DDICC Meeting Minutes
March 12, 2002

Celiac Disease
Meeting Summary

9:00a.m. – 12:30 p.m.
National Institutes of Health
Natcher Conference Center
Room F1/F2
Bethesda, MD

Participants

Chair:

Jay H. Hoofnagle, MD	National Institute of Diabetes and Digestive and Kidney Diseases

Executive Secretary:

Stephen P. James, MD	National Institute of Diabetes and Digestive and Kidney Diseases

Members:

James A. Butler, MD	National Naval Medical Center
Jorge Gomez, MD, PhD	National Cancer Institute
Gilman Grave, MD	National Insitute of Child Health and Human Development
Frank Hamilton, MD, MPH	National Institute of Diabetes and Digestive and Kidney Diseases
Brian E. Harvey, MD, PhD	Food and Drug Administration
Cay (Catherine) Loria, PhD	National Heart, Lung, and Blood Institute
Vishnudutt Purohit, PhD	National Institute on Alcohol Abuse and Alcoholism

Speakers:

Joseph Murray, MD	Mayo Clinic
Carlo Catassi, MD	University of Ancona, Italy
Marian Rewers, MD	University of Colorado
Alessio Fasano, MD	University of Maryland
Stephen Collins, MD	McMaster University, Canada
Frank Hamilton, MD, MPH	National Institute of Diabetes and Digestive and Kidney Diseases

Guests:

Robert Carp, MD	National Institute of Diabetes and Digestive and Kidney Diseases
Cynthia Cooper	Gluten Intolerance Group
James (Jay) Everhart, MD, MPH	National Institute of Diabetes and Digestive and Kidney Diseases
Lisa Ganshereff	National Institute of Diabetes and Digestive and Kidney Diseases
Robert Levy	Center for Celiac Research
Elaine Monarch	Celiac Disease Foundation
Diane Paley	Celiac Sprue Association
Michelle Melin-Rogovin	University of Chicago
Mary Schluckebier	Celiac Sprue Association
Allen Spiegel, MD	National Institute of Diabetes and Digestive and Kidney Diseases

Welcome

Jay H. Hoofnagle, M.D., DDICC Chair and Director, Division of Digestive Diseases and Nutrition (DDDN, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) convened the meeting at 9:00 a.m. and welcomed those present. For those who had not previously attended these meetings, he explained that the Digestive Diseases Interagency Coordinating Committee (DDICC) is a congressionally mandated group that meets four times a year to coordinate activities concerning digestive diseases. DDICC is composed of members from the institutes and offices of the National Institutes of Health and from other Federal Government agencies. Dr. Hoofnagle said that for today's meeting on celiac disease, the committee had brought together several of the investigators they fund to provide updates from the field and to recommend directions for future research. Dr. Hoofnagle then introduced those present.

Overview of Celiac Disease

Joseph Murray, M.D., Gastroenterologist, Mayo Clinic, Rochester, Minnesota, presented an overview of celiac disease, an inflammatory state of the small intestine that occurs in genetically predisposed individuals and resolves with the exclusion of dietary gluten. Recent European studies suggest that there are mono-symptomatic presentations of celiac disease that are treated without celiac disease being diagnosed. Serological screening has revealed a greater prevalence in the population than diagnosed cases and has provided a tool for primary care physicians to diagnose the disease.

Dr. Murray detailed a study that described a rise in the incidence of celiac disease in Olmstead County, Minnesota. Diagnosed cases rose from 1.1 per 100,000 (incredibly low) in 1991 to 9 per 100,000 (very high) in 2001, due to increased physician awareness of the disease and its presentations, such as iron deficiency anemia. He then looked at issues surrounding screening, morbidity (including increased risk of malignancy), and the ethical cost/benefit considerations of a gluten-free diet for asymptomatic individuals. Dr. Murray discussed the connection of celiac disease to the DQ2 and DQ8 genes.

Dr. Murray looked at problems with the use of animal models in studying celiac disease. His colleagues had sensitized transgenic mice with gluten, and then fed them gluten in large quantities. At 3 weeks they were sacrificed, and investigators looked at lymphocyte responsiveness and lymphocytes derived from the spleen and intestine. The DQ8 mice showed a dramatic response, while the DQ6 mice showed much less. Dr. Murray pointed out that celiac is a human disease; mice did not develop the enteropathy typical of celiac disease.

Epidemiology of Celiac Disease

Carlo Catassi, M.D., Clinica Pediatrica, University of Ancona, Italy, explained that sensitive tools—the anti-gliadin, anti-endomysial, and transglutaminase tests—developed in the 1980s have allowed discovery of celiac disease even when clinical suspicion is

low. This enhanced detection rate has led to atypical presentations of celiac disease, including anemia, liver problems, and osteoporosis.

Dr. Catassi showed results of a study in Italy that he coordinated between 1992 and 1995. The study screened 17,000 students ages 6 to 15. The study found that 1 in 184 children had the disease and that the ratio of diagnosed to undiagnosed cases was 1 to 7.
Dr. Catassi noted a study by Dr. Fasano showing that 1 in 250 blood donors have celiac disease. He said that donors should be screened for celiac disease, since iron deficiency is a common symptom of the disease and could be harmful for celiac sufferers.

Dr. Catassi said that the ratio of the incidence to the prevalence of the disease is mostly influenced by disease awareness. This helps explain the difference between countries that should have similar prevalence rates. He gave results from an epidemiological study in the Sahara that showed 5 percent of the general population is affected, probably due to genetic background and high consumption of gluten. He noted that mortality of celiac disease there was high, due to malnutrition, infections, and parasites. The prevalence in relatives of celiac patients is as high as 8 to 10 percent in the United States and Europe, and the disease is found in both first- and second-degree relatives of celiac patients. An Italian study showed a three-fold increase of risk of non-Hodgkin's lymphoma for those afflicted with celiac disease.

Dr. Catassi suggested that case-finding screening is probably the best way to find the true prevalence of the disease. He said that while the number of known celiacs in the United States is around 15,000, the true number of sufferers may be as high as 1,300,000. While awareness of the disease is not very high, he said that celiac disease is one of the commonest lifelong disorders, with a general prevalence of 0.51 percent.

Genetics of Celiac Disease

Marian Rewers, M.D., Clinical Director, Diabetes Center for Childhood Diabetes, University of Colorado, Denver, discussed the genetics of celiac disease. He said the major genetic determinant of celiac disease is the HLA class II region, which is responsible for 40-60 percent of the familiar clustering of the disease. The problem appears to be related to heterodimers formed by DQA105 and the DQ in B10201. An HLA class II molecule on the surface of an antigen-presenting cell presents gluten to the T-cell, and this is thought to trigger the process of autoimmune distraction.

Dr. Rewers described a study that screened relatives of type 1 diabetes patients for celiac disease. The results showed that 25 percent of diabetics with the DL33 gene had celiac disease, as defined by the presence of tTG antibodies. Fifteen percent of those with DL3X have celiac disease, as do 10 percent of those with DL3X and DL44. Three to four percent of children with those genotypes develop celiac disease by the age of four, compared to 0.3 percent of those with other HLA genotypes.

Dr. Rewers noted that celiac disease is polygenic and probably heterogeneous. He proposed a large, longitudinal study of celiac disease in the United States, which he called "CD USA." He said that the study should start from birth, since most celiac cases start by age 2 or 3, and that entire families should be enrolled.

Pathophysiology of Celiac Disease

Alessio Fasano, M.D., Director of Gastrointestinal Nutrition, University of Maryland, and Co-Director, Center for Celiac Research, described the pathophysiology of celiac disease. He noted that over the past few years there has been an explosion in the understanding of the pathophysiology of celiac disease. A key element, according to Dr. Fasano, is that the immune system has to be in touch with environmental factors to trigger an immune response meant to get rid of the invader, which leads to the autoimmune process. Dr. Fasano noted with interest that the environmental factor has to make the journey to the immune system. The intestine is the largest immune organ and very selective. Another key element, he said, is how the intestine's permeability increases in celiac disease.

He described a molecule called zonulin, which seems to modulate the permeability of the intestine. He and his colleagues found that zonulin was out-regulated during the acute phase of celiac disease. In order to activate the permeability of the intestine, there has to be a receptor that recognizes and engages zonulin. Since zonulin systems seemed to be out-regulated during celiac disease, the researchers asked what the primary role of gliadin was on that mechanism. They discovered that when normal intestinal cells are exposed to gliadin, there is a rearrangement at the site of the skeleton. When gliadin was put into a chamber that mimics intestinal bloodflow, there was a decrease in tissue resistance, and the intestine became leakier. They found a disassembly of tie junctions, which seems to be related to a release of zonulin. Gluten, they found, disassembles tie junctions by affecting the expression of one of the key elements that dictate the competency of tie junctions.

Dr. Fasano suggested some possible strategies for addressing celiac disease. Detoxifying grain is quite a challenge, he said. Another possibility is using a synthetic peptide to block the zonal receptor to prevent the opening of tie junctions. Another strategy would be to prevent deaminated gliadin from binding to the receptor, creating an induced immune tolerance. A final possibility would be to act on cytokine production.

Gut Inflammation in Celiac Disease

Stephen Collins, M.D., Chief of Gastroenterology, McMaster University, Canada, spoke about the relationship between celiac disease and irritable bowel syndrome (IBS). He noted that there are two models of the relationship. One is that the two conditions, one very common and one less common, simply co-exist and overlap in some cases. The other is that there may be some causal link in terms of pathogenesis that could lead to the expression of IBS, at least in a subset of IBS patients. He cited findings from two studies.

One study found that 14 of 300 IBS patients had celiac disease as reflected by a positive biopsy and antibody screen, and 52 had only positive antibodies. The other study showed that 65 percent of diarrhea-predominant IBS patients exhibited findings associated with celiac disease. Thirty-five percent of those were DQ-positive, and 23 percent had increased inter-epithelial lymphocytes.

Dr. Collins proposed a model wherein gluten exposure results in immune activation, not only in the epithelium, but also in the deep layers, accounting for the symptoms seen in IBS. He postulated that in the diarrhea-predominant IBS subset, gluten sensitivity may be a pathogenetic mechanism. Therefore, he said, diarrhea-predominant IBS patients should be screened for celiac disease.

NIH Research Portfolio

Frank Hamilton, M.D., M.P.H., Program Director for Intestinal Disease, NIDDK, discussed the National Institutes of Health (NIH) portfolio with regard to celiac disease. He said NIDDK is the lead organization at NIH for gastrointestinal research. Other institutes with interest in celiac disease are the Institute for Allergy and Infectious Diseases (NIAID), the Institute of Dental Research (NIDR), the National Center for Research Resources (NCRR), and the Institute of General Medical Science (NIGMS).

NIH began looking at celiac disease in 1992. At the time, there was a great deal of congressional interest in celiac disease, which led to issuance of a Request for Applications (RFA) on the role or pathogenesis of inflammatory bowel disease (IBD) and celiac disease. Two million dollars were set aside for this research. Eighty-six applications were received and 12 grants were funded, 2 in celiac disease and 10 in IBD.

In 1995, NIH attempted to stimulate the field by issuing an RFA on IBD and included autoimmune diseases, including liver diseases. Sixty-eight applications were received and 14 grants awarded, 2 in liver disease, 2 in celiac disease, and 10 in IBD. A new genetics grant was also funded at that point, focusing on mapping of non-HLA receptors and gluten-sensitive enteropathy. Currently, NIH funds a total of 26 grants in celiac disease, with around $3.5 million per year in funding.

Dr. Hamilton said that issuing Requests for Applications (RFAs) seems to be the most effective means of stimulating research on celiac disease. He said that it behooves the research community to work with NIH in encouraging young investigators to submit applications.

General Discussion

Dr. Stephen James led the discussion following the presentations. He spoke of the hope 2 or 3 years ago that a gluten-free diet would delay or prevent the onset of type 1 diabetes in those who are pre-diabetic. However, studies with diabetes animal models on gluten and gluten-free diets have produced conflicting results. Going back to celiac disease,

Dr. James mentioned that although animal models had been a fertile area for new advances in IBD, animal models have been a problem with celiac disease. Dr. Fasano said that it will be almost impossible to develop or identify a satisfactory model for the pathogenesis of celiac disease until we know what genes must come together to predispose a person to the disease. Current models (the rat, mouse, and dog) can only approximate the condition. The dog provides the closest model of the human intestine and digestive system. Mouse models have not been too successful. An NIH-generated mouse with a dominant negative TGF beta class 2 receptor gene is the closest model that produces spontaneous inflammation of the colon and small bowel that matches established celiac diseases.

Dr. Karp suggested that it might be more effective in overcoming the limitations in a mouse model by targeting a specific component of the disease instead of the entire disease process. Another suggestion was to combine a sensitizing variant of human DQ2 with the hundreds of laboratory inbred mouse strains, which might produce the right combination. Dr. Fasano responded that, since BB type 1 diabetes rats are related to a leaking gut and are also DQ2 and DQ8 negative, a less expensive route might be to try screening them.

A suggestion from a participant was that it might not be necessary to use animal models since tissue is easily obtained from disease sites during diagnostic biopsies necessary before and after use of a gluten-free diet. Having this tissue enables conduct of *ex vivo* direct human experiments. Dr. Fasano added that a multi-disciplinary approach is needed on samples involving genetics, pathophysiology, immunology, epidemiology, and alternative treatment disciplines.

Dr. Hoofnagle brought up the need for better epidemiology for the prevalence of celiac disease in African Americans and Asian Americans. Dr. Rewers responded that his group's data indicates that African Americans are as affected as non-Hispanic whites, but the disease is uncommon in Asian Americans because they lack the DQB0201 and DR3 genetic markers. Prevalence in American Indians and Hispanic Americans falls in between non-Hispanic whites and Asian Americans. He said that in Colorado, the Hispanic rate is one-third that of non-Hispanic whites and is probably due to the European genetic mixture. Another participant mentioned that a link has not been found between celiac disease and chromosome 21.

Ms. Monarch raised the issue of creating awareness in primary physicians and the need to provide access to a reliable screening test. She stressed that most patients are over 40 when diagnosed and already dealing with multiple autoimmune disorders such as diabetes, osteoporosis, and thyroiditis. Dr. Fasano answered that the problem is that, for payers, health care is necessarily a business not a mission. In order to get screening, it is necessary to show them a cost/benefit favorable to their profit margin. He said HMOs also would need to be shown how large the problem is before they will educate their physicians and maximize their resources for the required multi-disciplinary approach.

Dr. Rewers said that whom to screen, with what, and how often were issues. If children are screened at 5 years old what should be recommended for those who test positive but are disease-free now? Should they be put on a gluten-free diet? What about the long-term outcomes? He suggested that NIDDK form a policy group to look at the feasibility and importance of screening for celiac disease based on its prevalence in perhaps 1 percent of the population, the existence of an inexpensive screening test on a large scale ($2–3), the existence of a second-step test (HLA and biopsy) for verification, and the availability of effective treatment.

Dr. Allen Spiegel, director of NIDDK, gave the example of hemochromatosis, a monogenic disorder that met the same criteria—easy to diagnose, straightforward genetic test, readily treatable with few side effects. An NIDDK-funded study in conjunction with Kaiser Permanente did not produce a cost benefit. Symptoms in the control group vs. those in the group with the mutation were too similar. Dr. Spiegel said that NIH is not the key issue here. The Institutes' missions are to understand the pathogenesis of disease, find genes and gene-mutations relevant to diseases and disorders, develop better therapies, and so forth. It is other agencies—HRSA, CDC, CMS—who will need to be involved in determining health care policy on screening and reimbursement issues. He said that lessons acquired from the European experiences may bear on the cost-effectiveness of mass screening. Dr. Spiegel pointed out that we can find numerous persons with the HLA genotype and persons who are antibody positive, but we are left with the issue of their long-term consequences re the disease. He also expressed his concern over the dilemma of delayed diagnosis and its unfortunate outcomes for so many persons over 40 versus the hard, cold economic realities of mass screening.

Dr. Jorge Gomez reported that the National Cancer Institute is looking at the association of long-term celiac disease and carcinogenesis, particularly in lymphomas. The Institute is also studying nutritional links and cancer.

Another participant stated that in their clinical center's study of T-cell lymphomas, they have seen several patients with celiac disease. Some of these patients knew they had the disease, but due to the paucity of their symptoms, they did not conform to a gluten-free diet. Now at 50, they have serious long-term consequences. It was stressed that the problem is that these consequences, such as anemia or osteoporosis, tend to remain silent for years. The speaker asked if anyone had any clues to the triggering event that results in the disease. This still remains a mystery even though the genes are present, as it also does in type 1 diabetes.

Dr. Fasano suggested that we research the physiological function of the genes present in celiac disease. He said they must have a function for something else that is then triggered. Dr. Fasano said that although today we have much better diagnostic tools (FDA has approved the tTG and a quick test for HLA typing is being filed), minority populations are reluctant to participate in studies because they perceive they will be treated as guinea pigs. This is one of the difficulties in determining prevalence in these ethnic/cultural groups.

The question was asked as to whether there was consensus within the present group that celiac is or is not a rare disease. Based on a definition of "rare" as being less than 1 in 1,000, celiac disease would not be considered rare since its incidence is less than 1 in 10, which is considered uncommon, not rare.

Another issue that was raised was that of the cost and availability of gluten-free products in the United States versus Canada. The cost contributes to the difficulty of persons with celiac disease being able to maintain a gluten-free diet. Rice flour is $1.50 a pound versus regular flour at 40 cents. Gluten-free pasta costs $5.50 a pound, while ordinary pasta is 79 cents.

Dr. Michelle Melin-Rogovin from the University of Chicago asked that NIH fund studies and research to address the key questions about the some symptoms associated with celiac disease so that physicians can be aware of the issues and know when to test. She stated that if NIH does this and recognizes that celiac disease is not a rare disease, then persons will be diagnosed sooner.

Adjournment

Dr. Hoofnagle noted that the next step was to develop an overview of a research approach to address the clinical issues raised at the meeting. Dr. Hoofnagle agreed that celiac disease is a paradigm of autoimmune diseases and, as such, it presents some of the most interesting, challenging, and intellectual issues in medicine today. The meeting adjourned at 12:45 p.m. on March 12, 2002.

Approved by: _____ _____
Date

Jay Hoofnagle, M.D., Chair
Digestive Diseases Interagency
Coordinating Committee, NIDDK

Approved by: _____ _____
Date

Stephen P. James, M.D., Executive Secretary
Digestive Diseases Interagency
Coordinating Committee, NIDDK