GA1 Food Elimination Based on IgG Antibodies in Irritable Bowel Syndrome: a Randomised Controlled Trial

W Atkinson, T A Sheldon, N Shaath, PJ Whorwell Gut 2004:53 1459-1464 doi: 10.1136

BACKGROUND: Patients with irritable bowel syndrome (IBS) often feel they have some form of dietary intolerance and frequently try exclusion diets. Tests attempting to predict food sensitivity in IBS have been disappointing but none has utilised IgG antibodies. AIMS: To assess the therapeutic potential of dietary elimination based on the presence of IgG antibodies to food. PATIENTS: A total of 150 outpatients with IBS were randomised to receive, for three months, either a diet excluding all foods to which they had raised IgG antibodies (enzyme linked immunosorbant assay test) or a sham diet excluding the same number of foods but not those to which they had antibodies. METHODS: Primary outcome measures were change in IBS symptom severity and global rating scores. Non-colonic symptomatology, quality of life, and anxiety/ depression were secondary outcomes. Intention to treat analysis was undertaken using a generalised linear model. RESULTS: After 12 weeks, the true diet resulted in a 10% greater reduction in symptom score than the sham diet (mean difference 39 (95% confidence intervals (CI) 5-72); p = 0.024) with this value increasing to 26% in fully compliant patients (difference 98 (95% CI 52-144); p<0.001). Global rating also significantly improved in the true diet group as a whole (p = 0.048, NNT = 9) and even more in compliant patients (p = 0.006, NNT = 2.5). All other outcomes showed trends favouring the true diet. Relaxing the diet led to a 24% greater deterioration in symptoms in those on the true diet (difference 52 (95% CI 18-88); p = 0.003). CONCLUSION: Food elimination based on IgG antibodies may be effective in reducing IBS symptoms and is worthy of further biomedical research.

GA2 Food Allergy in Irritable Bowel Syndrome: New Facts and Old Fallacies

E Isolauri, S.Rautava, M.Kalliomaki Gut 2004; 53 1391-1393 10.1136

The notion of food allergy in irritable bowel syndrome (IBS) is not new. However, recent evidence suggests significant reduction in IBS symptom severity in patients on elimination diets, provided that dietary elimination is based on foods against which the individual had raised IgG antibodies. These findings should encourage studies dissecting the mechanisms responsible for IgG production against dietary antigens and their putative role in IBS.

GA3 Celiac Disease

Peter H.R Green, M.D. and Christopher collier, M.D. PhD The New England Journal of Medicine 2007; 357:1731-43

Celiac disease is a unique autoimmune disorder, unique because the environmental precipitant is known. The disorder was previously called celiac sprue, based on the Dutch word sprue, which was used to describe a disease similar to tropical sprue that is characterized by diarrhea, emaciation, aphthous stomatitis, and malabsorption.1,2 Celiac disease is precipitated, in genetically predisposed persons, by the ingestion of gluten, the major storage protein of wheat and similar grains.3 Originally considered a rare malabsorption syndrome of childhood, celiac disease is now recognized as a common condition that may be diagnosed at any age and that affects many organ system.

GA4 Alterations of Food Antigen-Specific Serum Immunoglobulins G and E in Patients with Irritable Bowel Syndrome and Functional Dyspepsia

X.L.Zuo, Y.Q. Li, W.J.Li, Y.T Guo, X.F. Lu, J.M. Li and P.V. Desmond Clinical and Experimental Allergy, 37, 823-830

Background Post-prandial worsening of symptoms as well as adverse reactions to one or more foods are common in the patients with functional gastrointestinal diseases, such as irritable bowel syndrome (IBS) and functional dyspepsia (FD). However, the role played by true food allergy in the pathogenesis of these diseases is still controversial and there are no well-established tests to identify food allergy in this condition. Objective To investigate serum food antigen-specific IgG, IgE antibody and total IgE antibody titres in controls and patients with IBS and FD, and to correlate symptoms with the food antigen-specific IgG titres in IBS and FD patients. Methods Thirty-seven IBS patients, 28 FD patients and 20 healthy controls participated in this study. Serum IgG and IgE antibody titres to 14 common foods including beef, chicken, codfish, corn, crab, eggs, mushroom, milk, pork, rice, shrimp, soybean, tomatoes and wheat were analysed by ELISA. Serum total IgE titres were also measured. Last, symptomatology was assessed in the study. Results IBS patients had significantly higher titres of IgG antibody to crab (P = 0.000), egg (P = 0.000), shrimp (P = 0.000), soybean (P = 0.017) and wheat (P = 0.004) than controls. FDpatients had significantly higher titres of IgG antibody to egg (P = 0.000) and soybean (P = 0.017) than controls. The percentage of individuals with detectable positive food antigenspecific IgE antibodies of the three groups did not show any significant differences (P = 0.971). There were no significant differences between IBS patients, FD patients and controls in the serum total IgE antibody titres (P = 0.978). Lastly, no significant correlation was seen between symptom severity and serum food antigen-specific IgG antibody titres both in IBS and FD patients. Conclusion Serum IgG antibody titres to some common foods increased in IBS and FD patients compared to controls. But there is no significant correlation between symptom severity and elevated serum food antigen-specific IgG antibodies in these patients.

GA5 Clinical Relevance of IgG Antibodies against Food Antigens in Crohn's Disease: A Double-Blind Cross-Over Diet Intervention Study

S. Bentz[a], M. Hausmann[a], H. Piberger[d], S. Kellermeier[a], S. Paul[c], L. Held[b], W. Falk[d], F. Obermeier[d], M. Fried[a], J. Schölmerich[d], G.Rogler[a]

[a]Division of Gastroenterology and Hepatology, University Hospital Zurich; [b]University of Zurich,Institute of Social and Preventive Medicine, Biostatistics Unit, Zurich , Switzerland; [c]Evomed MedizinServiceGmbH, Darmstadt, [d]Department of Internal Medicine I, University of Regensburg, Regensburg , Germany

Background: Environmental factors are thought to play an important role in the development of Crohn's disease (CD). Immune responses against auto-antigens or food antigens may be a reason for the perpetuation of inflammation. Methods: In a pilot study, 79 CD patients and 20 healthy controls were examined for food immunoglobulin G (IgG). Thereafter, the clinical relevance of these food IgG antibodies was assessed in a double-blind cross-over study with 40 patients. Based on the IgG antibodies, a nutritional intervention was planned. The interferon (IFN) _ secretion of T cells was measured. Eosinophil-derived neurotoxin was quantified in stool. Results: The pilot study resulted in a significant difference of IgG antibodies in serum between CD patients and healthy controls. In 84 and 83% of the patients, respectively, IgG antibodies against processed cheese and yeast were detected. The daily stool frequency significantly decreased by 11% during a specific diet compared with a sham diet. Abdominal pain reduced and general well-being improved. IFN _ secretion of T cells increased. No difference for eosinophil-derived neurotoxin in stool was detected.

GA6 Treating Irritable Bowel Syndrome with a Food Elimination Diet Followed by Food Challenge and Probiotics

Jeanne Drisko, MD, CNS, Bette Bischoff, MD, RD, Matthew Hall, PhD, Richard McCallum, MD Program in Integrative Medicine (J.D.), School of Medicine (B.B.), Preventive Medicine and Public Health (M.H.),Gastrointerology and Hepatology (R.M.), University of Kansas Medical Center, Kansas City, KS

Journal of the American College of Nutrition, Vol. 25, No. 6, 514–522 (2006)

Objective: In Irritable Bowel Syndrome, the gut-associated immune system may be up-regulated resulting in immune complex production, low-grade inflammation, loss of Class I bacteria, and translocation of inflammatory mediators and macromolecules outside of the GI lumen. Since food intolerance may be one of the reasons for this upregulation, our goal was to investigate the role of food intolerance in IBS patients. Methods: In this open label pilot study, we enrolled 20 patients with IBS by Rome II criteria (15 women, ages 24–81) who had failed standard medical therapies in a tertiary care GI clinic. Baseline serum IgE and IgG food and mold panels, and comprehensive stool analysis (CSA) were performed. Breath-hydrogen testing and IBS Quality-of-Life (QOL) questionnaires were obtained. Patients underwent food elimination diets based on the results of food and mold panels followed by controlled food challenge. Probiotics were also introduced. Repeat testing was performed at 6-months. We followed up with this cohort at 1 year after trial completion to assess the reported intervention and for placebo effect. Results: Baseline abnormalities were identified on serum IgG food and mold panels in 100% of the study subjects with significant improvement after food elimination and rotation diet (p _ 0.05). Significant improvements were seen in stool frequency (p _ 0.05), pain (p _ 0.05), and IBS-QOL scores (p _ 0.0001). Imbalances of beneficial flora and dysbiotic flora were identified in 100% of subjects by CSA. There was a trend to improvement of beneficial flora after treatment but no change in dysbiotic flora. The 1-year follow up demonstrated significant continued adherence to the food rotation diet (4.00 _ 1.45), minimal symptomatic problems with IBS (4.00 _ 1.17), and perception of control over IBS (4.15 _ 1.23). The continued use of probiotics was considered less helpful (3.40 _ 1.60). Conclusion: These data demonstrate that identifying and appropriately addressing food sensitivity in IBS patients not previously responding to standard therapy results in a sustained clinical response and impacts on overall well being and quality of life in this challenging entity.

GA7 IgG-Mediated Food Intolerance in Irritable Bowel Syndrome: A Real Phenomenon or an Epiphenomenom?

Fergus Shanahan, M.D[1] and Peter J. Whorwell, M.D[2]

[1]Alimentary Pharmabiotic Centre, University College Cork, National University of Ireland

[2]Department ofMedicine, Education & Research Centre, Wythenshawe Hospital, Manchester, UK

Am J Gastroenterol 2005;100:1558–1559

Abnormal reactions to food probably contribute to the complex pathophysiology of irritable bowel syndrome, but the mechanisms involved remain unclear. Following the recent identification of subtle mucosal inflammation in at least some patients with the disorder, perhaps now is the time to revisit some of the immunological reactions to dietary antigens that, in the past, have been dismissed as irrelevant.

GA8 Milk Protein IgG and IgA: the Association with Milk-Induced Gastrointestinal Symptoms in Adults

Anthoni S, Savilahti E, Rautelin H, Kolho KL. World J Gatroenterology 2009 Oct 21;15(39):4915-8

Hospital for Children and Adolescents, University of Helsinki, PO Box 281, FIN-00029 HYKS, Helsinki, Finland.

AIM: To study the association between serum levels of milk protein IgG and IgA antibodies and milk-related gastrointestinal symptoms in adults. METHODS: Milk protein IgG and IgA antibodies were determined in serum samples of 400 subjects from five outpatient clinics in Southern Finland. The questionnaire covered the nature and frequency of gastrointestinal problems, the provoking food items, family history and allergies. The levels of specific milk protein IgG and IgA were measured by using the ELISA technique. The association of the milk protein-specific antibody level was studied in relation to the milk-related gastrointestinal symptoms and dairy consumption. RESULTS: Subjects drinking milk (n = 265) had higher levels of milk protein IgG in their sera than non-milk drinkers (n = 123, P < 0.001).

GA9 Physiological and Pathophysiological Functions of Intestinal Mast Cells

Bischoff SC. Semin Immunopathol 2009 Jul;31(2):185-205. Epub 2009 Jun 17.

Department of Nutritional Medicine & Immunology, University of Hohenheim, Stuttgart, Germany.

Background: Environmental factors are thought to play an important role in the development of Crohn's disease (CD). Immune responses against auto-antigens or food antigens may be a reason for the perpetuation of inflammation.Methods: In a pilot study, 79 CD patients and 20 healthy controls were examined for food immunoglobulin G (IgG). Thereafter, the clinical relevance of these food IgG antibodies was assessed in a double-blind cross-over study with 40 patients. Based on the IgG antibodies, a nutritional intervention was planned. The interferon (IFN)gamma secretion of T cells was measured. Eosinophil-derived neurotoxin was quantified in stool.Results: The pilot study resulted in a significant difference of IgG antibodies in serum between CD patients and healthy controls. In 84 and 83% of the patients, respectively, IgG antibodies against processed cheese and yeast were detected. The daily stool frequency significantly decreased by 11% during a specific diet compared with a sham diet. Abdominal pain reduced and general well-being improved. IFNgamma secretion of T cells increased. No difference for eosinophil-derived neurotoxin in stool was detected.Conclusion: A nutritional intervention based on circulating IgG antibodies against food antigens showed effects with respect to stool frequency. The mechanisms by which IgG antibodies might contribute to disease activity remain to be elucidated.

GA10 Comparative Mapping of the Local Distribution of Immunoglobulin-Containing Cells in Ulcerative Colitis and Crohn's Disease of the Colon

Baklien K. et al: Clin Exp Immunol, 22, 197-209 (1975)

The local response pattern of immunoglobulin-containing cells was compared in Crohn's disease and ulcerative colitis by paired immunohistochemistry on specimens of the large bowel wall. In the "Crohn mucosa" with persisting glands the total cell count was on the average raised more than three times compared with controls. The numbers of IgA, IgM and IgG immunocytes were increased 2.0, 4.8 and 28.6 times, respectively. Only 0-2 IgD- and IgE-containing cells were generally found per section. No consistent differences in the mucosal response pattern were revealed when Crohn's disease was compared with ulcerative colitis. The deeper layers of the bowel wall were in both diseases more or less densely infiltrated by immunocytes-IgG cells compromising about 80%. Immunoglobulin-containing cells in the muscularis propria and subserosa were characteristically found in Crohn's disease. There was no indication of a primary defect in the secretory immunoglobulin system which appeared to be normal in areas with intact glands. The pronounced local humoral immune response, particularly that involving IgG, might be of pathogenetic importance by aggravating and perpetuating in the inflammatory bowel disease.

GA11 Study of IgG Subclass Antibodies in Patients with Milk Intolerance

Shakib F. et al: Clin Allergy, 16, 451-458 (1986)

An ELISA was applied to measure IgG sub-class antibodies to cow's milk betalactoglobulin (BLG), alpha-lactalbumin (ALA) and alpha-casein (AC) and to hen's egg ovalbumin (OA) in the sera of nineteen adult patients with milk intolerance causing either asthma, eczema or both. Results were compared with those of forty blood donors and twenty adult patients with either asthma or eczema due to inhalant allergy. Apart from one blood donor, high titres of IgG sub-class antibodies to all three milk proteins were found only in the milk intolerance group. The most frequently detected antibody was AC-specific IgG4; being high (i.e. > 9·98 μg/ml) in eight milk intolerance cases: six with eczema, one with asthma and one with both. A variable proportion of these eight patients also had high levels of IgG1, IgG2 and IgG3 antibodies to AC and IgG1, IgG2, IgG3 and IgG4 antibodies to BLG and ALA. In contrast, IgG antibody to the egg protein, OA, was remarkably restricted to IgG4 and was present in high titres in 68·4% of milk intolerant patients, 60% of inhalant allergy patients and 30% of blood donors. However, the greater incidence of high titres of IgG4 antibody to OA, compared to AC, was due to the superior coating efficiency of OA resulting in a more sensitive assay. We conclude that some adult cases of milk intolerance, particularly those with eczema, can be diagnosed by detecting raised serum levels of IgG sub-class antibodies to milk proteins.

GA12 Transglutaminases in Inflammation and Fibrosis of the Gastrointestinal Tract and the Liver

L. Elli[a], C.M. Bergamini[b], M.T. Bardella[a,c], D. Schuppan[d]

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[a]Center for Prevention and Diagnosis of Celiac Disease, Fondazione IRCCS Ospedale Maggiore Policlinico, Mangiagalli e Regina Elena, via F. Sforza, Milan, Italy, [b]Department of Biochemistry, University of Ferrara, Via Luigi Borsari, Ferrara, Italy, [c]Department of Medical Sciences, University of Milan, via F. Sforza, Milan, Italy, [d]Beth Israel Deaconess Medical Center and Harvard Medical School, 330 Brookline Ave, MA Boston, USA

Transglutaminases are a family of eight currently known calcium-dependent enzymes that catalyze the cross-linking or deamidation of proteins. They are involved in important biological processes such as wound healing, tissue repair, fibrogenesis, apoptosis, inflammation and cell-cycle control. Therefore, they play important roles in the pathomechanisms of autoimmune, inflammatory and degenerative diseases, many of which affect the gastrointestinal system.Transglutaminase 2 is prominent, since it is central to the pathogenesis of celiac disease, and modulatesInflammation and fibrosis in inflammatory bowel and chronic liver diseases.This review highlights our present understanding of transglutaminase function in gastrointestinal and liver diseases and therapeutic strategies that target transglutaminase activities.

GA13 Novel Immune Response to Gluten in Individuals with Schizophrenia

Diana Samaroo[a], Faith Dickerson[b], Donald D. Kasarda[c], Peter H.R. Green[d], Chiara Briani[e], Robert H. Yolken[f], Armin Alaedini[a]

[a]Department of Neurology and Neuroscience, Weill Medical College of Cornell University, New York, NY, United States, [b]Sheppard Pratt Health System, Baltimore, MD, United States, [c]Western Regional Research Center, U.S. Department of Agriculture, Albany, CA, United States, [d]Department of Medicine, College of Physicians and Surgeons, Columbia University, New York, NY, United States, [e]Department of Neurosciences, University of Padova, Padova, Italy, [f]The Stanley Laboratory of Developmental Neurovirology, Department of Pediatrics, Johns Hopkins University Medical Center, Baltimore, MD, USA.

Schizophrenia Research -04003 Pages 8, doi 10.1016/j.schres.2009.08.009

A link between celiac disease and schizophrenia has been postulated for several years, base primarily on reports of elevated levels of antibody to gliadin in patients. We sought to examine the proposed connection between schizophrenia and celiac disease by characterizing the molecular speci!city and mechanism of the anti-gliadin immune response in a subset of individuals with schizophrenia. Blood samples from individuals with schizophrenia and elevated anti-gliadin antibody titer were examined for celiac disease-associated biomarkers, including antibodies to transglutaminase 2 (TG2) enzyme and deamidated gliadin peptides, as well as the HLA-DQ2 and -DQ8 MHC genes. The anti-gliadin antibody response was further characterized through examination of reactivity towards chromatographically separated gluten proteins. Target proteins of interest were identi!ed by peptide mass mapping. In contrast to celiac disease patients, an association between the anti-gliadin immune response and anti-TG2 antibody or HLA-DQ2 and -DQ8 markers was not found in individuals with schizophrenia. In addition, the majority of individuals with schizophrenia and anti-gliadin antibody did not exhibit antibody reactivity to deamidated gliadin peptides. Further characterization of the antibody speci!city revealed preferential reactivity towards different gluten proteins in the schizophrenia and celiac disease groups. These !ndings indicate that the anti-gliadin immune response in schizophrenia has a different antigenic speci!city from that in celiac disease and is independent of the action of transglutaminase enzyme and HLA-DQ2/DQ8. Meanwhile, the presence of elevated levels of antibodies to speci!c gluten proteins points to shared immunologic abnormalities in a subset of schizophrenia patients. Further characterization and understanding of the immune response to gluten in schizophrenia may provide novel insights into the etiopathogenesis of speci!c disease phenotypes.

GA14 Gluten Causes Gastrointestinal Symptoms in Subjects Without Celiac Disease: A Double-Blind Randomized Placebo-Controlled Trial

Jessica R. Biesiekierski, B Appl Sci[1], Evan D. Newnham, MD, FRACP[1], Peter M. Irving, MD, MRCP[1] Jacqueline S. Barrett, PhD, BSc, MND[1], Melissa Haines, MD[1], James D. Doecke, BSc, PhD[2], Susan J. Shepherd, B Appl Sci, PhD[1], Jane G. Muir, PhD, PGrad Dip(Dietetics)[1] and Peter R. Gibson MD, FRACP[1].

The American Journal Of Gastroenterology, doi:10.1038/ajg.2010.487

OBJECTIVES: Despite increased prescription of a gluten-free diet for gastrointestinal symptoms in individuals who do not have celiac disease, there is minimal evidence that suggests that gluten is a trigger. The aims of this study were to determine whether gluten ingestion can induce symptoms in non-celiac individuals and to examine the mechanism. METHODS: A double-blind, randomized, placebo-controlled rechallenge trial was undertaken in patients with irritable bowel syndrome in whom celiac disease was excluded and who were symptomatically controlled on a gluten-free diet. Participants received either gluten or placebo in the form of two bread slices plus one muffi n per day with a gluten-free diet for up to 6 weeks. Symptoms were evaluated using a visual analog scale and markers of intestinal infl ammation, injury, and immune activation were monitored. RESULTS: A total of 34 patients (aged 29 – 59 years, 4 men) completed the study as per protocol. Overall, 56 % had human leukocyte antigen (HLA)-DQ2 and / or HLA-DQ8. Adherence to diet and supplements was very high. Of 19 patients (68 %) in the gluten group, 13 reported that symptoms were not adequately controlled compared with 6 of 15 (40 %) on placebo (P = 0.0001; generalized estimating equation). On a visual analog scale, patients were signifi cantly worse with gluten within 1 week for overall symptoms (P = 0.047), pain (P = 0 . 016), bloating (P = 0.031), satisfaction with stool consistency (P = 0.024), and tiredness (P = 0.001). Anti-gliadin antibodies were not induced. There were no signifi cant changes in fecal lactoferrin, levels of celiac antibodies, highly sensitive C-reactive protein, or intestinal permeability. There were no differences in any end point in individuals with or without DQ2 / DQ8. CONCLUSIONS: " Non-celiac gluten intolerance " may exist, but no clues to the mechanism were elucidated.

GA15 Application of food allergens specific IgG antibody detection in chronic diarrhea in children.

Ou-Yang WX, You JY, Duan BP, Chen CB. Department of Gastroenterology, Children's Hospital of Hunan Province, Changsha 410007, China. Zhongguo Dang Dai Er Ke Za Zhi. 2008 Feb;10(1):21-4.

OBJECTIVE: The causes of chronic diarrhea in children are complex. At present, food allergy is generally viewed as an important cause of this disorder, and IgG-mediated delayed allergy plays a major role in this process. This study aimed to explore the link between food specific IgG and chronic diarrhea in children, as well as the value of food allergens-specific IgG antibody detection in the management of this disorder. METHODS: Eighty-two children with chronic diarrhea and 30 healthy controls were enrolled. Serum levels of specific IgG antibody to 14 kinds of food were detected using ELISA. The results were classified into four grades: Grade 0 (negative), Grade 1 (mild allergy), Grade 2 (moderate allergy) and Grade 3 (severe allergy). The patients received a diet treatment based on the results of food specific IgG antibody detection. Children with negative IgG antibody were allowed to continue their current diet. In children with Grade 1 allergy, the food responsible for the IgG antibody positive test was given only at an interval of four days. In children with Grade 2 or 3, the offending food was eliminated from the diet. RESULTS: Of the 82 children with chronic diarrhea, 79 (96.2%) had increased specific IgG levels for one or more of the 14 foods tested compared to 8 (26.7%) of the controls (P <0.01). The majority of patients showed increased specific IgG levels for milk (68.3%) and egg (62.2%). A low proportion of patients (2.4%) was allergic to chicken, and no patient was allergic to pork. The symptoms were improved in 65 patients (79.3%) after 1 week to 3 months of diet treatment. CONCLUSIONS: Food allergy is one of major causes of chronic childhood diarrhea. Food specific IgG antibody detection may assist in the dietary management of this disorder.

GA16 Serum IgG subclass antibodies to a variety of food antigens in patients with coeliac disease.

M Hvatum, H Scott, P Brandtzaeg. Gut. 1992 May; 33(5): 632–638

Levels of serum IgA, IgG, and IgG subclass antibodies to a variety of dietary antigens were determined by enzyme linked immunosorbent assays in 14 adults with untreated coeliac disease and in 10 disease controls selected because of raised total IgG activities. The untreated coeliacs showed somewhat higher total IgG activity (p approximately 0.05) and significantly raised IgA and IgG1 + IgG3 activities to gliadin but reduced IgG4 activity (p less than 0.02) compared with the controls. High IgA and IgG1 + IgG3 activities were positively correlated (r = 0.67, p less than 0.01), and so were IgG and IgG4 activities (r = 0.64, p less than 0.02). Conversely, a high IgG2 response to gliadin appeared related to a low IgA response (r = 0.55, p less than 0.05). The IgG2 response was most prominent to oat flour antigens, followed by IgG1; and the main response to soy antigens resided in IgG1, followed by IgG2 in both disease groups. There was no difference in antibody activities to oat and soy between the two groups, and raised activity to bovine serum albumin was seldom encountered. The IgA activity to alpha-lactalbumin and ovalbumin tended to be increased in the coeliacs compared with the controls. The IgG4 subclass dominated the IgG response to beta-lactoglobulin and ovalbumin and was often raised to alpha-lactalbumin, especially in the disease controls. The IgG subclass pattern to casein parallelled that to gliadin with dominance of the IgG1- and IgG3-subclass activities, especially in the coeliacs. The phlogistic potential of a response in these two subclasses might be relevant to the pathogenesis of coeliac disease and could contribute to a raised IgA gliadin response by increasing mucosal permeability. IgA activity seemed to be highest against antigens usually involved in IgE mediated food allergy.