Gastroenterology and Hepatology From Bed to Bench.
2023 **RIGLD**, Research Institute for Gastroenterology and Liver Diseases

EDITORIAL

Marsh's legacy and persistency in subjective interpretation of coeliac disease's histology

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(Please cite as: **Rostami K, Danciu M. Marsh's legacy and persistency in subjective interpretation of coeliac disease's histology. Gastroenterol Hepatol Bed Bench 2023;16(2):108-109. https://doi.org/10.22037/ghfbb.v16i2.2783).**

This issue of GHFBB is dedicated to Professor Michael N Marsh who passed away on 12 July 2021. Professor Marsh was a pioneering figure in basic immune-histopathology of small intestine, in particular coeliac disease (CeD). As Professor Ensari highlighted, great minds deserve to be acknowledged while still alive though their true recognition usually takes place afterwards (1). Even though he personally may not have received the attention he deserved during his lifetime, but his name become inseparable from CeD as reflected in most of publications on CeD since late 1960s (1).

He defined the gluten induced inflammation and the spectrum of enteropathy in distinctive phenotypes. His pioneering work funded the platform of quantitative histology (2-5) by development of a computerized methodology for accurate measurement of mucosal specimens and reporting histology in clinical practice. *This was an enormous advance in understanding the damaged intestinal tissues seen in gluten sensitivity – both in comparison with "normal" tissues, and during the progress of these abnormal specimens – from 'normal' to their severest degree of mucosal changes* (6, 7).

Marsh classification has also been erroneously built into subjective and inaccurate interpretation that often doesn't correlate with clinical presentations of coeliac disease (8-10).

Professor Marsh's background was clinical medicine with a major academic component in biomedical research. He published over 200 research papers, chapters and abstracts, together with three monographs within the fields of intestinal immunopathology and abnormal structural morphology.

These studies engaged with the response of genetically-susceptible people to the effects of cultivated gluten containing grains that trigger immunopathological responses of the intestinal mucosa to these environmental antigenic challenges, whether from Gluten Immunogenic Peptides, microbial and parasite, or tissue histo-incompatibilities (11).

A significant part of his research career was focused on exploring the pathological remodeling of small intestinal mucosa known as the Marsh Classification (11). Professor Marsh heavily criticized the inaccurate translation of the flat mucosa under *"atrophy" or villus atrophy*. He demonstrated this kind of perception preclude accurate understandings of the mucosal histopathogenesis that may result in subjective and inaccurate interpretation and reporting of histology (8, 12). *In fact, neither CeD nor NCGS mucosal changes could be due to an atrophic process simply because structural recovery of villi recover*

Received: 08 March 2023 *Accepted*: 04 April 2023
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in most cases following removal of the immunogenic antigens (2, 13, 14).

Reporting histology is facing challenges related to technical errors incurred by subjective interpretations ensuing from the continued use of older and flawed methods of tissue evaluation like *atrophy concept* despite extensive refining and breakthrough in the *computing 3-D structure of intestinal mucosal specimens* initiated by Professor Marsh in 1970. All naturally occurring irregular tissue shapes could be well uniformly expressed by this novel, uniform 3-D numerical approach which was an expansive advance in understanding the abnormal intestinal tissues seen in gluten sensitivity – both in comparison with "normal" tissues, and during the progress of these abnormal specimens – from 'normal' to their severest degree phenotype. Quantitative histology represents the most reliable assessment tool to approximate the clinical presentation to histological finding during both initial and follow up histological assessments.

Professor Marsh's contribution was and still is a "wake-up call" to the scientific and medical communities, dealing with matters concerned with coeliac disease. Even though his legacy created a moment to turn away from all the old-fashioned concepts (1950-60 style), regrettably, the coeliac communities hanging on to meaningless terminologies like *villus atrophy* that translate in subjective reporting histology. It is important to point out that undertaking a gastroscopy procedure and biopsy is not only a risky procedure for the patients but very time consuming for both patients and endoscopists. More remarkably the endoscopy and biopsy-taking are also associated with potential harms and risks like bleeding perforation, discomfort and sedation related complications. Organizing such an expensive, time consuming and hazardous journey might not be of much value if reading and reporting histology continue to be subjective and unreliable. Quantitative histology, therefore, it should replace the current subjective practice. A simple start would be counting the intraepithelial lymphocytes and assessing the villus height/crypt depth ratio incorporated in a standard report. We hope using this opportunity of paying respect to Professor Marsh's accomplishment, will promote application of quantitative histology and would stimulate future original ideas for best practicing histology.

Conflict of interests

The authors declare that they have no conflict of interest.

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