumstances for alternate; serologic testing may be necessary.

(Slide.)

DR. MURRAY: Now, what about treatment for celiac disease, or, as one patient with celiac disease called it, "playing gluten-free roulette"?

(Slide.)

DR. MURRAY: The nuts and bolts of a gluten-free diet, basically one needs to avoid foods that contain the offending grains: wheat, barley, rye, and the wheatlike grains of spelt and kamut.

I put down at the bottom that many corn or rice commercial cereals do not appear to be gluten-free because of their incorporation of particularly barley extract in their flavor ingredients.

(Slide.)

DR. MURRAY: Now, one of the issues and of course the issue for today is, How much gluten is

too much? We will be hearing a lot more when you hear prospective and retrospective data later this morning on this. I am not going to dwell on it.

One thing from clinical appreciation is that symptoms are not a good indicator of gluten ingestion. Many patients can have significant damage to their intestine, despite the absence of symptoms when they ingest gluten.

Most patients diagnosed clinically with celiac disease have never suspected that wheat or gluten products are what are precipitating their symptoms. They may have or are often likely to have blamed other foods that they weren't able to digest because of the damage.

Antibodies such as tissue transglutaminase antibodies are really only positive of the substantial gluten contaminating the diet. At least in my practice if somebody admits to cheating more than once a month they will like continue to have injury in their gut. However, there is a high degree of variability in the sensitivity to gluten ingestion, at least clinically.

(Slide.)

DR. MURRAY: We will hear a little bit about Codex Alimentarius draft standards. This, however, is still a draft, I think a Stage IV draft. I want to put this up really to demonstrate that there is a variance between countries and what one allows.

We will hear more from our colleagues from Europe about some of the incorporation of rendered gluten-free foods which use the gluten-containing grains as a base and then remove the proteins from them.

(Slide.)

DR. MURRAY: What about non-responsive celiac disease? This is relatively common. By far, the most common reason is inadvertent gluten contamination of the diet and lymphocytic colitis, pancreatic insufficiency, bacterial overgrowth, and then only a few patients have true refractory disease that no longer responds to exclusion of gluten from the diet.

(Slide.)

DR. MURRAY: There are many potential sources of contamination of the diet with gluten, which include of course commercial cereals, eating out, communion wafers, lipstick, airborne flour or starch in certain work situations, so-called "soy" sauces made from wheat, mislabeled or unlisted ingredients have been an issue, and at least allegedly some medications.

(Slide.)

DR. MURRAY: Some ingredients that people are concerned about: seasonings and spice blends, modified food starch, malt and malt extract, modified hop extract or yeast-malts, sprout extract, dextrins, caramel color. There are a whole bunch of things that might be derived from gluten-containing grains.

(Slide.)

DR. MURRAY: What about complications associated with untreated celiac disease? We know the mortality of symptomatic celiacs who do not comply with the diet has doubled. The mortality of celiac disease even when it is diagnosed is also

double, even following out for several years after the diagnosis.

The predominant excess in death comes from GI malignancies. There are also morbidity consequences such osteoporosis or osteomalacia, stunted growth, infertility, chronic ill-health -- all of which could be prevented by early detection and treatment.

(Slide.)

DR. MURRAY: What are the dangers of non-compliance? The increased mortality we discussed, the osteoporosis. Children who were diagnosed and then did not remain on a gluten-free often have osteoporosis or diminished bone density when they get to adulthood, lymphoma, other cancers, and then the psychological effects of non-compliance.

(Slide.)

DR. MURRAY: One of the most feared complications of this are the T-cell lymphoma. This is celiac disease on this side, and the T-cell lymphoma on the other side is one of the more

feared complications with a very high mortality.

(Slide.)

DR. MURRAY: However, as I pointed out, most celiac disease is probably not symptomatic, at least when we look at a cross-section of the population. We do not know whether those identified by screening are less sick than clinically diagnosed celiac disease.

We don't know the benefit or negative effects of a gluten-free diet in those who are found by screening alone. We don't know if they are any more or less likely to comply with a gluten-free diet. We don't know whether intervening in those patients will actually affect their ultimate mortality.

(Slide.)

DR. MURRAY: George Dennison Prentice said, "What come call health, if purchased by perpetual anxiety about diet, isn't much better than tedious disease."

(Slide.)

DR. MURRAY: This comes to the future.

There is, I think, a promising future in celiac disease, a variety of approaches, which I have listed, that individuals and research groups are looking at as alternates to the gluten-free diet, though none of them are really even close to clinical use.

(Slide.)

DR. MURRAY: This is one that has been tested in patients using a lactobacillus digestion strategy, trying to reduce the potential, harmful effects of gluten.

In summary, I would like to suggest that gluten or celiac disease is common. It has been largely unrecognized until recently. There are many challenges that face patients and their physicians in the treatment.

The gluten-free diet is not simple. There is widespread use of grain proteins in good, and that makes it challenging for individuals with celiac disease. Food ingredient source identification is of great concern to patients.

Dietitians and those who counsel patients

with celiac disease, we are here because of regulation or potential regulations. Defining acceptable thresholds and verification of those may be very important to patients with celiac disease.

(Slide.)

DR. MURRAY: I finish with an aside on another food safety issue, an invitation to come to Minnesota and enjoy Joe's and have worms at the same time.

Thank you.

CHAIRMAN DURST: Thank you very much, Dr. Murray.

QUESTION-AND-ANSWER SESSION

CHAIRMAN DURST: I would like to ask the Committee if they have any questions or discussion, and also to point out that Dr. Murray will not be able to stay around for discussion this afternoon. If there are questions, now is the time to ask them.

Doug.

DR. HEIMBURGER: Thank you very much for that presentation. It is very helpful. I do care

for some patients with celiac disease. As you already mentioned, one of the big questions that they have is, "What really are my risks if I play with it a little bit? If I knowingly introduce a little bit of gluten in my diet, how absolutely obsessive do I need to be about it?"

With the mortality being primarily associated with the risk of lymphoma, what is the quality of the evidence that compliance with gluten restriction is really correlated with the risk of lymphoma?

DR. MURRAY: The evidence, the quality of the evidence is largely observational, taking cohorts and following them, and often their self-assessment of their level of compliance. The data is based on those cohorts. They are predominantly referral cohorts.

The longest follow up comes from Britain. In those, there is quite a clear increased risk not just for lymphoma but other malignancies in those who are considered not to be completely compliant with the diet. I would say the level of evidence

while it is not a prospective study, in retrospect in fact it appears to be reasonably strong.

DR. BRILEY: Margaret Briley. I would like to know what you can tell us what might be the reason for the increased detection of celiac disease? Is the serological test the definitive reason? What is going on with those? It seems to be more prevalent, as you said, in our society.

DR. MURRAY: I think there are probably two reasons, one is probably serologic detection has made this an acceptable diagnosis to primary care physicians, number one; and the second is suspicion, that is, the awareness of celiac disease as a possibility.

I do not believe, however, we can rule out the possibility that celiac disease is actually increasing in prevalence over time.

We don't know, but we know that there certainly were substantial increases in other inflammatory bowel diseases over the last 50 years, which may not have been accounted for by detection rates, for example.

I do agree with you it is probably the sero-detection. It is a combination of those two things, suspicion and ease of detection have made the biggest difference. However, I would not rule out the possibility of its actually increasing in prevalence.

CHAIRMAN DURST: Soheila.

DR. MALEKI: Soheila Maleki. I was wondering how long does a person that is asymptomatic go before they find they are symptomatic? How do they usually find out?

DR. MURRAY: First of all, we don't know when it starts. There is one study I didn't talk about from Denver that suggested that children, if you follow children at genetic risk for celiac disease based on HLA type, that they will convert, sero convert, by about the age of seven, though most of them are asymptomatic.

It reaches all but 1 percent of that childhood cohort, the same prevalence you find if you look at adults. The suggestion is that you have developed that celiac autoimmunity probably by

the age of seven.

However, the age, the median age, of diagnosis is 45 years of age. It is likely that those individuals have some clinical disease for a long time before they present.

In our population, the most common reason for presentation is postmenopausal anemia. Women who have anemia sometimes go a long time, especially when they are menstruating. The doctor says that menstruating is an excuse for the anemia. Now that they are menopausal and are no longer menstruating they no longer have an excuse for their anemia, and they are referred for evaluation for the cause of anemia.

Iron deficiency anemia at least is one of the most common, but there are other things. For example, the development of chronic GI symptoms. Largely, as the earlier questioner said, probably awareness of the possibility of this disease, with primary care doctors using sero-diagnosis to find celiac disease.

There a lot of atypical symptoms. There

are reservoirs of celiac disease, the Type I diabetics, the family members of celiacs, those with chromosomal disorders. As the doctors looking after those people become more aware of celiac disease, they are testing their patients more.

DR. BRILEY: Could you speak a little bit more about the evidence that you have in regard to physicians using the serological test? Is it a pretty common thing to do it at the very beginning of a patient's coming in with GI problems, or is it more likely it is down the road a while?

DR. MURRAY: If you look at the data on patients' presentation time, from presentation to diagnosis of celiac disease, it is somewhere between 8 and 11 years from the time they present to their physician with a complaint to the time their diagnosis is made.

I think that time period is now beginning to shorten, thankfully. The serology is done close to the end of that period, so it is often only when the suspicion is generated. Partly that is because it is not considered at the early differential

diagnosis of celiac disease.

It is also difficult. It is difficult because the symptoms are not very specific. Fatigue and some bowel disturbance and a little anemia, that is not a rare syndrome or not a rare collection of symptoms you will see in individuals in our community. It is hard to know where you look for celiac disease and when you look for it. It is often a very delayed diagnosis.

DR. BRILEY: Is the serological test one that is pretty accurate? Could one count on it if you did it early?

DR. MURRAY: If you use the more modern autoimmune tissue transglutaminase test, for example, it is reasonably good. It is not perfect, but it is quite efficient at detecting celiac disease at that level, in that period. It is not perfect, though, but it is a pretty good test.

DR. BRILEY: It sounds like we need to do some education, then.

DR. HEIMBURGER: A follow up to that -- Doug Heimburger -- what is currently understood to

be the sensitivity specificity of anti-tissue transglutaminase antibodies?

DR. MURRAY: Depending on the study, most studies suggest that the sensitivity of tissue transglutaminase for celiac disease is in the high 90 percent, so the high 90s.

The specificity is probably also in the mid- to high 90s, so quite effective when you are looking at a population you are suspicious of the disease.

DR. BRILEY: One more question. Margaret Briley. Do we have any data that shows the celiac patient also maybe has been identified with a lactose intolerance? Is there anything that combines those two that you would know or does that--?

DR. MURRAY: The combination is probably the damage that is caused by celiac disease, the damage to the entrocytes affects your disaccaridase including lactase throughout the surface of the small bowel, and, hence, you get a secondary lactose intolerance.

In general, if you think of the genetic basis or the ethnic groups that are involved, celiac disease tends to hit those of European extraction more so. I know that population will tend to retain their lactase activity for longer.

If you look at Subsaharan Africans, for example, we don't know actually what the prevalence of celiac disease is in Subsaharan Africans, but they are individuals who tend to lose their lactase.

Genetically, they are probably separate, but they come together because of secondary lactase deficiency caused by the damage in celiac disease.

DR. NELSON: Thank you, Dr. Murray. That really was a very interesting presentation. I think the last time I studied this was 30 years ago.

CHAIRMAN DURST: Identify yourself, please.

DR. NELSON: Mark Nelson. I wanted to touch base on the couple of slides where you talked about how much gluten is too much and the proposed

Codex definition for gluten-free foods.

You had a question mark after the threshold for damage being 20 to 100 milligrams per day, and I guess that is similar to the naturally gluten-free foods the Codex proposed.

Then, it goes on to talk about cheating is greater than once per month. Also, is there an issue of cumulative exposure, 20 milligrams per day, or is the cheating an excursion of whole wheat crackers, for example?

DR. MURRAY: Well, first of all, the comment on cheating that is what the patients tell me, those patients who will admit to gross cheating, that is, eating a piece of bread or a cookie or cake, which is what I regard as an obvious source of gluten.

However, that may reflect some other background, but a lack of detail of care, for example, attention to detail in the rest of their diet, maybe what they are not telling us. That only applies to what they have told me.

The issue of actual threshold, I have a

question mark after that because we will hear a lot more detail, science, about threshold testing for thresholds of gluten contamination.

The intermittent contamination, once a month obvious contamination. Something that is, to some degree, under the patient's control with appropriate education and exposure to information then essentially it is under their control.

It is the low-level contamination on a regular basis from sources they are not aware of, and those are the patients that I see that make up the majority of the patients I see who have difficulty. They are coming to me because they are trying to be gluten-free, but they are having contamination of their diet on a daily basis, probably a relatively small amount. We will hear a lot more about the threshold, the actual testing of the threshold using that type of low-level daily contamination.

DR. MALEKI: Soheila Maleki. Is there an adult onset or spontaneous development of celiac disease, or does this have to come with a genetic

component and hereditary?

DR. MURRAY: It probably only occurs in people who have that HLA or genetic type. You have to have it. However, that is 30-plus percent of the Caucasian population.

Can it start first in adulthood? We have very little data on that. The only data is the stuff I have mentioned, looking at children and showing about 1 percent by the age of seven or eight, positive by the age of seven or eight, the same prevalence if you look at adulthood.

There are a few cases of what we call "latent celiac disease," individuals who have got antibodies with apparently normal small intestinal biopsies as adults, then go on over a space of years to develop full-blown celiac disease within years of that initial identification of a positive serology. Those are very rare cases that have been found.

Of course, if you find somebody who suspects they have got a problem, they ought to change their diet anyway, and that changes

everything. There is very little data, I think, to be sure of whether it first occurs, starts, in adulthood.

If you look at the age of diagnosis, your eighth or ninth decade can be the first time that you are diagnosed with celiac disease. A lot of those patients have suspicious symptoms going back many years.

DR. BRITTAIN: Erica Brittain. Can you quantify the level of damage? Is that only possible with the biopsy, and is that very invasive?

DR. MURRAY: You can -- well, if you take biopsies, you can quantify the degree of injury. I showed that slide which shows a spectrum of injury. It tends to be variable, even within the same individual. It started in the first part of the small intestine and extends a variable distance down the small intestine.

There has really only been one study, which was done in the early 1960s, of taking multiple biopsies down the intestine -- a handful

of courageous volunteers.

It is not clear that there is a correlation between the extent of injury and the severity of symptoms. In fact, we don't know how to predict the occurrence of symptoms in patients with celiac disease, so that is a "black box."

DR. BRITTAIN: You are saying there is really no simple way to quantify the extent of damage? There is nothing that would correlate with these multiple biopsies?

DR. MURRAY: Some people have suggested that the level of the antibodies, the tighter the antibodies might correlate: The higher, the tighter, maybe the more severe the injury to the intestinal biopsies.

When we take a biopsy of the intestine, we are sampling a tiny fraction of a percentage of 1 percent, a fraction of 1 percent, of the intestinal lining. We have tried to look using other imaging techniques to assess the extent of injury. Using some of those techniques seems to be very variable between individuals, and it doesn't

seem to predict their symptoms.

Really right now it is a yes or no issue: yes, they have celiac disease; or, no, they do not. It is very hard to measure the severity of the disease.

We can look at the severity of consequences: have they developed osteoporosis, what their bone density is, have they lost a lot of weight, whether they have severe malabsorption based on fat malabsorption in their stool. We have got other measures to look at the consequences or impact of the disease, those we can assess.

DR. BRITTAIN: Do you think that it would correlate with the intestinal damage? Not necessarily?

DR. MURRAY: We have tried. I would say that the data is not very good on that. People with very mild injury may be more likely to be asymptomatic, but the data is not sound.

CHAIRMAN DURST: Suzanne.

DR. MALEKI: Suzanne Teuber. I had a question about the neurologic presentations. I

have read some on screening of pediatric populations, but with adults how often does it present as dementia without it being diagnosed as a GI problem? Is this something we should be adding to dementia screening?

DR. MURRAY: It is probably relatively rare. In fact, I think there has only been one good study. Maybe Dr. Collin, who is here as a speaker later, has done a study and has looked at and reported on that.

We occasionally see cognitive decline at the time of diagnosis, but there is really no good epidemiologic study to address that. Some of the other presentations, peripheral neuropathy, for example, or ataxia, there is more data on it. Many neurologists are beginning to include celiac disease as part of their differential diagnosis for those syndromes. Good epidemiology data is relatively small, very little data.

CHAIRMAN DURST: Ciaran.

DR. KELLY: Ciaran Kelly. This is actually more clarification than a question. Dr.

Murray is quite correct that there isn't a measure of either severity of intestine abnormality or even height of antibody levels that reliably reflects the degree of injury or correlates closely with symptomatology.

However, with treatment one can use a decline in antibody levels as a crude indicator of at least reduced exposure to gross amounts of gluten. It is not a very sensitive indicator, but it is useful. Of course, with repeat biopsy, if the histology has revered to normal, that of course can be used. However, the less invasive test of following antibody levels is used clinically to follow response.

DR. MURRAY: Quite right. I think you will agree, Joe.

DR. KELLY: If the antibody levels aren't dropping, that is used as an indication that the patient is successfully on a gluten-free diet.

DR. BRILEY: Margaret Briley. Can you give us any idea of any behavior data that you may have received from your patients regarding their

willingness to try foods that are not gluten-free labeled?

DR. MURRAY: Oh, well, there are many different attitudes among patients with regard to what they want to eat or what they are afraid to eat.

I advise my patients to be prudent, that they try to select things based on identification of ingredients, source ingredients, not containing things contained from gluten, the use of substitute grains that are gluten-free.

Many patients are quite willing to do that on their own. Many of them use support group information where maybe a group has cooperatively contacted manufacturers who in good faith provide information on their source ingredients.

There are some patients who are entirely paranoid about it, and want to obtain a kit to test the food. I don't know that we've got a very effective kit yet for testing food for gluten contamination. There are many different attitudes.

Fear is a major concern among my patients.

I mean, fear of even the slightest potential, not even actual but potential contamination. This can verge on, "Do we avoid taking prescription medications for things like hypertension?" resulting in life-threatening changes to their medication regimens because of fear of contamination.

I would say fear is a major part or a major influence on the quality of life. We will hear more I think shortly on the impact of a gluten-free diet on patients' lifestyles a little later. Certainly that does affect a substantial portion of my patients.

Patients go through a substantial grief reaction and feel socially isolated because of their difficulty of interacting with society, because so much of our society activities or social activities revolve around food. There is that safety sense of insecurity, which I think pervades or affects many patients with celiac disease.

DR. BRILEY: Thank you.

CHAIRMAN DURST: Soheila.

DR. MALEKI: Well, I just want to know if there are any coordinated studies for a determination of thresholds? I know you mentioned the level of PPMs. Do you know of any studies?

DR. MURRAY: There are and you will hear about them. There are both retrospective and prospective studies, and you will be hearing some data on those later this morning.

CHAIRMAN DURST: I have one question -- Dick Durst -- on the biopsy and histological studies to see the morphology, morphological changes, you showed from the shag rug. I am just curious whether just one of these cameras you can swallow would be able to detect those kind of changes without having to go through a biopsy?

DR. MURRAY: Yes, you can detect them. Nobody would suggest that it would replace the need for biopsies to make the diagnosis. There is really relatively little published data on it. There has been a paper suggesting that you can see those changes. With a magnified view, you can see with a capsule.

Yes, I think you can identify those changes in a lot of individuals with celiac disease, maybe all of them. Although, I really can't comment more on that, because it hasn't really been studied in any great detail.

CHAIRMAN DURST: Erica.

DR. BRITTAIN: Erica Brittain. Do you have any insight about the cumulative effect of decades of low levels, very, very low levels of gluten exposure? Certainly, we are going to have to think about what chronic exposure could do when we talk about the thresholds. Can you provide any insight into that?

DR. MURRAY: Probably the best clinical insight I can give are individuals who I see who were diagnosed 20 years ago and have not come back to medical attention in 20 years. I see those patients maybe every week.

I would see somebody who is diagnosed 20 years ago, and they got instruction at that time that allowed them to eat things like barley malt or that people weren't really instructed about some of

those rice or corn cereals that may have contained malt, for example.

Those patients come back with anemia, chronic GI complaints, maybe not as severe as they had initially, but they certainly have accumulated some health morbidity over those 20 years. Some of them will come back with frank lymphomas and will end up with a mortal complication of their celiac disease.

Yes, at least my clinical observation is that I frequently see individuals with problems that we get rid of, once they now move to a much more strict gluten-free diet, by eliminating those things -- largely, because in 20 years they didn't go back and get more education and realize that you had to exclude those minor ingredients. That is one way of looking at the effects of decades' accumulation of low-level contamination.

CHAIRMAN DURST: Dick Durst again. On your slide that showed the various causes, the different grains, and so on, I believe you indicated oats was not one of the causes. Could

you expand on that?

DR. MURRAY: We will hear a little more, I think, from Dr. Collin on that issue. While oats had been thought to be one of the offending grains in things done in the fifties and sixties, it turns out from recent very well-done studies that it doesn't appear to impair the healing of the intestine in newly diagnosed celiac disease. It doesn't seem to result in a significant worsening of production of damage in patients who are already diagnosed with celiac disease.

For the vast majority of celiacs, it is probably safe in its native, pure form. However, there are some sequences within oats that can produce an immune response, at least in vitro, in lymphocytes derived from a few celiacs.

It is not an absolute. There may be some individuals with celiac disease that can respond to oats, both in the laboratory test and possibly also clinically there are a few.

There are probably a relatively small minority of celiacs in which that occurs. A bigger

concern is the issue of contamination of oats with other grains that are well recognized to cause injury.

CHAIRMAN DURST: Marc.

DR. SILVERSTEIN: Marc Silverstein. I would like to inquire about the potential subsequent lifelong increased risk of GI cancers. I presume that the risk is predominantly small bowel, but I wonder if there is any increased risk of colorectal cancer?

Then, what are your thoughts about whether there is sufficient risk that patients with celiac disease should be in some sort of surveillance program for early detection of GI cancer?

DR. MURRAY: Clarifying the risk of cancers, it is particularly visceral cancer but also includes: esophageal cancer, non-Hodgkin's lymphoma of any site not just the intestine, and probably also B-cell lymphomas, as well as the T-cell lymphomas, small-bowel carcinoma.

There is a greatly increased relative risk of small-bowel carcinoma. Of course small-bowel

carcinomas is a very rare disease to begin with, so the lifetime risk of dying of a small-bowel cancer, even in a celiacs, is still relatively small. The data on colon cancer is mixed. There is some that suggests there is an association; and some, that does not.

When you look at other causes of mortality, even non-cancer causes of mortality such as infections, neurologic disorders and chronic lung infections, there are other excesses of mortality that occur in patients with celiac disease.

There are some reductions in cancer mortality. It appears, at least there is a suggestion, that breast cancer may be less common in celiac disease than non-celiac disease. There were a couple of suggestions that lung cancer might be less common in celiac disease than in non-celiac disease.

Now, whether there is some competing issue like smoking may be less common in celiac disease than non-celiac disease, so there may be some other

competing issues that are involved. Body size may make a difference. It may be another confounding issue that confounds or is a competing risk for malignancies.

While small-bowel cancers and lymphomas are the two that have the greatest relative risk, it is a small, absolute risk because of the relative rarity of those cancers.

CHAIRMAN DURST: Do we have any further questions for Dr. Murray?

(No verbal response.)

CHAIRMAN DURST: Thank you very much.

Our next speaker is Cynthia Kupper, who is the executive director of the Gluten Intolerance Group of North America who will present on patient perspectives on celiac disease.

PATIENT PERSPECTIVES ON CELIAC DISEASE

MS. KUPPER: Good morning. I am a dietician, not a doctor. I appreciate the honorary doctor status.

My job here today is to give a face for a person with celiac disease. I have been tasked

with letting you know who they are, letting you know how they get their information and education, and then also providing you with some information about labeling that they have.

(Slide.)

MS. KUPPER: First of all, living with celiac disease is very difficult. It is a chronic, lifelong condition, as you have heard, and people find this to impact greatly their quality of life.

Forty-four percent of the patients in a Canadian study say that the diet is very difficult to follow. In fact, there are some studies that suggest that the compliance with the diet can be as low as 50 percent in teenagers but probably ranges around 70 percent compliance.

Eighty-four percent of these patients in Canada suggested they have a difficult time determining what is gluten-free and what is not. They don't travel, and they don't eat out. It impacts their family life and their career.

If you have celiac disease and are an X-ray technician, oftentimes you change careers

because sometimes the X-ray slides are dusted with flour. Chronic exposure could impact your quality of life.

(Slide.)

MS. KUPPER: I did a study online of 620 patients a few months ago. In response to that study, 75 percent of them said that they can tell the difference between a gluten reaction and other intolerance or a food allergy.

When they discussed their reaction symptoms, they ranged from anaphylaxis, which is not a gluten reaction for celiac disease, to delayed reactions which could impact any aspect of their GI and other health systems, body systems.

The average time to reaction was somewhere between four to eight hours, but some of them complained of immediate, almost allergic type responses, and many of them said that their responses or the symptoms that they had would last for several days.

Keep in mind, there is no medication we can give them to make this go away, so they just

have to let it work its course. This is really disturbing to me.

(Slide.)

MS. KUPPER: As a dietitian, patients do not rely on medical communities and professionals for their information. They rely primarily on support groups.

Actually, the Internet should probably be the first one, because they are Internet savvy. They have been out there and they have gotten all kinds of information before they ever see a dietitian. Not only do they get information from the Internet and the support groups, but there are list serves and chat groups that they belong to.

These can be very useful tools for a person with celiac disease. However, they also provide some very frightening and unreliable information that the patients will hold onto as if it were gospel. Then, they work with self-help books as well.

Unfortunately, doctors, and especially dietitians, are seen as unreliable. It is sad for

me to say that as a dietitian my profession doesn't get this disease. They also treat it like it is a rare thing, and they don't know anything about it. In the United States, I can tell you that there is probably a handful of dietitians who would be considered experts in celiac disease.

Doctors don't get much more respect, primarily because it has taken so long for the patient to get a diagnosis that the patient has lost faith.

Then, they will go to research facilities like the University of Maryland, Chicago, and New York, or the Mayo Clinic. Lastly, they will go to medical Web sites. The bulk of our information is coming from potentially unreliable and non-research-based sites.

(Slide.)

MS. KUPPER: The consumers perceive that gluten exposure levels -- the question was asked to me, "What do consumers believe about gluten exposure? Are they concerned about the health risks?" The answer is yes and no.

On the study that I did, it depended upon their confidence of the labeling, and it depended on whether they accepted testimony or accepted research. There is a group of celiacs, as Dr. Murray suggested, who really don't want to listen to what research suggests.

As you move forward, with not only establishing how you are going to determine the threshold but what that threshold will be, you will have a fight in the celiac community for a lack of education and understanding of research.

Consumers oftentimes also have an inability to correctly interpret research findings. These are people who have just enough medical knowledge to be dangerous, so they don't have a full understanding of the terminology they are talking about.

There is this constant perpetuation of misinformation. I don't know how many times when we try to bury something that is inaccurate it gets dug up.

(Slide.)

MS. KUPPER: There are varying levels of gluten sensitivity, as you heard, too. There is the perception that gluten is poison. Not unlike the allergy people that we heard from yesterday, this is a huge issue to the celiac consumer.

They believe most of the time that when their gut hurts it is from gluten not from something else. Consequently, we are trying to help the patient understand that not everything that makes their gut hurt is gluten.

As Dr. Murray said, there is a huge fear reaction. If I had to put a psychological label to a group or at least a portion of the celiac community, they are filled with fear and a little bit paranoid about what they can and can't do.

How do we define "gluten-free" in the U.S.? This is a really interesting question. Of the consumers, only 19 percent realize that there is no definition right now for gluten-free in the U.S. Many of them define that the true definition is zero. This is a problem -- a lot don't know.

(Slide.)

MS. KUPPER: When I ask the question, "Do you trust gluten-free labeling?" It was interesting, too, because most of the people say they do trust it. However, when you ask them if they ever had a reaction to a product labeled gluten-free, you can see that up to 50 percent suggested that they might have had a reaction to a gluten-free product.

When I talk to manufacturers that manufacture only gluten-free products and ask them, "Do you test, and what do you test to," many of them are using older testing methods not the newer testing methods, the monoclonal tests that we talked about yesterday.

Some of them tested 200 parts per million, some of them tested 20 parts per million, some of them tested no detectible. For the gluten-free consumer today, the label "gluten-free" really has no meaning.

(Slide.)

MS. KUPPER: Again, the gluten-free consumer is compulsive about their medical needs.

This is their only treatment. It is often referred to as our drug of choice. There is nothing else we can do, except to follow a strict gluten-free diet.

They have very limited trust in the manufacturing industry. They believe that labels that say "may contain" and different things like that need to be distrusted. When they call the manufacturers, they are not quite sure that they are getting the right answer all the time.

Also, they have a limited understanding of what good manufacturing practices really mean, so they are always questioning what the manufacturer will say. Yet, at the same time they want accountability and they want reliability.

They may translate information to the extreme. Let me give you an example. A few months ago on one of the list serves, someone put out a message about bottled water being gluten-free.

That got taken in a week's time to the point where consumers were calling asking why water had gluten in it, and how dare the food industry do that to them. The reality is it never did.

A company, out of the graciousness of their heart, put it on a list of gluten-free products, and from that the consumer decided that every other bottled water had gluten in it. This is the extreme that the consumer can go to. Again, they don't find descriptive labeling helpful at all.

The changes that can occur in ingredients in manufacturing processes make it difficult for this consumer group to know what they can have. The term "modified food starch" usually means cornstarch, modified cornstarch, in this country.

However, if the manufacturer determines that wheat starch is cheaper in the fall and they switch and the consumer has determined that this product is gluten-free, now they are in trouble if they don't recheck.

When you talk to the food industry, you will find that their calls have dramatically increased over the last 2 to 5 years of consumers calling in, and 90 percent of the questions do not have to do with other allergens but have to do with

gluten.

(Slide.)

MS. KUPPER: When the consumer asks the question about gluten, the problem is that they are asking the wrong question. The consumers believe that if they don't have effective labeling how can anybody possibly know that they are going to be able to be healthy and protect themselves.

They want to know that if you call a company they are really giving you the right answer, and they are just never confident about that. Oftentimes, when the company answers too quickly, they get suspicious.

Oh, I've had that experience. I will call on a product and I'll say, "I need to know the source of the modified food starch."

"Oh, you're talking about gluten?"

"Yes. Tell me the source of your modified food starch. Let me make that decision about whether I'm talking about gluten." That makes a consumer suspicious.

Finally, you know, if a person eats a

gluten-free food and they get sick, whether it is related to gluten ingestion or not, they have determined that they can't trust that company any longer.

Again, these list serves and chat groups, I have seen them take small companies out of business because of the spreading of rumors -- which are probably unfounded.

(Slide.)

MS. KUPPER: In closing thoughts, I really encourage that through this entire process related to labeling thresholds, that we be talking a common language.

Let me use the example of threshold. Yesterday, as I listened to Anne Munoz talk about thresholds for allergens, I realized that we have three different definitions of thresholds -- or tolerance, excuse me. I want to use the word tolerance.

The consumer says, "Tolerance is zero." What that means is they think there should be zero gluten in their food.

The medical community says "zero tolerance." For them that means, you should be on a strict diet, and you should never cheat.

The manufacturing industry wants to know where that is. Is it 20? Is it 200? They know it is not zero.

We are not talking the same language. The consumer needs to know that the manufacturer and the industry or the legal ramifications around any labeling are all using common terminology in a language they can understand.

Education is a huge component. As much as I am a supporter of this regulation and this law, one of the things that is going to happen, as you heard yesterday in discussions about soy lecithin and other ingredients, it is going to become a bag of worms. For the consumer, it is going to be very confusing, and we need to have an education component as part of the new labeling laws.

I encourage you, too, although you heard it yesterday and you will probably hear it today, too, we know that there is no testing kit available

that tests to zero. We know, as you will probably hear later, that it is probably an impracticality or unnecessary to even go there.

I implore that when you set a threshold method and testing methods, when you set the threshold level, that it be reasonable and something that meets the health needs of the consumer but also allows the industry to meet the need.

(Slide.)

MS. KUPPER: As they found out in Australia, when you set zero as the tolerance level and as the magic number for food manufacturers, a lot of gluten-free products that patients used no longer can be labeled gluten-free. Now the consumer is once again confused and outraged.

CHAIRMAN DURST: Thank you very much.

Do we have any questions for our speaker?

Yes, Jeff?

DR. BARACH: Hi. Thank you. Jeff Barach with Food Products Association. If I interpret what you said correctly, you were talking about the

consumer really doesn't find descriptive labeling very helpful in the case of gluten-free.

I assume then the consumer would go to the ingredient list or the 800 numbers or their internal chat groups to find out whether the product really is gluten-free or not. Am I interpreting that right? Your constituency does not want gluten-free labeling?

MS. KUPPER: I would say that is probably right, that is the message I got from the survey. In fact, they found that labels that say "may contain" or "processed in a plant with" really is frightening to them. They will look at a product like that, and they will simply avoid it.

They do go to chat rooms and there are lists of gluten-free products. However, when you look at those lists and you ask how they were developed, there are no standards for developing those lists.

DR. HEIMBURGER: Doug Heimburger, a follow up to that. That is not the same, is it, as saying "gluten-free"? Do they not want a label except it

is gluten-free with a consistent and clear definition of that?

MS. KUPPER: They do want a label that says gluten-free with a clear and consistent definition.

DR. HEIMBURGER: Yes.

MS. KUPPER: I believe that gluten-free is not is not going to mean zero; it can't mean zero.

CHAIRMAN DURST: Any further questions or comments?

(No verbal response.)

CHAIRMAN DURST: Thank you very much.

CHAIRMAN DURST: Our next speaker is Dr. Donald Kasarda, who is a consultant and retired senior scientist from the Agricultural Research Service of the USDA. He will make a presentation on grains.

GRAINS

DR. KASARDA: Good morning everyone. I am a research chemist retired from the U.S. Department of Agriculture, although I still maintain a relationship with my old lab in Albany, California,

as a collaborator.

Now, Dr. Murray covered a lot of the things I am going to talk about. Maybe I will be able to add a little bit more detail to some of them, but he did an excellent job of talking about some of the grain topics.

(Slide.)

DR. KASARDA: Immunology textbooks often classify hypersensitivities into these four types. Celiac disease is a delayed type hypersensitivity that involves T-cells in the primary mechanism. It falls into Type IV. Allergy is Type I and is mediated by IgE antibodies.

Now, in the case of celiac disease, it is often suggested that there is a Th1 mechanism involved in which T-cells are presented with gliadin peptides, and, ultimately produce cytokines, inflammatory cytokines such as interferon gammas as an example.

Now, in the case of allergy, however, the same molecules that can induce the symptoms of celiac disease are also capable of producing

allergies. We do have a certain amount of confusion sometimes between immediate hypersensitivities and the delayed-type, celiac disease.

(Slide.)

DR. KASARDA: Now, this is the same diagram that Dr. Murray showed. I want to talk about primarily the endosperm, which is this white part here (indicating) in the cutaway diagram.

The starchy endosperm is made up of about 75 percent starch, but it also contains about 7 to 17 percent protein, depending on the use of the wheat. Most of this protein, about 75 percent of it, is gluten protein.

The proteins are storage proteins. They are used by the developing plant that comes from the germ here. The germ is separated from the outer layers and the endosperm during the milling process after crushing and sieving.

The storage proteins are broken down upon germination of the seed to produce a new plant. The resulting amino acids and nitrogen are used in

the synthesis of new molecules needed by the developing plant. Now, as I mentioned, about 75 percent of the storage protein is, in fact, gluten protein.

(Slide.)

DR. KASARDA: This is a picture of flour particles, a scanning electron micrograph. These round, spherical structures are starch granules. These (indicating) are A type, there are some B types which are small here. The surrounding rough-edged material is the gluten protein or storage protein.

(Slide.)

DR. KASARDA: If you mix together flour and water, as most of you have had the experience, you can form a cohesive elastic dough. If you need a dough under water, say, in a large container of water or under a stream of water, you can wash out the starch granules; they pop right out of the matrix. You are left with a cohesive, elastic mask consisting mainly of the storage or gluten proteins.

(Slide.)

DR. KASARDA: Now, this is the traditional cereal chemist definition of gluten. You cannot carry out this process with rye and barley. Therefore, to the traditional cereal chemist, there is no gluten in rye and barley. However, the celiac disease community has adopted the term "gluten" for any protein that is toxic or harmful to a celiac patient.

This terminology problem sometimes is confusing when patients go to a company where they might be dealing with a traditional cereal chemist, and there is a certain amount of confusion as to what is gluten. As I said, this is the traditional definition, but it has been expanded to include other grains that are harmful to celiac patients.

Now, from time to time, you will hear about these fractions of gluten. Going way back, at least over a hundred years, it has been traditional to divide gluten into two, roughly, equal fractions based on their solubility. This is not an exact separation. No solubility fraction is

ever perfect.

Traditionally, it was alcohol-water solution and sometimes we used detergent solutions. We divide it up into the soluble fraction, which we call "gliadin."

This is made up of monomeric proteins of the prolamin class. The prolamin terminology comes from Osbourne back around 1900. It is derived from the fact that there are two major amino acids found in the composition of these proteins. Proline and glutamine, hence, prolamin.

By structure, we have three types: the alpha type, gamma type, or omega types. Sometimes people speak of the alpha/beta. I will talk about that in a little as we go along.

Now, the insoluble fraction is called "glutenin" by the cereal chemists. In rye and barley, there is an equivalent fraction that we called just generically "glutelin."

Now, this polymeric fraction consists of prolamin subunits. Again, large amounts of proline and glutamine in the composition of the proteins.

These subunits are linked together by disulfide bonds into a higher level of polymer.

Of course, a protein is a polymer in itself. It is divided into two main types the low-molecular weight and the high-molecular weight glutenin subunits.

(Slide.)

DR. KASARDA: This just is a table showing the percentages in the various types of proteins. For example, you have the sum of glutamine and proline ranging from about 40 percent up to about 80 percent in some of the omega gliadins.

This is pretty unusual to have such a high percentage of glutamine and proline. This is key to the toxicity, because the toxic sequences involve glutamine and proline and usually an aromatic as well, either tyrosine or phenylalanine.

(Slide.)

DR. KASARDA: Now, the terminologies that we use really go back to early electrophoretic studies in the late sixties and early seventies. Again, if we follow this diagram here, this is an

acid gel in which the proteins are separated by an electric field in a polyacrylamide gel.

The terminology actually came from a sort of free-boundary electrophoresis that was carried out at our Northern Regional Research Center back in the sixties. When they developed the polyacrylamide gel electrophoresis, it was found that the fractions fit with the mobility in the electrophoretic gel.

You have the alpha, fastest moving; beta; gamma; and omega. Structurally, the alphas and betas are pretty similar. Some people will talk about alpha/beta types. I just lump them together as alpha types.

Now, the alpha type and gamma type are about the same size. If you carry out SDS page or polyacrylamide gel electrophoresis in detergent, sodium dodecyl sulfate, which is a very good dissociating agent for proteins.

Reduced or unreduced the gliadins give a pattern somewhat similar to this. It is not quite as good at resolving alpha, beta and gammas as you

find in the acid gels where aluminum lactate was one of the favorite buffers.

If we go over to the glutenin fraction, and these are the subunits linked together by disulfide bonds, if you try to take a purified glutenin fraction and run it into an acid gel or into a detergent gel, mostly you've just got a little bit of streaking around the origin because the polymers are too large to migrate into the gel.

(Slide.)

DR. KASARDA: Upon reduction, however, you begin to see this type of pattern here in which there is a group of high-molecular-weight subunits and a group of low-molecular-weight subunits. This only occurs for the glutenin fraction when you reduce the disulfide bond.

(Slide.)

DR. KASARDA: This is a two-dimensional pattern, electrophoretic pattern, of the gluten proteins. All you have to recognize is that each spot here represents a separated protein. There are quite a few different gluten proteins, and we

can count easily 50, 60, 70 spots in such a pattern. Therefore, there are at least 50, 60, 70 gluten protein components.

We know from genomic studies that, in fact, there are probably at least a hundred genes coding for these proteins, and probably several hundred genes coding for the proteins. The loci in the genome that code for these proteins are spread out over about nine different loci in the genome.

Now, as far as we know, all of these gluten proteins are toxic in celiac disease. This group here (indicating) are the omega gliadins, and they seem to be particularly active.

However, all of the gluten proteins have been tested by Paul Ciclitira's group and Peter Howdle's group in the U.K., and they all indicated by direct installation into the small intestine that these proteins, all of these different classes are toxic.

These omega gliadins are noted for being strong allergen in exercise-induced anaphylaxis. They are one of the really strong antigens involved

in that particular allergy.

(Slide.)

DR. KASARDA: This is a schematic diagram that illustrates the fact that all of these proteins are noted for a repetitive domain in which certain amino acid sequences are repeated over and over again.

They are somewhat degenerate, but we can derive consensus sequences. These are glutenin subunits, gamma-type gliadins. These red, staplelike lines indicate intramolecular disulfide bonds.

In a glutenin subunit, we also have free cysteines which can link up to another molecule to form these higher-level polymers. For example, here is an alpha-gliadin -- I'm going to talk about this a little bit more -- the end terminal, or the first half of the molecule, is made up of these repeating sequences.

The second half is not repetitive and contains most of the disulfide bonds. Toxicity seems pretty likely to be limited to the repeat

regions. These are the high-glutamine, the high-proline regions.

Now, the omega-type gliadin seems to have lost -- well, we are not entirely sure whether they lost this type of domain or not, but in any case they are made up almost entirely of repeating sequences.

(Slide.)

DR. KASARDA: This is a hypothetical model of the gluten polymer or glutenin in which the subunits are joined by intermolecular disulfide bonds, there are also these intramolecular disulfide bonds, to form a higher-level polymer that provides elasticity to a dough.

The gliadins and the glutenins are cohesive with one another, but the gliadins contribute more to the extensibility of the dough, and the elasticity comes primarily from the glutenin fraction.

(Slide.)

DR. KASARDA: Now, here I show some of the types of sequences that you find in the repeats.

Now, they look pretty similar, a lot of glutamine, which is represented by "Q"; a lot of proline represented by "P"; and usually an aromatic residue, either phenylalanine, "F," or tyrosine, "Y."

Somewhere, and these are often degenerate. They are not exactly according to the consensus that I show here. Somehow along the line these sequences have acquired toxicity in celiac disease.

(Slide.)

DR. KASARDA: Now, this is the complete sequence of an alpha gliadin. This is the end-terminal region up here (pointing). It starts at one, and there are 263 amino acid residues. Here, note the predominance of the blue Q's and the red P's for the proline and glutamine residues.

This half of the molecule here is the repeat region. There is also this interesting set of glutamines, which really hasn't been studied in celiac disease. It is probably not toxic, but, as I say, there has been almost no study of this polyglutamine stretch here.

Note also these vertical lines here which I show. Those are sites that we have observed where cleavages occur with gastric enzyme, pepsin and pancreatic enzymes, trypsin and chymotripsin.

Now, most proteins would be broken down by the digestive enzymes into single amino acids or very small peptides: diatride, tetrapeptides that are easily absorbed, which are probably not toxic.

(Slide.)

DR. KASARDA: In the case, as Dr. Murray mentioned, because we have a lot of proline which interferes with the breakdown by the proteolytic enzymes, we can get some pretty large stretches. This stretch here from 31 to 55 right here is something that we have tested as toxic.

Other people have dealt with sequences from this stretch and found them also to be at given toxic. The fact that this gliadin and glutenin proteins are difficult to digest by the digestive enzymes allows these toxic stretches to exist longer than you would find for other proteins.

Now, this half of the molecule has a fair amount of glutamine and proline, but as far as we know toxicity does not reside in this C-terminal half or sort of the end of the molecule. It is in sort of the forward end of the molecule.

(Slide.)

DR. KASARDA: Now, this is what I would call my string of beads model in which I have just taken that sequence, 1 to 263, and shown it as beads on a string.

Each bead represents a different amino acid. I tried to assign the different amino acids different code words to distinguish them. This is the end terminal region of repeats. This C-terminal where we have the disulfide bonds here. Toxicity resides in this part here.

This sequence here from 31 to 43 was synthesized by Mike Marsh in the U.K. first, and he instilled the synthetic peptide directly into the small intestine of several celiac patients and found changes in the mucosa that were indicative of celiac disease. So this does seem to be a toxic

sequence.

Here I show a computer molecular model of what that sequence would look like in the polyproline II left-handed helical confirmation that Dr. Murray mentioned. We think that these peptides do have a strong tendency to assume this polyproline II confirmation.

Here, I show the sequence in three-letter code as a string of beads model and here just a single-letter code. I know most people are not used to dealing with these codes. I apologize for using them in some of the slides, but often I am just trying to make a general point, and you don't really have to follow the sequences according to their exact correlations with the amino acids.

(Slide.)

DR. KASARDA: Now, this is a list of some of the either toxic or immunoactive peptides that have been described in the literature. This is from Sean, et al, from Chaitan Khosla's lab at Stanford. The 33-Mer appears to be a very active sequence. I have indicated some sort of homology

here by the yellow boxes here.

All of these sequences, with the exception of this one, have been found to be toxic by direct installation into the small intestine or they have been found to stimulate T-cells, T-cell clones, derived from biopsies of celiac patients.

These are just some of the toxic sequences. We don't know all of the toxic sequences at this point. There are certainly others to be found, so it is a pretty complicated situation in trying to sort out exactly what it is about the sequences that produces toxicity in celiac disease.

(Slide.)

DR. KASARDA: Now I want to move on and talk a little bit about the other grains. If we start with the class flowering plants, which is one of the major divisions or plants in terms of taxonomy.

We go down to the major two subclasses, monocotyledones plants and dicotyledones plants.