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REVIEW ARTICLE

No-biopsy diagnostic approach to coeliac disease

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ABSTRACT

This brief review outlines contributions that Michael Marsh and others made to understanding the structure and function of the upper small bowel mucosa and the formation of abnormalities that occur in coeliac disease (CD). He introduced his classification of lesions 30 years ago that has been widely adopted. The development and use of serological tests to screen for and diagnose CD in children and adults without the need for a small bowel biopsy in a considerable proportion is also recognised and will gain traction.

Keywords: Coeliac disease, Diagnosis, Small bowel mucosa, Small bowel biopsy, Serology.

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Introduction

Michael Marsh expended much of his research effort over many years in striving to improve understanding of the morphology of jejunal mucosa in health and disease, with reference to CD and how the lesions in this condition arise when patients ingest gluten. He had an enquiring, agile mind and was still generating ideas until the time of his death in July 2021 (1). I knew him for over 40 years. We had many discussions on aspects of CD and shared in several meetings together (Figures 1 and 2). He invited me to contribute a chapter on the malignant complications of CD in the book Coeliac Disease that he edited and published in 1992. I discussed with him the concept of the serological diagnosis of CD on a number of occasions and he said he could entertain this notion if the evidence for it was robust. He was always ready to embrace new ideas. I write this review in fond remembrance of him and his remarkable contribution to unravelling some of the mysteries surrounding CD.

In his landmark paper, on the coeliac affection, published in 1888 Samuel Gee proclaimed that, "Whether atrophy of the glandular crypts of the intestines be ever or always present I cannot tell" (2). In 1914 Poynton and colleagues presented case histories of nine children with chronic, recurrent diarrhoea in childhood possibly representing coeliac disease (CD) (3). The main importance of the report centres on the findings at autopsy carried out 24 hours after death in the only fatal case. Published photomicrographs of sections of mucosa lining the jejunum showed marked round cell infiltration. Although there was tangential cutting of the sections the villi appear absent and crypts elongated. Does this represent unrecognised villous atrophy is an intriguing question? In any event an attempt was being made probably for the first time to link clinical and histological findings in coeliac disease. Thaysen, in his influential monograph, non-tropical sprue. A study of idiopathic steatorrhoea published in 1932, based on limited evidence from only 4 cases considered that changes observed in the jejunal mucosa were non-specific (4). He had a high reputation as a pathologist and his erroneous views held sway for almost twenty years. Then Schein in 1947 observed that normal villi were, "replaced by broad based, squat, bulbous and plump villi" in an autopsy on a 15-years old boy with idiopathic steatorrhea (5) and confirmed these findings in a further six cases (6). Paulley at about the same time showed that the jejunal mucosa obtained at laparotomy from four patients with idiopathic steatorrhoea was abnormal with broadened villi and a

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Figure 1. Michael Marsh, Rosemary Holmes and Geoffrey Holmes enjoying the good life at a conference on the Epidemiology of Coeliac Disease held on Capri in 1991. Marsh gave a paper, *Gluten sensitivity and latency; the histological background* and Holmes on the *Long-term health risks for unrecognised coeliac patients.*

Figure 2. Michael Marsh and Rosemary Holmes at the same conference in Capri in 1991.

dense inflammatory cell infiltrate (7). It was beyond doubt that the upper small bowel in CD was abnormal. This forced the development of a method whereby peroral jejunal biopsies could be obtained quickly and safely (8). This allowed coeliac disease for the first time to be defined morphologically and provoked

intense speculation as to how the mucosa assumed these abnormal appearances. Unsurprisingly, an atrophic process was initially considered a likely explanation (9) but these researchers could only view the mucosa in two dimensions and when a three dimensional approach was undertaken matters were found to be more complex (10). Autolysis of the mucosa in health and disease showed that crypts outnumber villi. In the normal state, cells migrate out of the crypts along inter-villous ridges and on to the villi (11). Scanning and electron microscopy studies extended these observations (12, 13). A flat mucosa develops as the mucosa is remodelled with expansion upwards of inter-villous ridges and progressive shortening by about two-thirds of the villi resulting in irregular shaped plateaux that rise above the openings of the crypts. The villous core is also remodelled (14). The whole process is not so much atrophic as hypertrophic. Around 1960 a classification of lesions in CD based on the notion of atrophy was devised using terms such as partial and subtotal villous atrophy (15). Although this was based on a misconception, it was of value and brought some uniformity into the reporting of histological lesions and is still used but decreasingly so.

When those who are genetically predisposed to develop CD, are exposed to gluten, after a time that varies widely, the immunological cascade is triggered that leads to histological and usually but not always clinical disease. When a gluten free diet is taken this process reverses. The severe, flat lesion characteristic of CD must evolve through stages from normal mucosa because no one is born with CD. Evidence for the existence of early mucosal lesions came from observations made in dermatitis herpetiformis (DH) (16, 17) and first-degree relatives of those with CD (18). Moreover, it was shown that administration of a high gluten intake can provoke mucosal deterioration in those with DH from normal to that in keeping with CD (19).

These considerations stimulated researchers to explore in detail the structure of the small bowel mucosa and the influences that provoke mucosal damage. Marsh was at the forefront of this enterprise. In meticulously performed studies he contributed to better understanding of the morphology and function of cellular components of the mucosa culminating in his ground breaking paper published in 1992, Gluten, major histocompatibility complex, and the small intestine. A molecular and immunogenic approach to the spectrum of gluten sensitivity ("celiac disease") (20). In this he proposed a new classification of the mucosal lesions seen in CD that avoids any reference to atrophy and consists of stages 0 – 4 reflecting the pathological phases the mucosa passes through to become flat. Stage 4 is no longer used as it is now considered to represent lymphomatous destruction of the mucosa. This scheme is widely used and has made possible standardisation of lesions so that different researchers can better compare results with others. Oberhuber in 1999 proposed subdividing stage 3 into categories a, b and c depending on the degree of villous flattening (21). Marsh steadfastly rejected this modification because he maintained that villous structures are not present to grade in this way (13). In March 2013 he arranged a stimulating meeting in Manchester University when experts met to celebrate the 21st anniversary of the Marsh classification (Figure 3).

In earlier years patients presenting with classical symptoms of weight loss, diarrhoea and fatty stools indicative of malabsorption, a flat upper gastrointestinal mucosa with improvement on GFD, the diagnosis of CD was straightforward and secure. However, problems in establishing the diagnosis may arise in those who present with non-classical or mild symptoms and exhibit only minor changes in mucosal morphology. Do such patients have CD or not? Under and over diagnosis must occur causing attendant problems for patients. These considerations stimulated researchers to look for other indicators of CD and attention turned to blood markers. Antigliadin antibodies were detected in the serum and reduced following dietary gluten withdrawal (22). The predictive value of a positive test was only 50% so while of some value to clinicians was less than ideal.

A new era dawned with regard to serology when in 1983 endomysial antibodies (EMAs) were detected in the serum in CD and DH (23, 24). The enzyme tissue transglutaminase (TTG) was identified as the endomysial antigen in 1997 (25). These observations led to the development of serological tests for CD and with high sensitivity and specificity prove almost ideal investigations. These tests allowed large scale screening studies that showed CD to have a

The Marsh classification – 21st anniversary

A meeting to be held at the University of Manchester, UK.
on Tuesday 5th March 2013

0830-0930	Registration
0930-0940	Welcome & introduction - Prof. Peter Howdle *(University of Leeds)*
0940-1030	The Marsh classification: – Matters arising - Prof. M.N.Marsh *(University of Oxford)*
10:30-10:45	Distinguishing duodenitis from the early Marsh I -II lesion - Carol Semrad *(University of Chicago)*
10:45-11:00	General discussion
11:00-1140	Tea/coffee
11:40-12:00	What shall we do with Marsh I Lesions?" - Dr.Maria Esteve Comas *(University of Barcelona)*
12:00-12:40	Diagnostic applications - Dr. Shethah Morgan *(Astrazeneca, UK)*
12:40-12:55	Summary - Prof. Peter Howdle *(University of Leeds)*
12:55- 14:00	Lunch
1400-14:45	Gluten-related diseases: - beyond the gut - Dr. Marios Hadjivassiliou *(University of Sheffield)*
1445-1530	Lymphoma in coeliac disease - Dr. Geoffrey Holmes *(University of Derby)*
1530-1600	Dietary & other considerations - Ms. Sarah Sleet *(UK Coeliac Association, London)*
16:00-16:20	Tea/Coffee
1620-1630	Dimensional perspectives - Mr. Peter Crowe, *(University of Manchester)*
1630-1700	General discussion - Prof. David Sanders *(University of Sheffield)*

Figure 3. Programme for the 21st anniversary of the Marsh classification.

prevalence in many locations of about 1% making it one of the most common chronic disorders in the western world (26).

Upper gastrointestinal endoscopy to obtain duodenal biopsies is not without its difficulties. In many patients, sedation or even general anaesthetic is

required and is expensive and time consuming for all concerned (27). In addition, histological interpretation is not always straightforward. In light of these considerations researches asked whether serological tests could be employed to established the diagnosis of CD without the necessity of biopsy. Investigations have shown that using defined levels of TTG antibodies that equate to histology characteristic of CD about 50% of adults (28, 29) and paediatric cases (30) can be diagnosed using serological tests alone. Further abundant evidence supports this approach (31). This principle has been incorporated into the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) for the diagnosis of CD in 2012 (32) and modified in 2020 (33). Gastroenterologists in adult practice have been reluctant to move down this path, although the COVID-19 pandemic that restricted endoscopy has contributed to a reappraisal of practice (34). Several recent studies have indicated that this is a safe approach for the diagnosis of CD.

An investigation from Finland employing large groups of individuals with variable pre-test probabilities illustrated that a third of subjects with CD can avoid biopsy based on levels of TTG > X 10 upper limit of normal (ULN) and importantly no serious co-morbidities will be overlooked (35). Similar conclusions regarding this mode of diagnosis were arrived at in a study from Sheffield (36) and further support came from New Zealand (37). A service review of routine clinical practice in Scotland employing data from 14 Health Boards and presented as a "real world" experience offered further support in that with antibody levels ≥ 10 X ULN the positive predictive value (PPV) was 99.38% and no co-morbidities were found in this group at either upper or lower gastrointestinal endoscopy (38). Throughout Scotland 31% of new positive patients could have been diagnosed without the need for biopsy. These results indicate that the ESPGHAN guidelines can be safely extended to adults.

Taken together, these recent series should help allay fears of those who have reservations about a no-biopsy approach to the diagnosis of CD. Several issues need emphasis. TTG antibody positivity is insufficient to make the diagnosis. Values in terms of the ULN equating to characteristic mucosal architecture seen in CD using high performing kits locally validated have to be taken strictly into account. Small bowel biopsy still has an important place when serological criteria are not met or clinicians feel that they are not dealing with a straightforward patient. Also, expert dieticians and clinicians familiar with the coeliac condition must be involved in the supervision of patients if optimum care is to be provided. This field will further develop as new tests become available and their use refined. Morphological criteria for diagnosing CD have served clinicians well for decades but are giving way to the serological approach which offers many benefits for patients and their attendants.

Conflict of interests

All authors declare that they have no conflict of interest.

References

1. Rostami K, Ensari A, Marsh MN, Srivastava A, Villanacci V, Carroccio A, et al. Gluten induces subtle histological changes in duodenal mucosa of patients with non-coeliac gluten sensitivity: a multicentre study. Nutrients 2022;14:2487.

2. Gee S. On the coeliac affection. St Bartholomew's hospital reports 1888;24:17-20.

3. Poynton FJ, Armstrong RR, Nabarro DN. A Contribution to the Study of a Group of Cases of Chronic Recurrent Diarrhoea in Childhood. Proc R Soc Med 1914;7:10-32.

4. Thaysen ThEH, Ed. Non-tropical sprue. A study of idiopathic steatorrhoea. London: Oxford University Press; 1932.

5. Schein J. Syndrome on non tropical sprue with hitherto undescribed lesions of the intestine. Gastroenterology 1947;8:438-460.

6. Aldersberg D, Schein D. Clinical and pathological studies in sprue. J Am Assoc 1947;134:1459-1467.

7. Paulley JW. Observation on the aetiology of idiopathic steatorrhoea; jejunal and lymph-node biopsies. Br Med J 1954;2:1318-1321.

8. Shiner M. Jejunal-biopsy tube. Lancet 1956;270:85.

9. Sakula J, Shiner M. Coeliac disease with atrophy of the small-intestinal mucosa. Lancet 1957:876-877.

10. Cocco AE, Dohrmann MJ, Hendrix TR. Reconstruction of normal jejunal biopsies: three-dimensional histology. Gastroenterology. 1966;51:24-31.

11. Loehry CA, Creamer B. Three-dimensional structure of the human small intestinal mucosa in health and disease. Gut 1969;10:6-12.

12. Toner PG, Carr KE, Ferguson A, Mackay C. Scanning and transmission electron microscopic studies of human intestinal mucosa. Gut 1970;11:471-481.

13. Marsh MN, Johnson MW, Rostami K. Mucosal histopathology in celiac disease; a rebuttal of Oberhuber's sub-

division of Marsh III. Gastroenterol Hepatol Bed Bench 2015;8:99-109.

14. Ensari A, Marsh MN. Diagnosing celiac disease: A critical overview. Turk J Gastroenterol 2019;30:389-397.

15. Shiner M, Doniach I. Histopathologic studies in steatorrhea. Gastroenterology 1960;38:419-440.

16. Fry L, Seah PP, McMinn RM, Hoffbrand AV. Lymphocytic infiltration of epithelium in diagnosis of gluten-sensitive enteropathy. Br Med J 1972;3:371-374.

17. Fry L, Seah PP, Harper PG, Hoffbrand AV, McMinn RM. The small intestine in dermatitis herpetiformis. J Clin Pathol 1974;27:817-824.

18. Marsh MN, Bjarnason I, Shaw J, Ellis A, Baker R, Peters TJ. Studies of intestinal lymphoid tissue. XIV--HLA status, mucosal morphology, permeability and epithelial lymphocyte populations in first degree relatives of patients with coeliac disease. Gut 1990;31:32-36.

19. Weinstein WM. Latent celiac sprue. Gastroenterology 1974;66:489-493.

20. Marsh MN. Gluten, major histocompatibility complex, and the small intestine. A molecular and immunobiologic approach to the spectrum of gluten sensitivity ('celiac sprue'). Gastroenterology 1992;102:330-354.

21. Oberhuber G, Granditsch G, Vogelsang H. The histopathology of coeliac disease: time for a standardized report scheme for pathologists. Eur J Gastroenterol Hepatol 1999;11:1185-1194.

22. Hill PG, Thompson SP, Holmes GK. IgA anti-gliadin antibodies in adult celiac disease. Clin Chem 1991;37:647-650.

23. Chorzelski TP, Sulej J, Tchorzewska H, Jablonska S, Beutner EH, Kumar V. IgA class endomysium antibodies in dermatitis herpetiformis and coeliac disease. Ann N Y Acad Sci 1983;420:325-334.

24. Chorzelski TP, Beutner EH, Sulej J, Tchorzewska H, Jablonska S, Kumar V, et al. IgA anti-endomysium antibody. A new immunological marker of dermatitis herpetiformis and coeliac disease. Br J Dermatol 1984;111:395-402.

25. Dieterich W, Ehnis T, Bauer M, Donner P, Volta U, Riecken EO, et al. Identification of tissue transglutaminase as the autoantigen of celiac disease. Nat Med 1997;3:797-801.

26. West J, Logan RF, Hill PG, Lloyd A, Lewis S, Hubbard R, et al. Seroprevalence, correlates, and characteristics of undetected coeliac disease in England. Gut 2003;52:960-965.

27. Paul SP, Sandhu BK, Spray CH, Basude D, Ramani P. Evidence Supporting Serology-based Pathway for Diagnosing Celiac Disease in Asymptomatic Children From High-risk Groups. J Pediatr Gastroenterol Nutr 2018;66:641-644.

28. Hill PG, Holmes GK. Coeliac disease: a biopsy is not always necessary for diagnosis. Aliment Pharmacol Ther 2008;27:572-577.

29. Holmes GKT, Hill PG. Coeliac disease: further evidence that biopsy is not always necessary for diagnosis. Eur J Gastroenterol Hepatol 2017;29:1189-1190.

30. Werkstetter KJ, Korponay-Szabo IR, Popp A, Villanacci V, Salemme M, Heilig G, et al. Accuracy in Diagnosis of Celiac Disease Without Biopsies in Clinical Practice. Gastroenterology 2017;153:924-935.

31. Holmes G, Ciacci C. The serological diagnosis of coeliac disease - a step forward. Gastroenterol Hepatol Bed Bench 2018;11:209-215.

32. Husby S, Koletzko S, Korponay-Szabo IR, Mearin ML, Phillips A, Shamir R, et al. European Society for Pediatric Gastroenterology, Hepatology, and Nutrition guidelines for the diagnosis of coeliac disease. J Pediatr Gastroenterol Nutr. 2012;54:136-160.

33. Husby S, Koletzko S, Korponay-Szabo I, Kurppa K, Mearin ML, Ribes-Koninckx C, et al. European Society Paediatric Gastroenterology, Hepatology and Nutrition Guidelines for Diagnosing Coeliac Disease 2020. J Pediatr Gastroenterol Nutr 2020;70:141-156.

34. Johnston RD, Chan YJ, Mubashar T, Bailey JR, Paul SP. No-biopsy pathway following the interim BSG guidance reliably diagnoses adult coeliac disease. Frontline Gastroenterol 2020;13:73-76.

35. Fuchs V, Kurppa K, Huhtala H, Laurila K, Maki M, Collin P, et al. Serology-based criteria for adult coeliac disease have excellent accuracy across the range of pre-test probabilities. Aliment Pharmacol Ther 2019;49:277-284.

36. Penny HA, Raju SA, Lau MS, Marks LJ, Baggus EM, Bai JC, et al. Accuracy of a no-biopsy approach for the diagnosis of coeliac disease across different adult cohorts. Gut 2021;70:876-883.

37. Beig J, Rostami K, Hayman DTS, Hassan S, Gerred S, Ogra R. Is duodenal biopsy always necessary for the diagnosis of coeliac disease in adult patients with high anti-tissue transglutaminase (TTG) antibody titres? Frontline Gastroenterol 2022;13:287-294.

38. Hoyle A, Gillett P, Gillett HR, Borg R, Nottley S, Farrow S, et al. No-biopsy strategy for coeliac disease is applicable in adult patients: a 'real-world' Scottish experience. Frontline Gastroenterol 2023;14:97-102.