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THE UNIVERSITY OF CHICAGO
CELIAC
DISEASE CENTER

IMPROVING LIVES THROUGH AWARENESS, EDUCATION, AND RESEARCH

# Making Sense of Marsh

*Sonia S. Kupfer, MD*

## A patient recently brought me the pathology report of her small intestinal biopsy which read "Small Intestine, 3rd Portion Duodenum, Biopsy: CONSISTENT WITH CELIAC SPRUE (MARSH TYPE IIIb)". She inquired as to the meaning and implication of the Marsh type IIIb classification.

Sonia S. Kupfer, MD

The Marsh classification was introduced by M.N. Marsh in 1992[1] as a means to characterize the spectrum of changes seen in the small intestinal architecture under a microscope (known as histological changes). Marsh's original description ranged from type 0 to type 4 (Figure 1). This classification system has undergone some modifications since then but remains a cornerstone of diagnosing celiac disease. It was the great merit of Dr. Marsh to understand that there is a spectrum of inflammatory changes that can occur in celiac disease. Until his description, it was thought that only the most advanced changes (i.e. "Marsh III") were the hallmark of celiac disease.

Patients being evaluated for celiac disease should undergo an upper endoscopy (also known as an esophago-gastro-duodenoscopy or EGD) to obtain tissues samples called biopsies from the first part of the small intestine known as the duodenum. These samples must be obtained when an individual is on a diet that contains gluten, the trigger of intestinal inflammation in celiac disease. At least four biopsies should be taken from the 2nd or 3rd portion of the duodenum to assure an adequate amount of tissue for interpretation. These biopsies are sent to the pathology department where slices of the tissue are cut, placed on glass slides and stained with a dye to highlight the appearance of intestinal lining cells and inflammatory cells.

I describe the normal architecture of the small intestine as having finger-like projections of lining cells called epithelial cells. These projections, called villi, are responsible for normal absorption of nutrients including iron. Between villi are crevices called crypts that contain regenerating epithelial cells. The normal ratio of villous length to crypt length should be between 3:1 and 5:1. Finally, in health, there should be no more than 30 immune cells known as lymphocytes interspersed between the top layer of villous epithelial cells per 100 cells. The current Marsh classification spans from Marsh I to Marsh IV with Marsh III being subdivided into IIIa, IIIb and IIIc. The majority of celiac patients (50-60%) fall into the Marsh III category.

Marsh I histology comprises normal villous architecture with an increase in the number of intraepithelial lymphocytes (Figure 2a&b). This finding is not specific for celiac disease as it can be seen in other inflammatory and infectious diseases involving the small bowel or with drug injury. Marsh II histology includes increased intraepithelial lymphocytes along with a finding known as crypt hypertrophy in which the crypts appear enlarged (Figure 3).

Marsh III was originally described as the "destructive" change because it characterized flattening (also known as atrophy) of the villi. Later, Marsh III was sub-divided into IIIa, IIIb and IIIc to reflect the spectrum of villous atrophy along with crypt hypertrophy and increased intraepithelial lymphocytes. Marsh IIIa refers to partial villous atrophy (Figure 4a) in which the finger-like projections are partially shortened. Marsh IIIb, known as sub-total villous atrophy (Figure 4b), has finger-like projections that are visibly shortened but are still recognizable. Finally, Marsh IIIc, known as total villous atrophy (Figure 4c), is characterized by near total absence of villi. Marsh IV histology is called "hypoplastic" or completely atrophic and describes histology at the extreme end of gluten sensitivity. It is in this extremely uncommon setting that a lymphoma is more likely to occur.

In the majority of cases, patients with positive antibodies in the blood that are

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Stefano Guandalini, M.D.
**Founder and Medical Director**
University of Chicago Comer Children's Hospital
Section Chief, Pediatric Gastroenterology, Hepatology and Nutrition



The University of Chicago Celiac Disease Center is dedicated to raising awareness and diagnosis rates and meeting the critical needs of people affected by celiac disease nationwide through education, research and advocacy.

The contents of this newsletter are not intended to diagnose or recommend treatment for celiac disease. Please consult your healthcare provider with questions about your condition.

For more information about The University of Chicago Celiac Disease Center, please contact our office:

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Leo Rugai (right) and his siblings, Mia and Vinny, raise awareness and funds for celiac disease.

# Enterprising Seven-Year-Old Supports the Celiac Center

The University of Chicago Celiac Disease Center survives entirely on donations, and one youngster absorbed that fact very early on and worked hard to fundraise on our behalf. Leo Rugai, with the help of his parents and his siblings, Mia and Vinny, ran a highly professional lemonade stand one Saturday in July, and raised a considerable sum for The Celiac Center. In addition to lemonade, the stand also offered gluten-free cookies and brownies for sale. Leo was diagnosed with celiac disease at age five, and wanted to give something back to his doctor and dietitian at The University of Chicago Medical Center, "who helped [me] get better and understand about celiac disease." We appreciate Leo's hard work, and the support that he and his family offered to The Celiac Center.

## ANNUAL FREE CELIAC DISEASE BLOOD SCREENING—OCTOBER 10, 2009

**The annual free celiac disease blood screening is now full.** We are maintaining a waiting list for the screening. If you wish to be placed on the waiting list, please call our office at (773) 702-7593. The screening is open to individuals with a risk factor for celiac disease: a first or second degree relative with celiac disease, a related condition like type 1 diabetes, or symptoms. For more information, please see our website: www.celiacdisease.net/free-blood-screening.

During the screening, at 10:30 a.m., there will be a Q&A panel of experts taking questions on celiac disease. Anyone is welcome to attend the panel; no registration is necessary for that. In addition, all are invited to visit the gluten-free food vendors who are exhibiting at the event, as well as the information booth of our sponsor, Prometheus Laboratories.

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associated with celiac disease are found to have some degree of villous atrophy (Marsh III). However, a recent study[2] found that patients with positive blood tests (specifically anti-endomysial antibodies) and no villous atrophy but inflammation (Marsh I and II) still benefited from a gluten-free diet. Moreover, there are also so-called "seronegative" celiac patients (approximately 15% in one study[3]) who do not have positive blood tests but still have histological changes, albeit less severe changes, on their small intestinal biopsies.

In conclusion, the Marsh classification system is a standardized way in which to describe histological changes seen in the spectrum of celiac disease. While not all pathologists name a specific Marsh type, all reports should include descriptions of the number of intraepithelial lymphocytes, crypt hyperplasia and degree of villous atrophy. These descriptions help clinicians to assess the severity of the small intestinal damage as well as monitor response to a gluten-free diet. More research is needed to better understand how and why these histological changes occur and how they change in response to a gluten-free diet, so that we can all make the most of Marsh.

(Endnotes)
1 Marsh MN *Gastroenterology* 1992
2 Kurppa K *Gastroenterology* 2009
3 Abrams JA *Digestive Disease Sciences* 2004
4 Green PH *Best Practice and Research Clinical Gastroenterology* 2005

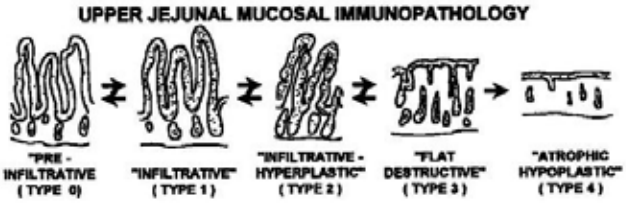
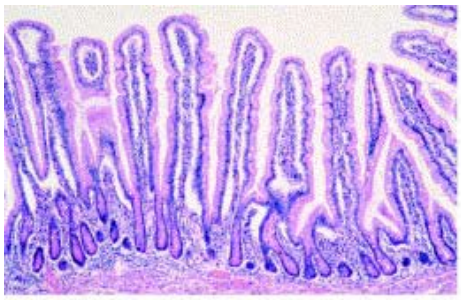
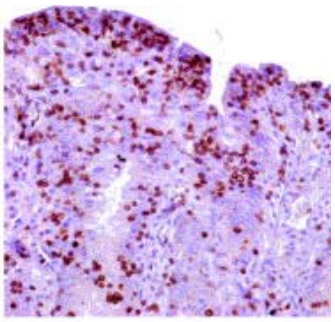


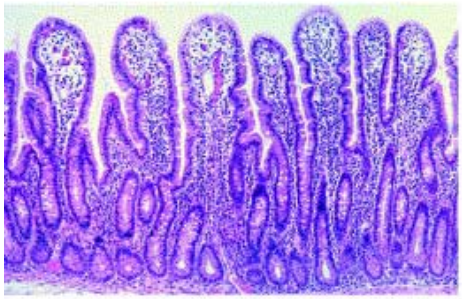

Figure 1: Original Marsh description of histology spectrum in celiac disease *Source: Marsh MN*[1]



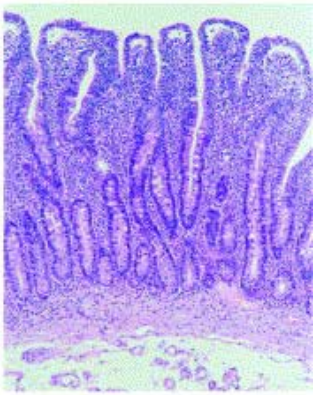
Marsh I: lymphocytic enteritis



Intraepithelial lymphocytosis
HE CD3 IEL

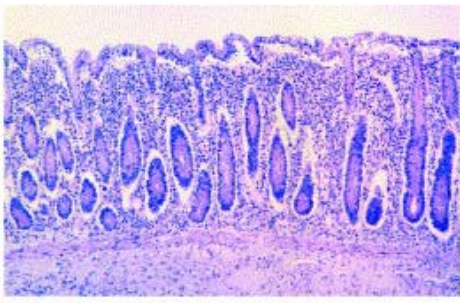


Marsh II: lymphocytic enteritis with crypthyperplasia



Marsh III A: partial villous atrophy

Marsh III B: subtotal villous atrophy



Marsh III C: total villous atrophy

# RESEARCH UPDATE

The University of Chicago Celiac Center research team continues to make strides toward developing the world's first mouse model of celiac disease. Once the mouse model is complete it will open the doors for therapeutic intervention to make living with celiac disease much easier, a vaccine to prevent celiac disease altogether or even a cure for the disease. Our campaign to raise $2 million and make this happen is underway. We need your help! If you can donate or would like to learn more please call 773-702-7593.


# University of Chicago Leads the Nation in Gluten-Free Food Options!

**The University of Chicago Medical Center recently announced that its kitchens are now certified gluten-free by the Gluten-Free Food Service Accreditation Program, achieving the nation's highest standards for gluten-free foodservice.** Patients and visitors who require a gluten-free diet can now enjoy safe gluten-free meals from their hospital bed, and in the food court of the Duchossois Center for Advanced Medicine, at Jazzman's Café in the Knapp Center for Biomedical Discovery and in the Billings Cafeteria. Approximately three million Americans suffer from celiac disease, the world's most common genetic autoimmune disorder, triggered by the ingestion of gluten—the protein found in wheat, barley and rye. Its only treatment is adherence to a strict, life-long glutenfree diet. Left untreated, celiac disease can lead to osteoporosis, thyroid disease and cancer.

"This is a major accomplishment," remarked Cynthia Kupper, RD, and executive director, Gluten Intolerance Group of North American, which oversees the Gluten-Free Food Service Accreditation Program. "Few have been able to meet and exceed our rigorous standards so quickly, let alone become the standard to be followed."

Mark Urquhart, vice president of facilities at The University of Chicago Medical Center, is pleased with the efforts put into the new venture: "We are going to great lengths, with the help of our partner Sodexo, to make certain our kitchens can safely and consistently provide gluten-free foods that are nutritionally balanced and taste good too."

Stefano Guandalini, MD, who founded The University of Chicago Celiac Disease Center in 2001 and serves as its medical director today, is delighted at this latest development. "Our patients have always received the best care in diagnosing the disease." Guandalini said. "It is wonderful that we can now participate fully in their treatment as well.

The University of Chicago Medical Center, in partnership with Sodexo, is offering a variety of gluten-free foods for inpatient menus, as well as retail sales. While the list of options is sure to expand, it currently includes trail mix, snack bars and chocolate bars and cookies from Enjoy Life Natural Brands; french fries and lasagna from Moo Moo's, as well as cheese and sausage pizzas from Marcello's Father & Son Restaurants. For visitors, these and more items can be found in dedicated cases, along with a dedicated preparation station for gluten-free foods.

## THE PORT CLINTON ART FESTIVAL WELCOMES THE CELIAC CENTER

The University of Chicago Celiac Disease Center was delighted to be selected as the sole non-profit organization to exhibit at the 2009 The Port Clinton Art Festival in Highland Park, IL this summer. Thousands of visitors learned about celiac disease, our Center and its many services. This event was an amazing opportunity to raise awareness and to educate the general public about the disease. Many thanks to Amdur Productions, Inc., and to the fabulous volunteers who staffed our booth. It is events like these that help us to achieve our mission!


## CARE PACKAGE SUPPORT

The Celiac Center wishes to recognize and give special thanks to our Silver Level Care Package Sponsors:

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Thank you to these sponsors and all our Care Package sponsors. For the complete list, please visit **www.CeliacDisease.net**.

**Save the Date** for our Annual Benefit … **May 14, 2010** at the Swissôtel!