

Zonulin! The Wheat Conundrum Solved (Well, Mostly ...)

Joseph Pizzorno, ND, Editor in Chief



At the May 2013 Institute for Functional Medicine (IFM) conference on “Energy” in Dallas, Texas, I heard one of the most clinically important lectures ever. IFM honored Alessio Fasano, MD, with its highest honor, the Linus Pauling Award. His lecture was remarkable, and I now finally understand why so many of my patients with chronic disease became healthier avoiding gluten, even if they apparently did not have an immunological response to wheat proteins. The standing ovation in appreciation of his remarkable work was most deserved. Following is my evolving understanding. I say *evolving* as there are still important areas needing to be researched.

Fasano’s team discovered zonulin, which regulates the opening of the tight joints between enterocytes. They also discovered that zonulin is released by gliadin, one of the primary components of gluten. And therein lies a remarkable story.

The following quote from Fasano says it all:

Together with the gut-associated lymphoid tissue and the neuroendocrine network, the intestinal epithelial barrier, with its intercellular tight junctions, controls the equilibrium between tolerance and immunity to nonself antigens. Zonulin is the only physiological modulator of intercellular tight junctions described so far that is involved in trafficking of macromolecules and, therefore, in tolerance/immune response balance. When the finely tuned zonulin pathway is deregulated in genetically susceptible individuals, both intestinal and extraintestinal autoimmune, inflammatory, and neoplastic disorders can occur.¹

To which I would add, the hybridization of wheat to dramatically increase gluten (read gliadin) content and its overconsumption—multiple times per day, every day—in the typical diet chronically disrupts this tolerance/immune response balance leading to much of the chronic disease burden now suffered by Western societies.

Zonulin

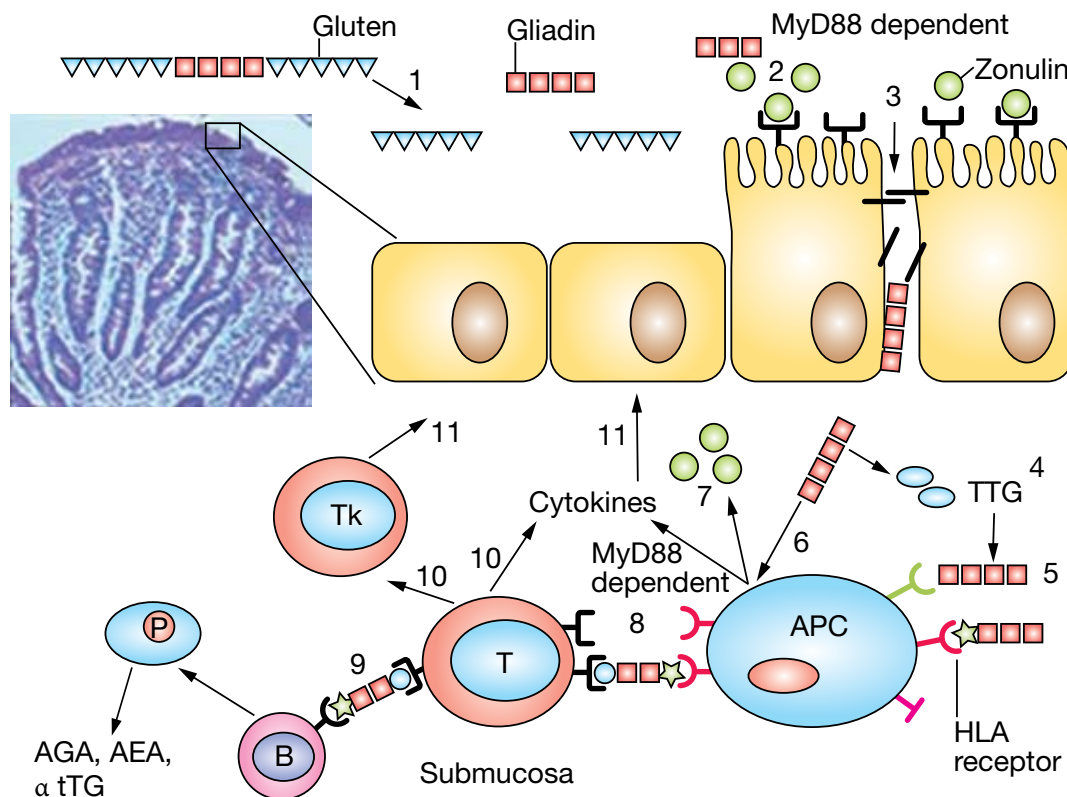
Fasano’s early research was trying to discover the mechanisms by which the body responds to serious infectious disease such as cholera by flushing fluids into the intestines. A key question was: What molecule(s) are released by the gastrointestinal mucosa in response to

contact with the bacterium *Vibrio cholerae* or its toxin? They discovered that the enterocytes release zonulin, which causes disengagement of the protein zonula occludens-1 from the tight junction (TJ) complex between the mucosal cells.² This opens the space between cells in the gastrointestinal mucosa allowing water to flush into the gut, washing out the cholera organisms and toxins. This opening also dramatically increases gut permeability (Figure 1). As we all know, increased intestinal permeability is as a common underlying mechanism in the pathogenesis of allergic, inflammatory, and autoimmune diseases (ie, most chronic diseases). This zonulin-driven opening of the paracellular pathway apparently evolved as a defensive mechanism, to flush out microorganisms and prevent bacterial colonization of the small intestine. (For those who want to look more deeply into this discovery, they labeled the enterotoxin elaborated by *Vibrio cholerae* that affects the TJ competency “zonula occludens toxin” [ZOT]).

The great discovery of Fasano’s team is that zonulin release is also stimulated by contact with gliadin (α -gliadin the most effective). Chemokine receptor CXCR3 is the receptor for specific gliadin peptides that cause zonulin release and subsequent increase in intestinal permeability.³ In vitro research with chemokine receptor CXCR3 transfectants found that several peptides from gliadin, especially 33-mer, bind to the receptor. Zonulin and CXCR3 are over expressed in the intestinal mucosa of patients with celiac disease and autoimmune disease. (Readers interested in learning more about this mechanism will find Fasano’s 2012 review article in *Clinical Gastroenterology and Hepatology* quite informative.⁴)

A key concept here is that the TJ formerly considered static structures are now being shown to be dynamic and to adapt to a variety of developmental, physiological, pathological, and dietary circumstances. The TJs are involved in passive absorption of nutrients, surveillance of gut microbial content, defense against some infectious agents, transport of leukocytes into the gut—the list is growing. The increase in intestinal permeability in response to gliadin is time and dose dependent.

Figure 1. Gliadin Release of Zonulin to Open Tight Junctions and Activate Immune System^{a,b,c}



^aThe enterocytes that release zonulin occur in the jejunum and distal ileum, but not in the colon. This opening is rapid and reversible, except in those with celiac disease.

^bZonulin, Fasano’s team discovered, is the precursor to haptoglobin-2 and was known in earlier research as pre-Hp 2.⁵

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Haptoglobin

Haptoglobin (Hp), identified as a marker of inflammation several decades ago, is an α_2 -globulin found in human plasma at a concentration of 82 to 236 mg/dL. It is an acute phase plasma protein whose primary role appears to be binding free hemoglobin released when erythrocytes are damaged, thus decreasing the oxidative damage of the freed iron. It is composed of four polypeptide chains: two α chains and two β chains connected by disulfide bridges. Human Hp occurs primarily as three major phenotypes: type 1-1, type 2-1, and type 2-2. The population distribution of these phenotypes and their association with celiac disease is shown in Table 1.

A small portion of various populations has either no Hp or uncommon variations on the three main types. Most Hp is due to acquired ahaptoglobulinemia (<1.0% of the population has a genetic polymorphism that results in nonproduction). Hp is very common in Western Africa (as high as 47%) and other areas where hemolytic diseases, such as malaria, are common.

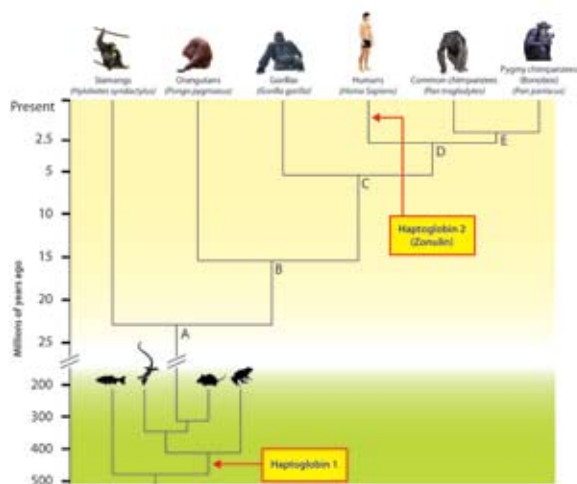
Some conditions, such as cancer and coronary artery disease, can raise, while other diseases, such as jaundice and cirrhosis, can significantly lower, the total amount of Hp in plasma.

Of particular interest is that the genotypes have very different affinity for iron and significant disease associations (discussed below). Hp 1-1 has the strongest and Hp 2-2 the weakest affinity for hemoglobin. Hp 1 is the original form, evolving about 800 million years ago. Hp 2 is a mutation found only in humans, believed to have occurred in India about 2 million years ago, 500 000 years after humans and chimpanzee lineages split (Figure 2).

Table 1. Hp Type Prevalence and Risk of Celiac Disease

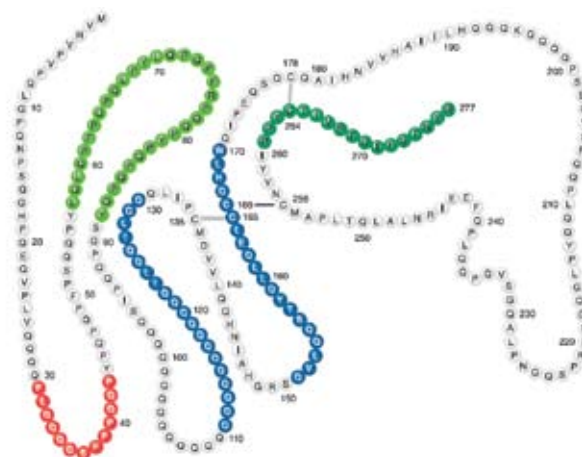
Hp Phenotype	% in Healthy US Population	% in CD Patients
Hp 1-1	20.6%	7.1%
Hp 1-2	43.5%	35.7%
Hp 2-2	35.9%	57.2%

Figure 2. Evolutionary Development of Hp



Note: Evolutionary tree of Hp gene. The appearance of the gene encoding Hp 1 has been mapped ~450 million years ago, soon after the split between bony fish, reptiles, and mammals. Hp 2 appeared much later, 500 000 years after, then chimpanzees and humans split 2.5 million years ago.

Figure 3. Immunologically Active Peptide Sequence in α -Gliadin⁶



Note: Mapping of α -gliadin motifs exerting cytotoxic activity (red), immunomodulatory activity (light green), zonulin release and gut-permeating activity (blue), and CXCR3-IL-8 release in CD patients (dark green). There are at least 50 toxic epitopes in gluten peptides exerting cytotoxic, immunomodulatory, and gut-permeating activities (122). The 33-mer gliadin fragment is the most immunogenic peptide, apparently because it harbors six overlapping epitopes (ie, antigenic determinants).

Gliadin

Gliadin is a class of proteins present in wheat and several other cereal grains (Figure 3). Gliadin is also found in rye and barley, but not other grains like rice, corn, and oats.

Prolamins are a group of plant storage proteins found in the seeds of cereal grains of the grass genus *Triticum*: wheat (gliadin), barley (hordein), rye (secalin), corn (zein), sorghum (kafrin), and oats (avenin). They are characterized by a high level of glutamine and proline content. Storage proteins account for about 50% of the total protein in mature cereal grains. Gliadins and glutens give bread the ability to rise properly during baking. There are three main types of gliadin (α , δ , and ω), distinguished by their amino acid sequences, all of which are reactive in celiac patients, with the α form the strongest. The very big question then is: Do other prolamins have amino acid sequences similar enough to gliadin to stimulate the release of zonulin? (See below for further discussion.)

Mechanism of Damage

While there are several mechanisms by which gliadin consumption causes disease in susceptible individuals, the three most important appear to be (1) substantial and diverse nutritional deficiencies due to loss of absorptive area in the small intestine, (2) loss of enterocyte discrimination of what can enter the body due to loss of control over the pericellular junctions, and (3) increased activa-

tion of the inflammatory and immune systems in response to gliadin and other molecules passing through the pericellular junctions. These diverse mechanisms help explain the surprisingly dissimilar range and severity of disease caused or aggravated by the consumption of wheat by susceptible individuals.

There is a wide range in response among those reacting to gliadin: Some may have only minimal changes in the intestinal epithelium and no obvious symptoms, others may have severe damage to the lining of the intestine, and still others may suffer autoimmune reactions throughout the body. Further complicating the clinical picture is that some people develop celiac disease soon after wheat is introduced into their diet as infants while others may not manifest significant symptoms and pathology until adulthood.

I think to better understand what is going on we need to differentiate between nutritional deficiencies, increased inflammation set point, and immunologically mediated responses. In any given patient, one or more of these mechanisms may be involved. Also of particular importance is to recognize that the increased permeability caused by gliadin in susceptible individuals in itself is adequate to increase inflammation and disease even where there is no immunological reaction. The presence of anti-gliadin or antiendomysium antibodies clearly indicates a more severe condition.

Table 2. The Major Diseases Associated With Zonulin^a

Autoimmune Diseases

- Ankylosing spondylitis
- Asthma
- Celiac disease
- Inflammatory bowel disease
- Multiple sclerosis
- Rheumatoid arthritis
- Systemic lupus erythematosus
- Type 1 diabetes

Diseases of the Nervous System

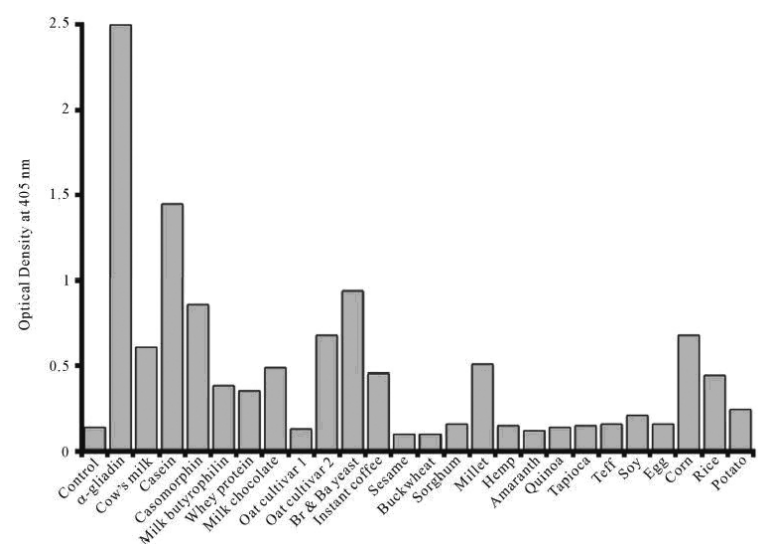
- Chronic inflammatory demyelinating polyneuropathy
- Schizophrenia

Cancers

- Brain cancer
- Breast cancer
- Glioma
- Lung adenocarcinoma
- Ovarian cancer
- Pancreatic cancer

^aModified from Fasano and others.

Figure 4. Cross Reactivity of Antigliadin Antibodies With Other Food Antigens



Reaction of affinity-purified α-gliadin 33-mer polyclonal antibodies to gliadin and different food antigens.

Abbreviations: Br yeast = Brewer's yeast; Ba yeast = Baker's yeast.

Symptoms most commonly appear during the first 3 years of life, after cereals are introduced into the diet. A second peak incidence occurs during the third decade, and while celiac disease is often thought of as a disease diagnosed early in life, more diagnoses are made in adulthood than childhood. Celiac disease occurs in about 1% of the population, but wheat reactions appear far more common. Lack of celiac disease is definitely not the same as not reacting to gliadin.

In gluten sensitive enteropathy, (ie, celiac disease), there are several types of immune engagement: innate immunity (cellular immune priming), HLA-DQ, and antibody recognition of gliadin and antibody development to body constituents, such as transglutaminase.

The research is clear that the mechanism of action is highly dependent upon Hp, the type of grain eaten, the frequency and dosage of gliadin, and other factors such as digestive function and gut microbiome.

Bottom line: Gliadin causes release of zonulin in the 80% of the population that is Hp 1-2 or Hp 2-2. This causes opening of the tight junction complex between enterocytes increasing gut permeability and increasing the risk of immunological reactions to gliadin—as well as other wheat polypeptides. Patients can have either or both, thus complicating the clinical picture and confusing wheat intolerance with celiac disease. Further complicating this is that the immunological reaction can be mediated through the innate, complement, and humoral immune systems.

Disease Associations

As chronic stimulation of zonulin increases gut permeability, it is no surprise that there appears to be an association with almost all chronic diseases, especially autoimmune disease (Table 2).

Beyond the scope of this article is that zonulin is also found in the lungs and blood-brain-barrier and activates the complement system.⁷ The importance of this for chronic inflammatory lung and neurological disease is obvious. The progression of immunological reaction to gliadin to autoimmune disease appears dependent on several factors, especially HLA class.

Cross Reactivity With Other Foods

As the reaction to gliadin is based on specific peptide sequences, it seems logical to assume other foods may have similar sequences.⁸ For example, several studies have found a high incidence of reaction to dairy products, especially casein, in celiac patients.⁹ Sadly, I ran out of time and space to fully address this fascinating topic for this editorial. Looks complex, and I hope I can address it in the future. I think Figure 4 showing the cross reactivity of affinity-purified α-gliadin 33-mer polyclonal antibodies to gliadin with other food antigens is the tip of the iceberg.¹⁰ While the cross reactivity with casein, brewer's yeast, oats, millet, and corn does not necessarily mean these will also stimulate zonulin secretion, the results are still clinically important.

Table 3. Summary of Clinical Responses to Wheat and Clinical Recommendations

Response to Wheat	% Pop.	Characteristics	Intervention
Safe	34%	Hp 1-1; no grain antibodies	None needed
Inconsistent, dose-dependent response (some research is labeling severe form nonceliac gluten sensitivity—NCGS)	43%	Hp 1-2; low to elevated blood zonulin	Limit wheat, rye, barley; optimize protein digestion; reseed with <i>Bifidobacteria</i> and other healthy gut bacteria
Immune reactions to grains	15%	Antibodies to some grain proteins	Avoid all grains
Celiac disease	3%	Hp 1-2 or Hp 2-2; elevated antibodies to gliadin; HLA-DQ2 or DQ8	Strictly avoid wheat, rye, barley; may need to avoid other grains as well
Autoimmune disease	5%	Hp 1-2 or Hp 2-2; elevated anti-self antibodies	Strictly avoid all allergens: DHEA, vitamin D, etc

Prevention

While genetics is clearly the most dominant factor in gliadin susceptibility, breastfed babies have a decreased risk of developing celiac disease.^{11,12} This protection is more complete when infants continue to be breastfed after dietary gluten is introduced. The risk of celiac disease is greater when gluten was introduced in the diet in large amounts than when introduced in small or medium amounts. Early introduction of cow’s milk also increases risk of celiac disease.¹³ One cell culture study found that several different *Bifidobacterium* strains counteract the inflammatory effects of gliadin-derived peptides in the intestinal epithelium by decreasing its activation of enterocytes.¹⁴

Another consideration is how well a person’s digestive system is in breaking down the protein polypeptides. Obviously, if all that is left are amino acids before contact with the enterocytes, reaction will be much less. Once again, I ran out of time to fully review the research in this area. I did find a very interesting study that showed substantially increased incidence of hypo- and achlorhydria in both dermatitis herpetiformis (more common) and celiac disease. However, they did not find a correlation between atrophic gastritis or achlorhydria and small-intestinal villous atrophy.¹⁵

Another study showed that pancreatic exocrine insufficiency is common in celiac disease, and supplementation with pancreatic enzymes is very effective in reducing symptoms (19/20 with persistent diarrhea experienced improvement).¹⁶

The fact that celiac disease can develop later in adult life provides further support for the importance of effective digestion. As people age, their production of hydrochloric acid and pancreatic digestive enzymes decreases, thus increasing the amount of gliadin exposed to the enterocytes. Improving digestion, a common problem, certainly appears an important part of clinical care.

Clinical Recommendations

As I have summarized in Table 3, there appear to be five distinct responses to wheat consumption ranging from safe to several autoimmune diseases (of course, there will be some

overlap). To fully understand a patient’s response to wheat, the key laboratory tests are: Hp type, serum zonulin, HLA type, antibodies to wheat, and antiseif antibodies. Thinking about all the research I have read the past few weeks for this editorial, I made an estimate of the percentage of the North American population in each category. Yes, this is not consistent with “official” numbers, and I am sure some will disagree with my assessment. Nonetheless, I think it accurately reflects what is real as many of these conditions are significantly underdiagnosed. Finally, I included recommended interventions according to category.

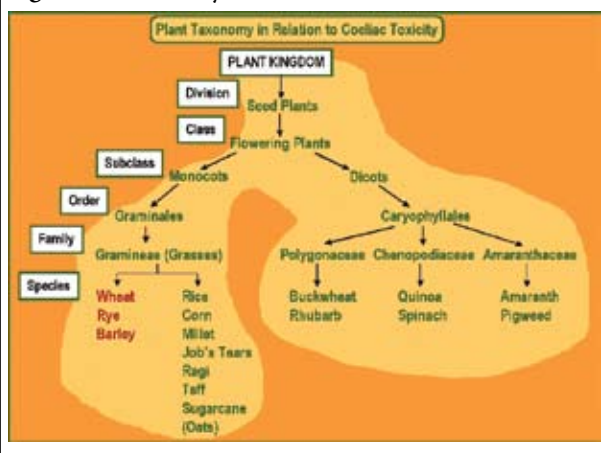
While Hp 1-1 has much lower probability of immunological reaction, be clear it is not zero. As noted in Table 1, there is still some risk of celiac disease. There is growing recognition of the nonimmunological reaction to wheat (category 2 above), which is now being identified as nonceliac gluten sensitivity (NCGS).

Despite the clear genetic susceptibility, research shows that breastfeeding and delayed feeding of cow’s milk and cereal grains are primary preventive steps that can greatly reduce the risk of developing celiac disease. Most likely this strategy is only effective in those who are not Hp 2-2.

Species falling in the genus *Triticum* are almost certain to be harmful to gliadin-sensitive patients. While the hybridization of wheat to higher concentrations of gluten has clearly aggravated the problem, this does not mean that so called “ancient wheats” are safe for those who react to gliadin. This is a surprisingly complex issue needing more research, as the level of gliadin or similar prolamins is dependent upon which chromosome sets are in the specific grass species. Nonetheless, *Triticum spelta* (spelt or spelta), *Triticum polonicum* (Polish wheat or Kamut), and *Triticum monococcum* (einkorn or small spelt) still contain gliadin or very similar prolamins with the same toxic peptide sequences and must also be avoided.^{17,18} They may be acceptable in modest dosages in those who are wheat intolerant, but not reacting immunologically, although one study found that while their total gluten is less, their α -gliadin may actually be higher.¹⁹

The clinician must consider the nongliadin proteins in wheat, which can also be allergenic. For example, α -amylase

Figure 5. Taxonomy of Grains



has been documented as a second route of allergic sensitization.²⁰ α -Amylase inhibitors are also found in rice, which might explain the reason avoidance of all grains helps those who have developed immunological reactions to gliadin as antibodies to other wheat constituents at the same time would seem likely. While oats, rice, and corn do not have gliadin and are supposedly safe for celiac patients, my clinical experience has shown that celiac patients still suffering symptoms have consistently improved when these other grass-family grains are also removed. Whether this is simply due to contamination from storage and processing in facilities that have been used for wheat or antibodies to other amino acid sequences is unclear.

Looking at plant taxonomy (Figure 5), grasses are monocots. Fortunately, there are other grain-like foods that are dicotyledonous plants (dicots) and thus unlikely—but not necessarily—to contain the same peptide sequences as gliadin. These include buckwheat, amaranth, and quinoa. If a person ate these foods heavily while his or her intestines were still damaged from gliadin (or other causes), then allergy must be still be considered.

As well said by Fasano about patients suffering celiac disease,¹ “Once gluten is removed from the diet, serum zonulin levels decrease, the intestine resumes its baseline barrier function, the autoantibody titers are normalized, the autoimmune process shuts off and, consequently, the intestinal damage (that represents the biological outcome of the autoimmune process) heals completely.”

In This Issue

Following are comments by associate editor, Sid Baker, MD, on “Teaching Meditation to Children as Part of Psychotherapy” by Carolyn Williams-Orlando, PhD:

My cheeks are damp with tears of joy and appreciation from savoring this gem of a MS [manuscript]. *IMCJ* is fortunate to be chosen for its submission. It is a gem. Its value lies in its lucid literary style and impeccable choice of words. That value is magnified in its generous respect for the reader as well as the children who gave wings to the spirit of this essay. That spirit is straightforward, kind, modest and empowering of the reader. The writings of experts often leaves me feel-

ing respectful but a disabled in my ability to perform the requirement of scientific enterprise; replication. In fact those who publish the results of wet bench science are not above.

Enough said.

Sara D. Murray, BS, Amisha Mehta, MD, and Mikhail Kogan, MD, provide us “The Implementation of Dietary Approaches in Hyperuricemic Individuals: Alternatives to Drug Therapy to Decrease Serum Uric Acid” as alternatives to drug therapy. In addition to reviewing the integrative medicine research, they include an illustrative case history.

Our interview this issue is with Edward Levitan, MD. I think his team’s model of integrative care is quite interesting and provides guidance on a model that is financially viable and scalable.

We have been working to increase the voice of clinicians in *IMCJ*. This has been a challenge because on the one hand we would like every article to be “peer-reviewed” while on the other we want to hear from successful clinicians about what they are actually thinking and doing. Bruce Milliman, ND, in “Recognizing’ the Patient: A Reflection on its Role in a Clinical Encounter” provides many useful insights into the patient/doctor relationship. The concept of “recognition” is quite interesting.

I enjoy reading John Weeks every issue as he helps keep us informed on the business and policy of integrative medicine. Perhaps most of interest to me personally is John’s commentary on the publication by the *Canadian Medical Association Journal (CMAJ)* of a study by Dugald Seely, ND, et al: “Naturopathic Medicine for the Prevention of Cardiovascular Disease: A Randomized Controlled Trial.”²¹ “This is the first, positive study led by a naturopathic physician investigator, of real world naturopathic practice, to make its way into a journal of a national MD professional association,” Weeks writes.

Associate Editor Bill Benda, MD, continues his unbroken string of engaging—and often challenging—insights. I must admit to fully agreeing with him about Facebook. What started as a way of keeping up with friends and family has degenerated into uninteresting banality and unwanted advertising. And I agree with his concerns about the digitalization and devitalization of life and social contact.

At times I am stunned and humbled by the huge impact of some who were once my students. One of the brightest and most prolific is Alex Vasquez, DC, ND, DO, FACN. While this interview is about the excellent conference he has organized for late September, I think all will find his comments on mitochondrial dysfunction quite useful. Wish I could attend, but I will be lecturing in London the same weekend.

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*Source: The Global Economic Burden of Non-communicable Diseases Report. World Economic Forum, 2011.