

COLUMBIA UNIVERSITY
COURSE DIRECTOR **COLLEGE OF PHYSICIANS & SURGEONS**
Department of Medicine
and the
Celiac Disease Center
at
COLUMBIA UNIVERSITY MEDICAL CENTER

GUEST FACULTY
present

CELIAC DISEASE
AND OTHER FOOD
INTOLERANCES

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Friday, October 22, 2004

at

Bard Hall
Columbia University Medical Center
New York, New York

COLUMBIA UNIVERSITY **PROGRAM DESCRIPTION & OBJECTIVES**

This course is designed for dietitians, nurse practitioners, and other health care professionals who are interested in the most current research and developments in the field of celiac disease. Experts in this subject will be discussing recent advances and current issues in celiac disease, with an emphasis on diagnosis, prevalence, dietary guidelines and quality of life issues. At the conclusion of the conference attendees will have gained practical knowledge on current labeling standards, patient management strategies, and a deeper understanding of the scope of celiac disease.

Peter H. R. Green, M.D., Professor of Clinical Medicine

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William R. Tream, M.D., Professor of Pediatrics, Director, Division of Pediatric Gastroenterology, Hepatology and Nutrition

ACCREDITATION

The College of Physicians and Surgeons of Columbia University is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to sponsor continuing medical education for physicians.

The College of Physicians and Surgeons designates this educational activity for a maximum of **5.0 category 1 credits** towards the AMA Physician's Recognition Award. Each physician should claim only those credits that he/she actually spent in the activity.

RDs/DTRs: This program is approved by the Commission on Dietetic Registration on behalf of Registered Dietitians and Dietetic Technicians, Registered for 5.0 CPEUs.

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What We Know About Grain Safety

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Learning Objective: To review the relationship of the harmful grains in celiac disease to other grains that might suitably be included in the diet of celiac patients and to discuss how the proteins of these grains relate to celiac disease and allergy.

Celiac Disease and Allergy—Definitions

Celiac disease and food allergy are often classified as hypersensitivity reactions (Johansson et al. 2004; Janeway et al. 1999;). Here I shall be concerned only with hypersensitivities that involve immune responses to normally innocuous foods, substances that do not cause a problem for most people.

Celiac disease is often classified as a Type IV hypersensitivity (Janeway et al. 1999) involving cellular mechanisms (T-cells play an important role). People with celiac disease (gluten-sensitive enteropathy) must avoid eating wheat, rye, and barley storage proteins in order to avoid adverse changes to their intestinal mucosa that can lead to serious malabsorption of almost all nutrients (Green and Jabri 2003; Kasarda 2000; Feighery 1999; Maki and Collin 1997; Wieser 1995). The symptoms of celiac disease frequently include diarrhea and other gastrointestinal problems, although these symptoms are not always present. Because active disease produces damage to the epithelial layer lining the small intestine, which is the site of absorption of almost all nutrients, including vitamins, minerals, proteins, carbohydrates, and lipids, clinical manifestations can be wide-ranging, including anemia, osteoporosis, peripheral neuropathy, and others. The large number of observed manifestations, along with considerable variation from patient-to-patient, makes celiac disease difficult to diagnose. Dermatitis herpetiformis is a closely related condition that differs mainly by having skin manifestations in addition to the more usual characteristics of celiac disease. Hives and respiratory distress, which are common symptoms of allergy, are not characteristic of celiac disease.

Food allergy is often classified as a Type I hypersensitivity (Janeway et al. 1999) mediated by E-type immunoglobulins (IgE antibodies). The symptoms of food allergy may include gastrointestinal disturbances, such as diarrhea, but hives and other skin manifestations are also common, as are respiratory symptoms, such as bronchospasm, (Sampson 2004). In rare cases, severe generalized anaphylactic shock may occur. Almost all grains, whether having celiac disease toxicity or not, appear to have proteins capable of producing an allergic response in at least a small percentage of the human population (Breiteneder and Radauer 2004), particularly those populations that commonly consume the grain in question. Unlike celiac disease, allergy does not seem to

result from proteins of only a few closely related grain species and response to food proteins is highly variable among populations. When a patient has gastrointestinal symptoms, it is important to distinguish food allergy from celiac disease. In allergy, the mucosal architecture is frequently normal (Veres et al. 2001), in contrast to the villous atrophy of the mucosa that is a usual characteristic of celiac disease.

Wheat, rye, and barley

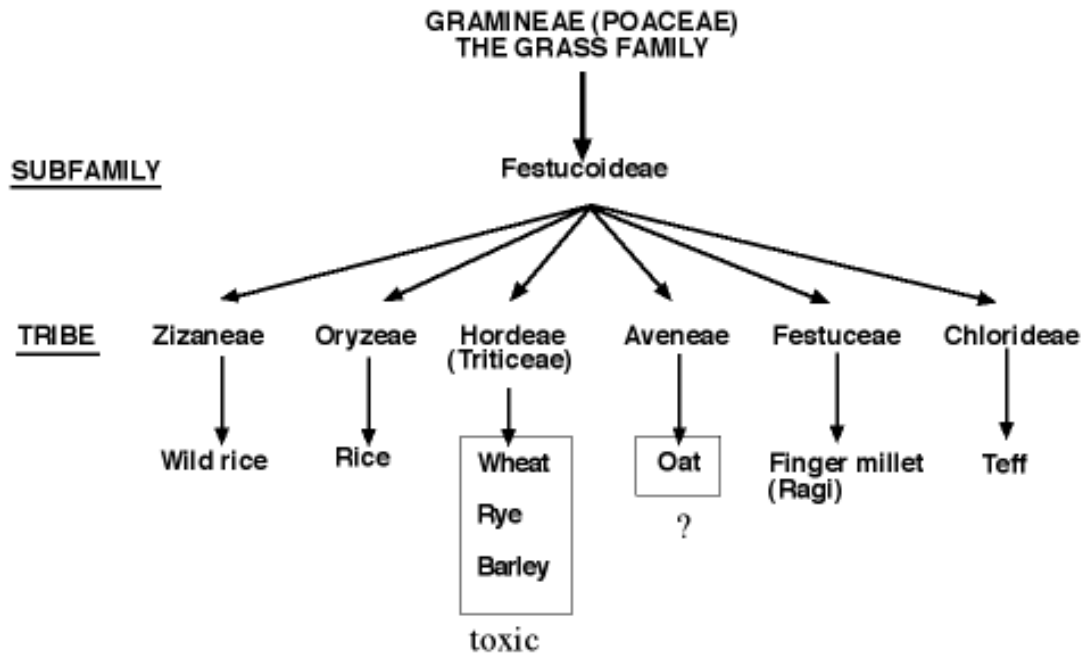
Since the discovery by W. K. Dicke in 1950 that wheat was a key environmental factor that triggered celiac disease in susceptible individuals, the relationship of the disease to ingestion of wheat gluten proteins has become an essential part of the definition. By and large, if wheat doesn't trigger enteropathy (or at least, changes in the mucosa that presage enteropathy), it isn't celiac disease. Most reviews of celiac disease tend to avoid the question of toxicity—or lack thereof—in grains, seeds, or foods other than wheat, to a considerable extent because studies of these grains are lacking or inadequate. This may be reasonable from a scientific standpoint, but patients, dietitians, and primary care physicians would like something more. Only wheat and, in recent years, oats have been extensively studied with modern approaches (such as measurement of intraepithelial lymphocyte infiltration and cytokine production) for their toxicity in celiac disease—with wheat obviously being toxic, whereas conclusions regarding the toxicity of oats are not straightforward and will be discussed in a further section. Rye and barley have many nearly identical storage proteins to those in wheat, although they lack an important wheat protein type, the α -gliadins. Despite minimal testing, these strong protein sequence similarities between the proteins of wheat and those of rye and barley, combined with the experience of celiac patients over many years with these grains, are supportive of some degree of toxicity for these grains in celiac disease. It is very difficult to quantify the toxicity of any given grain, but it is at least possible that the lack of α -type gliadins (one of the most studied toxic protein fractions) in rye and barley results in lesser toxicity for these two grains in comparison with wheat. Furthermore, it is also very difficult to quantify the toxicity of a given gluten protein relative to a different gluten protein type. It appears at present that all classes of wheat gluten proteins have toxicity. Although no studies have been carried out to determine toxicity for each of the types of proteins found in rye and barley grain, their sequence similarity to equivalent proteins in wheat suggests that they are likely to be toxic.

Oats

In the case of oats, some early work in which patients were not biopsied indicated toxicity for oats. Dicke et al. (1953) stated that rice flour, maize starch, wheat starch, and potatoes were safe, but that wheat, rye, and oats were harmful. More recent, extensive work that may be accorded greater confidence has provided impressive evidence for a lack of oats toxicity in celiac disease and dermatitis herpetiformis (Hogberg et al. 2004; Peraaho et al. 2004a; Peraaho et al. 2004b; Storsrud, S et al. 2003; Kilmartin et al. 2003; Picarelli et al. 2001; Janatuinen et al. 2000; Hoffenberg et al. 2000; Hardman et al. 1999; Srinivasan et al., 1999; Reunala et al., 1998; Janatuinen et al., 1995; Hardman et al. 1997; Srinivasan et al., 1996; Dissanayake et al. 1974). The cross-reactions between antibodies to oat or wheat storage proteins has muddied the waters at times, suggesting a closer

sequence relationship than may be warranted. Oat avenins correspond in a general way (sequence similarity/homology) to the C-terminal domains (approximately the C-terminal

Attachment 1 - Kasarda



half) of α - and γ -gliadins, which is not the region primarily considered responsible for toxicity in celiac disease (Arentz-Hansen et al., 2002; Anderson et al., 2001). Avenins lack the large proline-, glutamine-rich repetitive domain most strongly associated with toxicity (Kasarda 1997). There are, however, some proline- and glutamine-containing sequences in oats near the N-terminal end of the protein polypeptide chain, that appear to be toxic for a few patients and which may correspond to a vestigial repeat region. Lundin et al. (2003) and Arentz-Hansen et al. (2004) have described three patients who apparently have a reaction to pure oats that cannot be distinguished from celiac disease. Given the large number of studies cited above in which the final conclusion was that oats are safe for celiac patients, the results of Lundin et al. (2003) and Arentz-Hansen et al. (2004) are surprising. Arentz-Hansen et al. (2004) state, "Our observations demonstrate that even if oats seem to be well tolerated by many celiac patients, there are patients who have an intestinal T-cell response to oats. Until the prevalence of oat intolerance in celiac disease patients is established, clinical follow-up of celiac disease patients eating oats is advisable. Clinicians should be aware that oat intolerance may be a reason for villous atrophy and inflammation in patients with celiac disease who are eating oats but otherwise are adhering to a strict gluten-free diet."

Peräaho et al. (2004), while citing the results of Lundin et al. (2003), conclude that, provided safe (pure) oat products are available, the majority of celiac disease and dermatitis herpetiformis patients tolerate oats well. It should be noted, however, that in the study of Peräaho et al. (2004b) the oats-containing gluten-free diet caused more intestinal symptoms than the traditional diet. Peräaho et al. (2004) noted that mucosal integrity was not disturbed in their subjects, but more inflammation was evident in the

oats group. Allergic reactions to oats may occur in some patients as is the case for all grains.

The question of whether the amount of contamination of oats by wheat, particularly in the US, is sufficient to cause harm to celiac patients remains to be answered. Lundin et al. (2003) have noted serious contamination of a particular commercial oats sample in Norway.

Rice and corn (maize)

Rice and corn have generally been considered safe grains for celiac patients. Once again there has been lack of rigorous, controlled, scientific study of these grains in relation to celiac disease, especially with up-to-date methods. I am not aware, however, of any major evidence against their safety for celiac patients during the past 50 years. There are people who are sensitive to rice and corn and probably to any grain. Some have clearly allergic reactions, such as hives or respiratory distress in response to these grains, but gastrointestinal symptoms, such as diarrhea, may result from allergy as well (Janeway et al. 1999). If we accept celiac disease as being properly classified as a Type IV hypersensitivity mediated by T cell responses, there remains the possibility that celiac disease might be combined in a given patient with immediate hypersensitivities, such as allergies (Type I), to wheat or to any other grains, including rice and corn. Intestinal biopsy might pick up the celiac disease, but not necessarily other sensitivities. As far as I know, these potential complications are not thoroughly understood although significant progress is being made (Sampson 2004). It seems unreasonable, however, to suggest to a celiac patient who indicates that he or she responds badly to a particular grain or food other than wheat, rye, or barley, that he or she is imagining things. Adverse reactions to what I shall somewhat arbitrarily term safe grains for celiac patients may not be common, but they do exist. Such adverse reactions need more research to clarify the mechanisms involved.

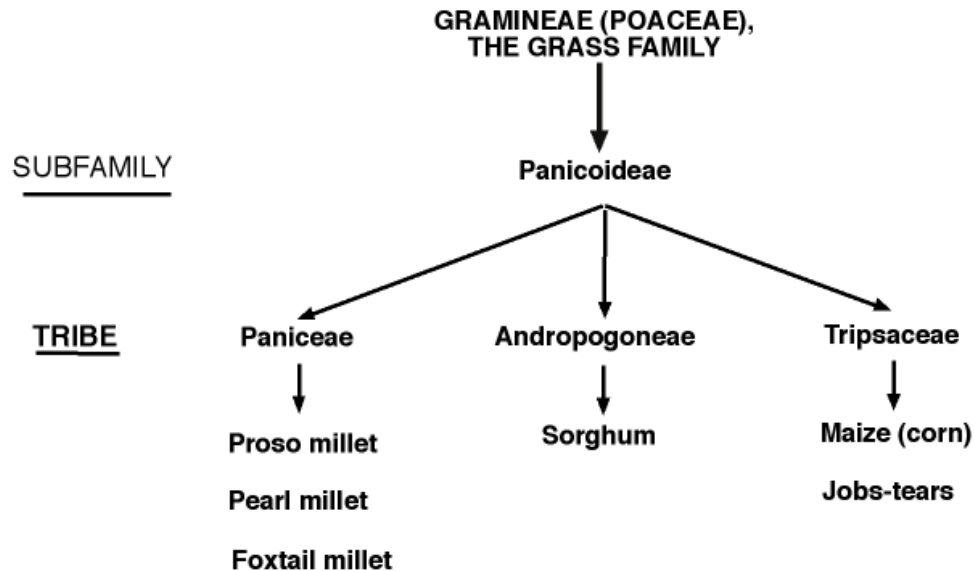
Plant classification, protein sequences, and grain safety

We do not have a unifying theory based on rigorous scientific investigation that will include or exclude various bad reactions to the ‘safe’ grains in celiac disease, but I suggest that it is unhelpful at this time to try to include responses to grains or other foodstuffs that occur in some people with celiac disease, but not in others, as part of the celiac disease syndrome. In the absence of solid scientific studies of the toxicity of most grains or seeds, I suggested in 1991 (see: Kasarda 2001) that plant classification might provide useful guidance in separating safe grains from unsafe grains. I update that approach here.

I suggest that an alternative to extensive testing (which may not be forthcoming) is to combine our knowledge of wheat and oats, which is fairly solid, with plant classification or taxonomy, and with protein sequence data to provide recommendations concerning which grains or grain-like seeds are likely to be harmful to celiac patients and which are likely to be safe (Kasarda 2001). We have learned a great deal during the past 50 years, but our knowledge is far from complete. Because studies of food reactions in celiac disease usually require human subjects, and biopsies (before and after challenge) are usually also required, it is extremely difficult and expensive to carry out such studies—first of all, even to recruit a reasonable number of clearly diagnosed celiac

patients is a considerable challenge. It is not likely that studies will be carried out in the near future on many of the grains, seeds, or foods of possible interest to celiac patients. As scientific investigation continues, of course some of my conclusions may have to be modified. New information about oats toxicity provides an example (Arentz-Hansen et al. 2004).

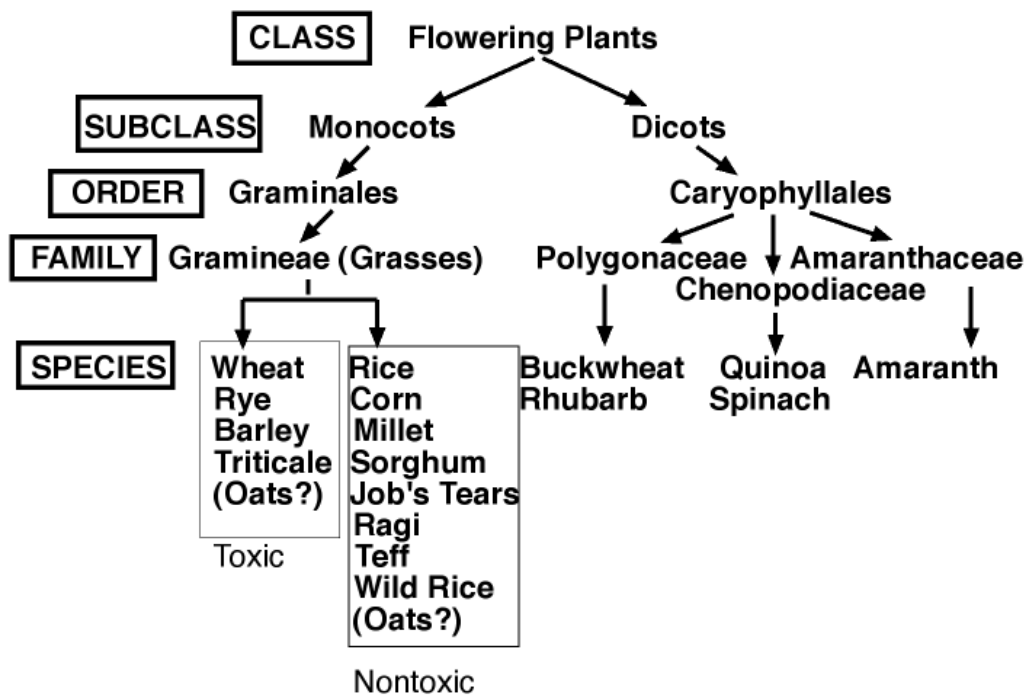
Attachment II Kasarda



Given that wheat is toxic and assuming that rice and corn (maize) are not toxic, I suggested that grains that were closer in their taxonomic relationships to corn or rice than to wheat would not be toxic in celiac disease. Such grains included millet, sorghum, Job's tears, ragi, teff, and wild rice. Furthermore, in plant classification, wheat, rye, and barley are included in the tribe of the grass family called the Hordeae or Triticeae, while oats fall in a separate tribe. There is, however, a significant similarity in protein sequence between oat avenins and some major wheat gliadin proteins, indicating relative closeness of the two tribes. Although oats now seem to be toxic for rare individuals (Arentz-Hansen 2004; Lundin et al. 2003), it appears that many celiac patients tolerate oats. If oats are included in the nontoxic category, then all toxic grains would be found in a single tribe, the Triticeae (see attachments I and II). Such grains include bread wheat, durum wheat (used in pasta), spelt wheat (spelta), polonicum (Polish wheat), Kamut, monoccum (einkorn), farro, triticale (a cross between wheat and rye), and many wild grass species not usually consumed by man. All grasses not in the tribe, Triticeae, were consequently classified as safe, including rice, corn, various millets, ragi, teff, Job's tears, wild rice, and oats (see attachment III), although, as discussed, oats may have a rare

celiac-toxic action that does not accord with allergy. Plants that did not fall in the grass family, such as the dicotyledenous plants, which are very distantly related to the grass family, would be highly unlikely to have seed proteins toxic in celiac disease. Some of the dicot seeds of interest include all beans, buckwheat, quinoa, and amaranth. These relationships are summarized in Attachment III. Rigorous studies of the safe grasses (and of grain-like seeds from various dicots) that would be desirable remain undone for the reasons I mentioned above. The approach I have suggested as the best available in the absence of the pertinent scientific studies has been growing in use among celiac patients. I have not received any clear evidence that the grains indicated by this approach to be safe for celiac patients are causing significant harm and have heard many favorable comments to the contrary. Some people do not tolerate these grains and I would recommend that a celiac patient avoid any food that he or she associates with adverse reactions. I emphasize again, however, that because some patients seem to tolerate the grains I have put in the safe category, it seems to me unreasonable for now to urge that such grains should be avoided by all celiac patients.

Attachment III — Kasarda



The recent findings that very infrequently individuals with celiac disease also respond to oats (Arentz-Hansen et al. 2004) has made me wonder, however, if grains other than those I have designated as toxic (wheat, rye, barley) might also, in rare individuals, trigger a celiac disease-like response (villous atrophy, for example). I know of no solid evidence for this speculation, but note that there have been odd mentions of protein intolerances to milk, soy, rice, fish, and chicken (see: Vitoria et al. 1982, and

references therein; also Ferguson et al. 1982 and references therein) that produced changes in mucosal morphology reminiscent of celiac disease, although the authors indicated that these intolerances were mostly not permanent in contrast to celiac disease. Research is needed to examine more carefully those celiac patients who have digestive problems with maize (corn), buckwheat, and other presumably safe grains to provide a better understanding of the nature of their responses. In a few cases where unresponsive celiac disease was diagnosed, an elemental diet was found to elicit improvement (personal communication, K. E. A. Lundin), which might be a consequence of the patient reacting to some food protein other than those associated with celiac disease. Nevertheless, I suggest that the rarity of such reactions, while worthy of note, does not negate the general conclusions I have drawn in my attempt to classify toxic vs. safe grains.

Protein sequences

The gluten proteins, as is typical of proteins, are made up of about 20 different amino acids strung together through peptide bonds like beads on a string into long polymer chains, called polypeptides. There are many gluten proteins, which vary in size, incorporating from about 250 to 850 amino acids in the polypeptide chain. The number of each type of amino acid and the sequence of incorporation of these amino acids into the polypeptide chain largely defines any given protein. When a gluten protein polypeptide is broken down into smaller polypeptides (often called just 'peptides') by digestive enzymes, some of the peptides, incorporating from about 12-33 amino acids, are quite resistant to digestion by digestive tract enzymes (Shan et al. 2002; Bronstein et al. 1966; Frazer et al. 1959) and this is an important aspect of their toxicity, along with the presence of key glutamine and proline residues. A few of these peptides have been shown to be toxic to celiac patients by instillation studies of the equivalent synthetic peptides (Fraser et al. 2003; Marsh et al., 1997; Marsh et al. 1995; Sturgess et al., 1994). It is unlikely that all toxic peptide sequences have been identified at this time. The amino acid sequences of the known toxic peptides do not, however, seem to have exact duplicates in proteins other than those of grains falling in the tribe Triticeae, particularly when proteins that are likely to appear in organisms at more than trace levels, such as signal transduction proteins, are considered (Kasarda 1997). Thus, these sequences provide support for the taxonomic classification approach. I have not taken into account the extent to which similar, but not identical, sequences may exhibit toxicity in celiac disease because I don't think we have enough of a handle on what the degree of variation in peptide sequence is that is compatible with toxicity.

Peptides that trigger allergic reactions have also been described. For example, Matsuo et al. (2004) reported that the sequences QQIPQQQ, QQFPQQQ, QQSPEQQ, and QQSPQQQ from ω -5 gliadin were dominant epitopes for triggering wheat-dependent exercise-induced anaphylaxis. Maruyama et al. (1998) found that the QQQPP motif in certain low-molecular-weight glutenin subunits was primarily responsible for IgE binding when tested with sera from patients with wheat-associated allergy.

Disclaimer

Although retired, I maintain a relationship with the U. S. Department of Agriculture as a Collaborator. The material presented here represents my personal

interpretations and does not represent official policy of the U. S. Department of Agriculture.

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