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CELIAC DISEASE

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Celiac disease (or celiac sprue or idiopathic sprue as it was known) was first recognized as being gluten induced in the late 1940s by Dutch pediatricians. Since then, the field has made major advances in understanding of the root causes, clinical care, cellular mechanisms of disease, and detection of this disorder. Here, we review major milestones in celiac research and care presented in the pages of *Gastroenterology*, arguably the journal that has led the charge in understanding this malady.

Early days: from idiopathic to defined and staged

One of the earliest and most influential papers that documented a benefit for adults with idiopathic sprue was published in *Gastroenterology* in 1957 by Schwartz et al¹. This paper cemented the role of gluten as the trigger for celiac disease in adulthood. This led to a sea change in the management of the previously “idiopathic” celiac disease in the United States.

No paper from *Gastroenterology* on the topic of celiac disease has a greater impact on the field than that by Mike Marsh². This paper, cited over 1,600 times is a single-authored publication by a true giant in the field, and continues to influence the thinking that an interaction between gluten, HLA, and the small intestine produces a spectrum of histologic change and disease. This paper ushered in a new era in the thinking of celiac disease and continues to influence clinical pathology. For example, many pathologists will refer to Marsh staging and, while Mike Marsh himself may not necessarily agree that he intended this to be a classification system for use in clinical pathology, it has nevertheless made the field aware of the variety of immunopathogenic changes that occur in response to gluten. This is not the only landmark article that influenced contemporary thinking on celiac

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disease. A paper by the giants of the field from the 1960s³ provided unique insight into the distribution and extent of the gluten-induced injury in the small intestine and how this can be reproduced by challenging any location of the small intestine with gluten. This provided proof positive the immune response within the mucosa of the small intestine to endoluminally applied gluten that produces the characteristic lesions of celiac disease.

Looking forward, however, the lessons learned from these papers continue to inform and indeed challenge us as we move into an era of clinical trials for alternative treatments for celiac disease.

Celiac disease as a defined system that serves as a platform for the study of basic, broadly-applicable immune mechanisms

In addition to being an important clinical problem, over the last few decades celiac disease has provided a framework for key advances in the basic science of the GI tract. This is especially the case in the arena of mucosal immunology and innate immune-epithelial interactions, including crosstalk between villus enterocytes and the intraepithelial lymphocytes (IELs). As examples, we consider several highly-cited papers in *Gastroenterology* that helped define the role of interleukin (IL)-15 in regulating IEL activity, epithelial function, and in directing the “conversations” between IELs and enterocytes that go wrong in celiac disease and other disorders.

In a 2000 paper addressing the basic changes in mucosal cellular populations during celiac disease, Jabri and colleagues showed that IELs include a rich group of natural killer (NK) T cells which appear poised for action, in that they expand in the mucosa of celiac patients⁴. Proliferation and differentiation of these cells was in part controlled by IL-15, a cytokine that plays a recurring part in the story of celiac disease but also has a significant role in other GI disorders such as inflammatory bowel disease and non-alcoholic fatty liver disease. Since intestinal epithelial cells (as well as other cell types) express IL-15, and this expression level seems to increase in celiac disease, the findings from Jabri and colleagues raised the possibility of a critical, active regulation of the immune system by the epithelium, a concept that is central to many models of intestinal disorders today.

Later that same year, work from Maiuri and colleagues, also publishing in *Gastroenterology*, showed that IL-15's role in celiac disease extends to direct effects on the intestinal epithelium. Using cultured biopsy specimens from celiac patients, they showed that IL-15 given to mucosa from untreated patients with active disease could induce essentially the same levels of apoptosis in enterocytes as gliadin⁵. Furthermore, a neutralizing antibody to IL-15 reduced gliadin-triggered apoptosis in these cultures, suggesting that induction of this cytokine might be a necessary intermediate for some of the damaging effects of gluten exposure. Interestingly, cultured biopsies from “treated” (on a gluten-free diet for more than a year) patients showed an increase in cells positive for the proliferative marker Ki67 after IL-15 exposure, suggesting that the cytokine may have a role in proliferative/repair responses as well.

Bringing together these two threads, in 2003 Mention and colleagues demonstrated that IL-15 levels were high in multiple cell types (including the epithelium) of celiac patients⁶. Curiously, increased IL-15 protein levels in the epithelium were not accompanied by elevated steady-state mRNA expression, suggesting a post-transcriptional regulatory step; furthermore, IL-15 was not robustly secreted by these cells but rather retained at the cell surface. This IL-15 displayed on the surface of epithelial cells could trigger expansion and modification of IEL populations in a way that led to increased cytotoxic activity and interferon- γ secretion, suggesting an important cell-cell direct interaction driving pathogenesis of celiac disease. In a sense, this study closed the loop on the crosstalk between the epithelium and the IELs and back again. Furthermore, it drew a distinction between activity of secreted versus cell surface (now commonly referred to as “tethered”) IL-15, a distinction which today is a common regulatory element for signaling by multiple cytokines and growth factors in the gastrointestinal tract.

Celiac disease has relatively defined triggers and an effective dietary therapy. Thus, it provides a powerful platform for investigating mechanisms of epithelial-immune interaction, auto-immune reactions, and repair responses in the gastrointestinal tract. Basic research into celiac disease over the last few decades, including a number of landmark studies published in *Gastroenterology*, has contributed to a broader understanding of the biology of the intestinal mucosa through experiments focused on untangling the cellular mechanisms of pathogenesis.

Ever onward: Non-invasive testing and the future of celiac disease diagnosis

In addition to malabsorption, diarrhea, poor growth in children, and abdominal pain, untreated celiac disease increases the risk of complications such as osteopenia, infertility, and malignancy. Thus, the medical community has maintained a strong interest in diagnosing individuals with small intestine enteropathy as early as possible even before signs and symptoms of the disease developed. The initial serologic test for celiac disease developed in the early 1980s measured serum IgG and IgA antibodies to gliadin. These early tests had sensitivities and specificities in the 80%-90% range with lower specificities generally seen in adults compared to children. Endomysial antibody testing which came along in the mid-1980's moved celiac disease serologic testing forward especially in terms of specificity. However, this test was based on immunofluorescence that required either monkey esophagus or human umbilical cord tissue as a substrate. Each sample also required individual microscopic evaluation which increased the test expense and inter-observer and inter-site variability. There was an obvious need for tests that would be simpler to perform, highly sensitive and specific, and suitable for large-scale screening while also being economical.

Two *Gastroenterology* articles by Dieterich and colleague⁷ and Sulkanen and colleagues⁸ published in December 1998 heralded the modern era of celiac disease testing by reporting that IgA antibodies against tissue transglutaminase (tTG) were specific for celiac disease. The lab of Dieterich and colleagues had recently introduced enzyme-linked immunosorbent

assay (ELISA) for measurement of tTG antibodies, the major endomysial autoantigen. Their study in *Gastroenterology* aimed to develop and validate an improved ELISA that would reproducibly detect tTG antibodies to screen large populations⁷. This was a multicenter European study of children and adults in which 106 samples with untreated celiac disease were compared to 49 patients with celiac disease consuming a gluten-free diet and 114 healthy controls or individuals with other diagnoses. Similarly, with the aim of developing a simple, observer-independent laboratory test, Sulkanen and colleagues⁸ studied 136 serum samples from a Finnish population consisting mostly of children with untreated celiac disease and compared them to 207 controls. Both of these studies concluded that ELISA testing for IgA anti-tTG was well suited to detecting untreated celiac disease with sensitivities and specificities of 95%. The investigators also showed that the new ELISA test correlated well with the traditional endomysial antibody test and clearly showed improved predictive potential compared to the ELISA that was the one most commonly used assays at that time—IgA gliadin antibody ELISA. Additionally, IgA anti-tTG IgA titers were shown to fluctuate with dietary gluten exposure and to be reduced after introduction of a gluten-free diet.

These two studies published in *Gastroenterology* were instrumental in showing that screening for celiac disease could be simple, cost effective and accurate, paving the way for IgA anti-tTG to rapidly become the serologic test of choice in most settings. Guidelines from major gastroenterological organizations and the National Institutes of Health now recommend that the initial test to screen for celiac disease should be the IgA anti-tTG. The diagnostic ease made available to physicians and hospitals was in large part responsible for the rapid growth in celiac disease diagnosis seen in many parts of the world. These serologic tests have also permitted large-scale population-based studies published in *Gastroenterology* and elsewhere which have greatly expanded our understanding of hidden celiac disease as well as providing insight into long-term outcomes of undiagnosed celiac disease, permitting a type of sero-archeology. This has driven the awareness of celiac disease as a common chronic disorder.⁹⁻¹¹

Combining the diagnostic accuracy of the IgA anti-tTG with other serologic markers has brought into current discussion the possibility of a non-biopsy strategy to diagnose celiac disease. Given that IgA anti-tTG titers with levels >10 times the upper limit of normal have a high likelihood for (Marsh 3) villous atrophy, some medical experts are proposing that for certain patient populations such as symptomatic children or individuals living health-care resource limited countries, serologic screening alone may be sufficient to diagnosed celiac disease. This strategy would avoid the need for endoscopy with small intestine biopsy and the need for general anesthesia or sedation.

Clearly, investigators continue to assess and evaluate techniques and markers that might further improve about the diagnostic accuracy for celiac disease. It is also the most commonly used test for confirming response to a gluten-free diet. Additionally while IgA anti-tTG is the most commonly used test to confirm response to a gluten-free diet, there is clearly a need for the development of improved serologic tests or other biomarkers to monitor adherence to a gluten-free diet or intestinal recovery. Undoubtedly, a noninvasive marker of celiac disease activity would be of great clinical and research utility.

Recent papers in *Gastroenterology*¹²⁻¹⁴ have illustrated the difficulty of utilizing these types of measures for celiac disease trials. In addition, in clinical pathology, there are substantial challenges related to adequate sampling, vagaries of sample orientation, and inter-observer variability in interpretation that potentially detract from pathology's place as the gold standard for the diagnosis of celiac disease. Recently there has been an appreciation that patients may have gluten- or wheat-induced symptoms that are not due to celiac disease. Historic and recent papers in *Gastroenterology* have contributed to this debate. It suggests that there may be many patients on a gluten-free diet in whom there is little evidence that the problem is due to gluten, while many patients with celiac disease go undiagnosed and treated.¹⁵⁻¹⁷

In closing

The pages of *Gastroenterology* have chronicled the major advances in celiac disease in the last 75 years. It is expected in the next several years that new treatments, less invasive diagnostic tests, and further basic understanding of what triggers celiac disease will be featured in the next quarter century, topping what has truly been the golden age of *Gastroenterology*.

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