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Breaking bread!

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Humankind has existed for 2·5 million years but only in the past 10 000 years have we been exposed to wheat. Therefore, it could be considered that wheat (gluten) is a novel introduction to humankind's diet! Prior to 1939, the rationing system had already been devised. This led to an imperative to try to increase agricultural production. Thus, it was agreed in 1941 that there was a need to establish a Nutrition Society. The very roots of the Society were geared towards necessarily increasing the production of wheat. This goal was achieved and by the end of the 20th century, global wheat output had expanded by 5-fold. Perhaps, as a result, the epidemiology of coeliac disease (CD) or gluten sensitive enteropathy has changed. CD now affects 1 % or more of all adults. Despite this, delays in diagnosis are common, for every adult patient diagnosed approximately three–four cases are undetected. This review explores humankind's relationship with gluten, wheat chemistry, the rising prevalence of modern CD and the new entity of non-coeliac gluten or wheat sensitivity. The nutritional interventions of a low fermentable oligo-, di- and mono-saccharides and polyols diet and gluten-free diet (GFD) for irritable bowel syndrome and the evidence to support this approach (including our own published work) are also reviewed. There appears to be a rising interest in the GFD as a 'lifestyler', 'free from' or 'clean eater' choice, causing concern. Restrictive diets may lead to potential nutritional implications, with long-term effects requiring further exploration.

Coeliac disease: Gluten: Wheat: Low FODMAP diet: Irritable bowel syndrome

What is gluten?

Gluten is the main storage protein used by some classes of flowering plants to nourish seeds during development and germination[1]. It is a high molecular weight protein found in the endosperm of grass-related grains, including wheat, barley and rye. It is the composite of two classes of protein, a glutenin and a prolamin (gliadin in wheat), which can be fractionated to produce α, β and γ peptides. As plant seeds are the plant tissue most consumed by men, seed storage proteins have been long studied and characterised. Wheat gluten was first isolated in 1745[2] and since then further advances in the knowledge of protein structure have established that the prolamin components of gluten are responsible for the ability to process wheat to form dough by means of creating a viscoelastic network[3,4].

History of gluten and mankind

Humankind has existed for about 2·5 million years with cereal crops being introduced to the human diet relatively recently, during the Neolithic Revolution about 10 000 years ago. This saw a transition from hunting and gathering of food to settled agriculture. The first signs of cultivation have been found in the Fertile Crescent in South West Asia and the subsequent farming expansion lasted until 4000 BC[5].

Cereal harvesting and consumption have gradually increased since then, until its major outbreak in the 20th century. Between the two World Wars, the need to develop a more efficient rationing system and increased agricultural production became evident. The improvement of wheat cultivation became one of the main objectives of the Nutrition Society which was founded in 1941 in Britain to advance the scientific study of nutrition and its application to the maintenance of health[6]. This goal was achieved, with modern day global wheat production amounting to over 700 million tonnes per year (http://faostat.fao.org).

Moreover, the need to ensure an efficient agricultural production has led to the artificial breeding and selection of wheat variants with better adaption to extreme climate conditions, bread-making qualities and resistance to diseases[7]. This has contributed to a dramatic change in the genetic variety and possibly immunogenic qualities of wheat over time[7]. Currently, about 95 % of the wheat grown worldwide is bread wheat (*Triticum aestivum*), a hexaploid species which resulted from the spontaneous hybridisations between more ancient tetraploid (Emmer) and diploid species (Wild grass) and was then selected by farmers for its superior qualities and yields, such as higher number and bigger seeds[8]. Furthermore, the awareness of the potential role of gluten in processing food has led to the industrial extraction of gluten from plant seeds and its use in the baking industry as an additive with various functions, such as increasing elasticity and stability of food products or as a protein supplement to low-protein food[9].

It is, therefore, believed that the rate of increase in gluten exposure, from the development of wheat cultivation to modern intensive farming, along with its genetic modification, has been too high to give our immune system the time to develop optimal adaptive mechanisms, although this 'evolutionary theory' has yet to be fully clarified[10]. Nevertheless, perhaps as a result of all these factors have come the changing epidemiology of coeliac disease (CD) and other gluten-related disorders.

Coeliac disease

CD is a chronic inflammatory enteropathy caused by dietary exposure to gluten[11]. Although the manifestations of CD may have been described more than 100 years ago, it is only from the 1940s that the relationship between gluten and CD has been established[12]. However, more than 70 years later, the pathogenesis of CD has yet to be fully elucidated, but it is agreed that the ingestion of gluten in genetically predisposed individuals carrying the HLA-DQ2 and/or DQ8 alleles can arise in a T-cell mediated immune reaction, leading to small bowel villous atrophy and subsequent clinical manifestations[13,14].

Historically, CD was rare with an incidence in the UK of 1 in 8000 being reported in the 1950s[15]. However, contemporary epidemiological studies estimate a worldwide prevalence of approximately 1 in 100 or 1 %[16,17]. Nevertheless, a considerable proportion of patients still remain undiagnosed with estimates that for every patient diagnosed with CD approximately three cases are yet to be detected[18]. Furthermore, our understanding of the coeliac patient has drastically changed. Whereas previously most cases diagnosed were children, it has now been shown that in fact adult cases (characteristically presenting between the fourth to sixth decades) are more frequent occurring at a ratio of 9:1 compared with the paediatric cohort. We are also seeing new horizons of CD where previously rice-based cultures such as China and the Indian sub-continent are now 'Westernising' their diet with the introduction of bread, pasta and pizza, CD is being reported in epidemiological studies[19–22].

The clinical manifestations of CD are heterogeneous. The classical presentation of malabsorption characterised by chronic diarrhoea, weight loss and failure to thrive is relatively rare. Far more commonly, patients present with non-classical symptoms which include irritable bowel syndrome (IBS)[23], iron deficiency anaemia[24], osteoporosis[25], ataxia or peripheral neuropathy[26]. Indeed, given that IBS is extremely common affecting about 11 % of the population national guidelines now propose that all patients presenting with such symptoms should have CD excluded[25]. In fact, a meta-analysis has shown that CD accounts for 4 % of those cases presenting with IBS[27,28].

To date, the only therapy for CD is a lifelong gluten-free diet (GFD)[29]. Adherence to a restrictive GFD leads to gradual healing of the mucosa of the small bowel and to the resolution of malabsorptive symptoms[30], although there is a consistent proportion of patients who continue to show a low grade of mucosal inflammation even on a GFD[31]. The Codex standard (which is used in the UK and Europe), and similarly the Food and Drug Administration in the USA, suggest that foods containing 20 mg/kg or less of gluten or 20 parts per million of gluten can be labelled as 'gluten-free' and that foods containing between 21 and 100 parts per million of gluten can be labelled as 'very low gluten'.

Non-coeliac gluten sensitivity

The definition of non-coeliac gluten sensitivity (NCGS) encompasses a spectrum of gastrointestinal and extra-intestinal symptoms which are triggered by the ingestion of gluten-containing food, yet in the absence of the serologic and histological hallmarks of CD or wheat allergy[32,33]. This terminology was defined following double-blind placebo-controlled studies showing gluten *per se* to induce symptoms in the absence of CD[34]. The symptoms reported include abdominal pain, diarrhoea, constipation and bloating, as well as chronic fatigue, behavioural changes, bone or joint pain and muscle cramps[32–34]. Symptoms typically occur shortly after the ingestion of gluten, resolve on a GFD and relapse after gluten challenge.

NCGS is part of a spectrum of gluten-related disorders, as outlined in Fig. 1. It is often self-reported or suspected by the patients themselves and then confirmed by physicians after other forms of gluten-related disorders have been excluded[32]. In fact, while the diagnosis of CD can be made in most patients on the basis of positive serology (presence of endomysial and/or tissue transglutaminase
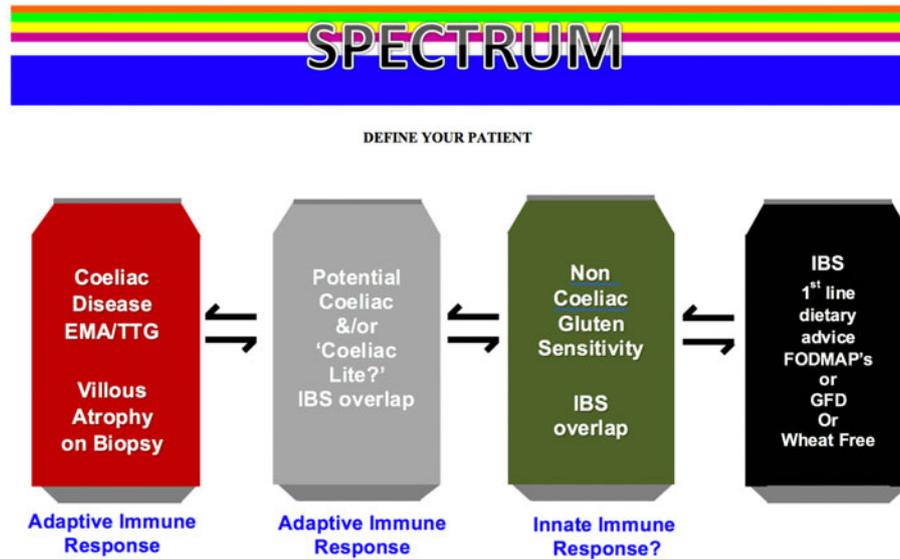
Fig. 1. (Colour online) Spectrum of gluten-related disorders. EMA, endomysial antibodies; TTG, tissue transglutaminase; IBS, irritable bowel syndrome; FODMAP, fermentable oligo-, di- and mono-saccharides and polyols; GFD, gluten-free diet.

antibodies) and villous atrophy at duodenal biopsy[29,35], patients with NCGS present with negative serology and absence of villous atrophy[33]. However, the presence of antigliadin antibodies has been described in up to 50 % patients with NCGS[36–38], and an increase in duodenal intraepithelial lymphocytes, corresponding to the grade 1 of the Marsh–Oberhuber histologic classification, has been observed in a subset of patients with NCGS in the absence of other criteria for CD[36]. Moreover, the prevalence of NCGS seem to be higher in first-degree relatives of subjects with CD, and carriers of HLA-DQ2 and/or DQ8 seem to be at greater risk of experiencing symptoms related to NCGS than the general population although these data have not been confirmed in different epidemiological studies[36,38].

The growing interest in this clinical entity has led to the advancing of several hypotheses about NCGS pathogenesis, yet all of them still remain to be fully elucidated. Altered intestinal permeability similar to that involved in the pathogenesis of CD and activation of the innate immune system following gluten exposure have been considered and are under investigation[33,39–41].

In the absence of clear serologic or histopathologic criteria to orient toward a diagnosis, NCGS has often been perceived as being an IBS-like entity, mainly due to an evident overlap of clinical features between those two syndromes[42]. Furthermore, it has also been observed that IBS patients, previously naive to the effects of gluten, may benefit from a GFD[43]. To date, the reference standard for the diagnosis of 'true' NCGS is an elimination diet followed by double-blind placebo-controlled gluten challenge, a method which could hardly be introduced into clinical practice[33]. Recently, a diagnostic algorithm based on the absence or presence of, clinical, serologic and histological criteria has been proposed to

diagnose and differentiate NCGS from CD[44]. This novel study provides a clinically pragmatic approach as it takes into consideration the difficulties that arise when evaluating patients who present with gluten-based sensitivity and are already taking a GFD, which in cases of CD can lead to negative coeliac serology and normal duodenal biopsies[44]. It has been suggested that where available a negative HLA-DQ2 and DQ8 genotype is useful in that it can exclude CD with certainty given its 100 % negative predictive value; this will account for almost half of presenting cases[45]. However, if HLA-DQ typing is not readily available, or is positive, then a gluten challenge followed by coeliac investigations is required[44]. Traditionally, a gluten challenge has been suggested to be ≥10 g gluten (equivalent to about four slices of bread) daily for 6 weeks, prior to formalised testing. More recently this could be as little as ≥3 g gluten (equivalent to 1·5 slices of bread) daily for 2 weeks[46], which may be more suited to patients specifically presenting with gluten sensitivity. By adopting this approach in secondary-care gastrointestinal practice only a minority of adult patients will have a diagnosis of CD (7 %), with the remaining 93 % subsequently diagnosed as NCGS[45]. Furthermore, individuals with NCGS do not appear to suffer the nutritional deficiencies (anaemia and haematinic deficiencies) and low mean BMI commonly associated with CD, which is a reflection of the state of normal villi as seen in NCGS as opposed to the villous atrophy in CD[45].

Gluten, fermentable oligo-, di- and mono-saccharides and polyols and irritable bowel syndrome

Diet appears to play a pivotal role in symptom generation in patients with IBS, with two-thirds of patients

Table 1. Main characteristics of the gluten-free diet and the low fermentable oligo-, di-, and mono-saccharides and polyols (FODMAP) diet

	Gluten-free diet	Low FODMAP diet
Food component to avoid	Gluten	Fructose Lactose Fructans Galactans Polyols
Food containing the component	Wheat, including varieties (spelt, kamut, farro and durum), barley, rye and triticale Gluten used as an additive in various manufactured food	High fructose: apples, pears, peaches, mango, sugar snap peas, watermelon; honey, sweeteners High lactose: Milk, yoghurt, fresh cheese High fructans and Galactans: artichokes, asparagus, beetroot, Brussels sprout, broccoli, cabbage, fennel, garlic, leeks, okra, onions, peas, shallots; cereals (wheat and rye); chickpeas, lentils, red kidney beans, baked beans; watermelon, custard apple, white peaches, rambutan, persimmon Polyols: apples, apricots, cherries, longan, lychee, nashi pears, nectarine, pears, peaches, plums, prunes, watermelon; avocado, cauliflower, mushrooms, snow peas; sweetener
Minimal threshold of daily intake	≤20 mg/d or 20 ppm 'gluten-free' 21–100 mg/d or 21–100 ppm 'very low gluten'	Not clearly defined. (Wheat and rye: small quantities are allowed)

developing symptoms soon after food ingestion[47–49]. A proportion of patients presenting with IBS may have a sensitivity to wheat. In a large retrospective study involving 920 patients fulfilling the Rome II criteria for IBS, 30 % (276/920) demonstrated wheat sensitivity or multiple food hypersensitivities, including wheat[36]. Participants from this study were subsequently followed up prospectively, demonstrating persistent wheat sensitivity over a median follow up of 99 months[50].

It is unclear which component of wheat is the causal agent for symptoms in IBS; gluten has been proposed as a causal factor, as well as fructans, which are part of the fermentable oligo-, di-, and mono-saccharides and polyols (FODMAP) family. Other agents such as α-amylase trypsin inhibitors and wheat germ agglutinins have also been suggested as causal agents[51]. Research has recently focused on the role of a low FODMAP diet and GFD for symptom relief in patients with IBS. Table 1 outlines the main characteristics of these diets.

There have been several trials assessing the role of a GFD in IBS. A randomised control trial in forty-five patients, who had been diagnosed with diarrhoea-predominant IBS, demonstrated increasing bowel movements daily on a gluten-containing diet v. a GFD, especially in those who were HLA-DQ2/8 positive[43]. Also increased bowel permeability was noted in HLA-DQ2/8 positive patients, suggesting that gluten may alter intestinal barrier in patients with diarrhoea-predominant IBS (IBS-D)[43]. A prospective study by our own group, in forty-one patients with IBS-D, demonstrated a statistically significant reduction in mean IBS symptom severity scores after 6 weeks of a GFD, following evaluation by a dietitian[52]. There have been several double-blind placebo-controlled trials demonstrating the efficacy of a GFD in IBS, as seen in Table 2.

The benefits of a low FODMAP diet was hypothesised at Monash University, Australia[53], with the group focusing on the implementation of a low FODMAP diet in IBS[54]. A double-blind placebo-controlled trial by this group demonstrated that dietary reduction in fructose or fructans was likely to lead to symptom improvement in IBS, demonstrating the benefits of FODMAP restriction in general[55]. There have been several randomised control trials demonstrating the efficacy of a low FODMAP diet, as seen in Table 3.

It is likely that there is significant overlap between both the GFD and low FODMAP diet, as it is unclear which component of wheat leads to induction of symptoms[56]. Regardless of the mechanism, there appears to be compelling evidence to use both these dietary therapies in IBS. The implementation of these diets are best led by a dietitian, on the basis that most studies have been dietitian-led[57], with a dietitian identifying the most appropriate diet for the patient based on a detailed history. This could be implemented through group education rather than one-to-one sessions, to help prevent a strain on existing resources[58].

Gluten-free diet as a 'lifestyler' choice

Historically, gluten-free products have been of limited availability with knowledge of CD amongst the general population shown to be lacking[59]. This inevitably contributed to the social phobia that individuals with CD experienced when dining out[60]. However, over the past decade, there has been a paradigm shift with a drastic rise in the availability of gluten-free products paralleled by an increase in awareness among the public[61]. Such findings are not only as a consequence of a rise in the incidence and recognition of CD. In fact, surveys conducted among the general population confirm that a greater number of consumers worldwide are following a GFD irrespective of the presence of CD[45,62]. Observational studies have reported that up to 13 % of the population may self-report sensitivity to gluten-based

Table 2. Summary of double-blind placebo-controlled (DBPC) trials assessing the effect of gluten-free diet in irritable bowel syndrome

Lead author for study	Year	Study design	Study duration	Outcome
Biesiekierski[34]	2011	DBPC trial	6 weeks	Worsening of overall symptoms on VAS (P = 0·047) following gluten introduction
Carroccio[36]	2012	Crossover DBPC trial	5 weeks	Increase in overall symptoms following the introduction of wheat (P < 0·0001)
Biesiekierski[74]	2013	Crossover DBPC trial	2 week run in of low FODMAP then 1 week of high-gluten, low gluten, or placebo for 1 week followed by 2 week washout period	No effect of gluten on GI symptoms
Shahbazkhani[75]	2015	DBPC trial	6 weeks	Statistically significant worsening of symptoms in gluten-containing group *v.* placebo (P < 0·001)
Zanwar[76]	2016	DBPC trial	4 weeks	Worsening of symptoms following intake of gluten (P < 0·05)

VAS, visual analogue scale; GI, gastrointestinal; FODMAP, fermentable oligo-, di-, and mono-saccharides and polyols.

Table 3. Summary of randomised controlled trials (RCT) assessing low fermentable oligo-, di-, and mono-saccharides and polyols (FODMAP) diet in irritable bowel syndrome (IBS)

Lead author for study	Year	Study design	Study duration	Outcome
Staudacher[66]	2012	Unblinded RCT	4 weeks	Greater adequate control of GI symptoms on patients with low FODMAP diet (13/19) *v.* habitual (5/22) (P = 0·005)
Pedersen[77]	2014	Unblinded RCT	6 weeks	Reduction in IBS-SSS in low FODMAP diet in comparison with Danish diet (IBS-SSS 75, P < 0·01)
Halmos[78]	2014	Single blind crossover RCT	21 d	Reduction in overall gastrointestinal symptom score on low FODMAP diet *v.* Australian diet (22·8 *v.* 44·9, P < 0·001)
Bohn[67]	2015	Single blind RCT	4 weeks	No difference between low FODMAP diet and traditional diet (P = 0·62)
Eswaran[79]	2016	Unblinded RCT	4 weeks	No significant difference in composite end-points between low FODMAP diet and modified NICE guidelines (P = 0·13)
McIntosh[80]	2017	Single blind RCT	3 weeks	Significant difference between proportion of patients defined as responders (IBS symptom reduction >50) between low FODMAP group *v.* high FODMAP group (P = 0·01)
Staudacher[72]	2017	Single blind RCT	4 weeks	Significantly lower IBS-SSS in patients on low FODMAP diet *v.* sham diet (P = 0·001)
Harvie[81]	2017	Unblinded RCT	6 months	Reduction in IBS-SSS on low FODMAP diet *v.* normal diet at 3 months (P < 0·0002), reduction in IBS-SSS sustained after re-introduction of FODMAPs at 6 months
Hustoft[82]	2017	Double blind crossover RCT	6 weeks	Significant improvement of all symptoms following 3 weeks of low FODMAP diet with mean reduction of IBS-SSS 163·8

GI, gastrointestinal; IBS-SSS, IBS symptom severity score; NICE, National Institute for Health and care Excellence.

products and that up to 5 % of the population may be taking a GFD of their own volition[45,62]. Despite the prevalence of CD remaining stable in the US general population, the prevalence of people avoiding gluten has significantly increased[63].

In some, the avoidance of gluten-containing food is viewed as a healthier lifestyle change rather than an actual treatment, whereas in others it is a consequence of reporting ill-effects to ingestion of gluten-based products. In fact, the relationship between the ingestion of gluten-containing products and the development of clinical symptoms even in the absence of CD has been described since the late 1970s[64,65]. Healthy people have started to take a GFD as a lifestyle choice, leading to the rising interest of a GFD as a 'lifestyler', 'free from' or 'clean eater' choice.

Our own group has investigated the role of a GFD in healthy individuals, by performing a double-blind placebo-controlled trial, in which twenty-eight participants were recruited. Following a 2-week run-in period of a GFD, participants were randomised to receive either gluten-containing (14 g/d) or gluten-free products for 2 weeks. No significant difference in the primary endpoint of Gastrointestinal Symptom Rating Scores was noted between both groups. On the basis of this study, we suggest that gluten is unlikely to be the culprit agent in healthy individuals, and would not recommend commencement of a GFD in a healthy population.

Nutritional implications of restrictive diets

The use of restrictive diets, such as the low FODMAP diet and GFD, can lead to nutritional consequences. A reduction in calcium intake and short-chain fermentable carbohydrate intake has been demonstrated in those in a

low FODMAP diet, in comparison with a habitual diet after 4 weeks[66]. A statistically significant reduction in energy intake has also been demonstrated in patients following a low FODMAP diet ($P < 0.001$), in a randomised control trial comparing the low FODMAP diet with traditional dietary advice[67]. It must also be noted that there is emerging data that utilisation of an adapted FODMAP diet may be nutritionally adequate, with a long-term follow-up postal questionnaire study demonstrating no significant difference in carbohydrate and calcium intake between an adapted low FODMAP diet and habitual diet at long-term follow up, between 6 and 18 months[68]. Lower intakes of magnesium, iron, zinc, manganese and folate have been demonstrated in patients with CD following a GFD[69]. A statistically significantly higher fat content on a GFD has also been demonstrated in children with CD[70]. It is, therefore, imperative that these diets are only implemented when necessary.

There are also concerns with restrictive diets with regard to the gut microbiota. A reduction in total bacterial abundance $v.$ a normal diet has been demonstrated in patients with IBS taking a low FODMAP diet[71], as well as a significant reduction in luminal bifidobacteria after 4 weeks of a low FODMAP diet[66]. It is interesting to note that a recent placebo-controlled study, in 104 patients with IBS, demonstrated that patients had a lower abundance of Bifidobacterium species in faecal samples on a low FODMAP diet in comparison with a sham diet, but higher levels when given a probiotic[72]. Supplementation with probiotics could therefore potentially avoid this potentially deleterious effect of a low FODMAP diet, although long-term data are lacking. Similar changes in gut microbiota have also been demonstrated on a GFD, with a study in ten healthy subjects on a GFD demonstrated reductions in proportions of *Bifidobacterium*, *Clostridium lituseburense* and *Faecalibacterium prausnitzii* after 4 weeks[73]. The effect on the gut microbiota of these restrictive diets requires further exploration, with long-term data lacking.

Conclusion

The rise in gluten production and consumption has led to the recognition of gluten-related disorders. CD affects 1 % of the population, which is important to diagnose in the first instance in patients presenting with symptoms induced by gluten. However, there is a growing body of evidence to show that individuals without CD are taking a GFD of their own volition. This clinical entity is defined as NCGS, although it is not without its controversy and uncertainty given the lack of diagnostic biomarkers and associated conflicting substrates which can provoke similar symptoms. Current evidence suggests there is a role for a GFD in the management of IBS, in addition to the role of a low FODMAP diet as a treatment in this group of patients. However, as demonstrated by our double-blind placebo-controlled study, there appears to be no role of a GFD in healthy individuals, which should be discouraged.

References

1. Shewry PR, Napier JA & Tatham AS (1995) Seed storage proteins: structures and biosynthesis. *Plant Cell* **7**, 945–956.
2. Beccari B. De frumento. De Bononiensi Scientiarum et Artium Instituto atque Academia Commentarii. II-1: Bononiae : ex typographia Laelii a Vulpe; 1745.
3. Field JM, Shewry PR & Miflin BJ. (1983) Solubilisation and characterisation of wheat gluten proteins: correlations between the amount of aggregated proteins and baking quality. *J Sci Food Agric* **34**, 370–377.
4. Shewry PR, Halford NG, Belton PS *et al.* (2002) The structure and properties of gluten: an elastic protein from wheat grain. *Philos Trans R Soc Lond B Biol Sci* **357**, 133–142.
5. Harlan JR & Zohary D (1966) Distribution of wild wheats and barley. *Science* **153**, 1074–1080.
6. Copping AM (1978) The history of the nutrition society. *Proc Nutr Soc* **37**, 105–139.
7. van den Broeck HC, de Jong HC, Salentijn EM *et al.* (2010) Presence of celiac disease epitopes in modern and old hexaploid wheat varieties: wheat breeding may have contributed to increased prevalence of celiac disease. *Theor Appl Genet* **121**, 1527–1539.
8. Dubcovsky J & Dvorak J (2007) Genome plasticity a key factor in the success of polyploid wheat under domestication. *Science* **316**, 1862–1866.
9. Kasarda DD (2013) Can an increase in celiac disease be attributed to an increase in the gluten content of wheat as a consequence of wheat breeding? *J Agric Food Chem* **61**, 1155–1159.
10. Catassi C (2005) Where is celiac disease coming from and why? *J Pediatr Gastroenterol Nutr* **40**, 279–282.
11. Mooney PD, Hadjivassiliou M & Sanders DS (2014) Coeliac disease. *Br Med J* **348**, 1561.
12. van Berge-Henegouwen GP & Mulder CJ (1993) Pioneer in the gluten free diet: Willem-Karel Dicke 1905–1962, over 50 years of gluten free diet. *Gut* **34**, 1473–1475.
13. Marsh MN (1992) Gluten, major histocompatibility complex, and the small intestine. A molecular and immunobiologic approach to the spectrum of gluten sensitivity ('celiac sprue'). *Gastroenterology* **102**, 330–354.
14. Sollid LM, Markussen G, Ek J *et al.* (1989) Evidence for a primary association of celiac disease to a particular HLA-DQ alpha/beta heterodimer. *J Exp Med* **169**, 345–350.
15. Davidson LS & Fountain (1950) Incidence of the sprue syndrome; with some observations on the natural history. *Br Med J*. **1**, 1157–1161.
16. Fasano A, Berti I, Gerarduzzi T *et al.* (2003) Prevalence of celiac disease in at-risk and not-at-risk groups in the United

States: a large multicenter study. *Arch Intern Med* **163**, 286–292.

17. Volta U, Bellentani S, Bianchi FB et al. (2001) High prevalence of celiac disease in Italian general population. *Dig Dis Sci* **46**, 1500–1505.

18. West J, Fleming KM, Tata LJ et al. (2014) Incidence and prevalence of celiac disease and dermatitis herpetiformis in the UK over two decades: population-based study. *Am J Gastroenterol* **109**, 757–768.

19. Wu J, Xia B, von Blomberg BM et al. (2010) Coeliac disease: emerging in China? *Gut* **59**, 418–419.

20. Ramakrishna BS, Makharia GK, Chetri K et al. (2016) Prevalence of adult celiac disease in India: regional variations and associations. *Am J Gastroenterol* **111**, 115–123.

21. Gupta R, Reddy DN, Makharia GK et al. (2009) Indian task force for celiac disease: current status. *World J Gastroenterol* **15**, 6028–6033.

22. Makharia GK, Verma AK, Amarchand R et al. (2011) Prevalence of celiac disease in the northern part of India: a community based study. *J Gastroenterol Hepatol* **26**, 894–900.

23. Sanders DS, Carter MJ, Hurlstone DP et al. (2001) Association of adult coeliac disease with irritable bowel syndrome: a case-control study in patients fulfilling ROME II criteria referred to secondary care. *Lancet* **358**, 1504–1508.

24. Corazza GR, Valentini RA, Andreani ML et al. (1995) Subclinical coeliac disease is a frequent cause of iron-deficiency anaemia. *Scand J Gastroenterol* **30**, 153–156.

25. Kemppainen T, Kröger H, Janatuinen E et al. (1999) Osteoporosis in adult patients with celiac disease. *Bone* **24**, 249–255.

26. Hadjivassiliou M, Gibson A, Davies-Jones GA et al. (1996) Does cryptic gluten sensitivity play a part in neurological illness? *Lancet* **347**, 369–371.

27. Richey R, Howdle P, Shaw E et al. (2009) Recognition and assessment of coeliac disease in children and adults: summary of NICE guidance. *Br Med J* **338**, 1684.

28. Ford AC, Chey WD, Talley NJ et al. (2009) Yield of diagnostic tests for celiac disease in individuals with symptoms suggestive of irritable bowel syndrome: systematic review and meta-analysis. *Arch Intern Med* **169**, 651–658.

29. Rubio-Tapia A, Hill ID, Kelly CP et al. (2013) ACG clinical guidelines: diagnosis and management of celiac disease. *Am J Gastroenterol* **108**, 656–676; quiz 77.

30. Lee SK, Lo W, Memeo L et al. (2003) Duodenal histology in patients with celiac disease after treatment with a gluten-free diet. *Gastrointest Endosc* **57**, 187–191.

31. Lanzini A, Lanzarotto F, Villanacci V et al. (2009) Complete recovery of intestinal mucosa occurs very rarely in adult coeliac patients despite adherence to gluten-free diet. *Aliment Pharmacol Ther* **29**, 1299–1308.

32. Catassi C, Bai JC, Bonaz B et al. (2013) Non-Celiac Gluten sensitivity: the new frontier of gluten related disorders. *Nutrients* **5**, 3839–3853.

33. Sapone A, Bai JC, Ciacci C et al. (2012) Spectrum of gluten-related disorders: consensus on new nomenclature and classification. *BMC Med* **10**, 13.

34. Biesiekierski JR, Newnham ED, Irving PM et al. (2011) Gluten causes gastrointestinal symptoms in subjects without celiac disease: a double-blind randomized placebo-controlled trial. *Am J Gastroenterol* **106**, 508–514.

35. Ludvigsson JF, Bai JC, Biagi F et al. (2014) Diagnosis and management of adult coeliac disease: guidelines from the British Society of Gastroenterology. *Gut* **63**, 1210–1228.

36. Carroccio A, Mansueto P, Iacono G et al. (2012) Non-celiac wheat sensitivity diagnosed by double-blind placebo-controlled challenge: exploring a new clinical entity. *Am J Gastroenterol* **107**, 1898–1906.

37. Volta U, Tovoli F, Cicola R et al. (2012) Serological tests in gluten sensitivity (nonceliac gluten intolerance). *J Clin Gastroenterol* **46**, 680–685.

38. Volta U, Bardella MT, Calabrò A et al. (2014) An Italian prospective multicenter survey on patients suspected of having non-celiac gluten sensitivity. *BMC Med* **12**, 85.

39. Sapone A, Lammers KM, Mazzarella G et al. (2010) Differential mucosal IL-17 expression in two gliadin-induced disorders: gluten sensitivity and the autoimmune enteropathy celiac disease. *Int Arch Allergy Immunol* **152**, 75–80.

40. Sapone A, Lammers KM, Casolaro V et al. (2011) Divergence of gut permeability and mucosal immune gene expression in two gluten-associated conditions: celiac disease and gluten sensitivity. *BMC Med* **9**, 23.

41. Brottveit M, Beitnes AC, Tollefsen S et al. (2013) Mucosal cytokine response after short-term gluten challenge in celiac disease and non-celiac gluten sensitivity. *Am J Gastroenterol* **108**, 842–850.

42. Verdu EF, Armstrong D & Murray JA. (2009) Between celiac disease and irritable bowel syndrome: the "no man's land" of gluten sensitivity. *Am J Gastroenterol* **104**, 1587–1594.

43. Vazquez-Roque MI, Camilleri M, Smyrk T et al. (2013) A controlled trial of gluten-free diet in patients with irritable bowel syndrome-diarrhea: effects on bowel frequency and intestinal function. *Gastroenterology* **144**, 903–911.

44. Kabbani TA, Vanga RR, Leffler DA et al. (2014) Celiac disease or non-celiac gluten sensitivity? An approach to clinical differential diagnosis. *Am J Gastroenterol* **109**, 741–746.

45. Aziz I, Lewis NR, Hadjivassiliou M et al. (2014) A UK study assessing the population prevalence of self-reported gluten sensitivity and referral characteristics to secondary care. *Eur J Gastroenterol Hepatol* **26**, 33–39.

46. Leffler D, Schuppan D, Pallav K et al. (2013) Kinetics of the histological, serological and symptomatic responses to gluten challenge in adults with coeliac disease. *Gut* **62**, 996–1004.

47. Simrén M, Månsson A, Langkilde AM et al. (2001) Food-related gastrointestinal symptoms in the irritable bowel syndrome. *Digestion* **63**, 108–115.

48. Monsbakken KW, Vandvik PO & Farup PG (2006) Perceived food intolerance in subjects with irritable bowel syndrome-- etiology, prevalence and consequences. *Eur J Clin Nutr* **60**, 667–672.

49. Böhn L, Störsrud S & Simrén M (2013) Nutrient intake in patients with irritable bowel syndrome compared with the general population. *Neurogastroenterol Motil* **25**, 23–30.

50. Carroccio A, D'Alcamo A, Iacono G et al. (2017) Persistence of Nonceliac Wheat Sensitivity, Based on Long-term Follow-up. *Gastroenterology* **153**, 56–58.

51. Aziz I, Hadjivassiliou M & Sanders DS (2015) The spectrum of noncoeliac gluten sensitivity. *Nat Rev Gastroenterol Hepatol* **12**, 516–526.

52. Aziz I, Trott N, Briggs R et al. (2016) Efficacy of a gluten-free diet in subjects with irritable bowel syndrome-diarrhea unaware of their HLA-DQ2/8 genotype. *Clin Gastroenterol Hepatol* **14**, 696–703.

53. Gibson PR & Shepherd SJ (2005) Personal view: food for thought--western lifestyle and susceptibility to Crohn's disease. The FODMAP hypothesis. *Aliment Pharmacol Ther* **21**, 1399–1409.

54. Gibson PR & Shepherd SJ (2010) Evidence-based dietary management of functional gastrointestinal symptoms: The FODMAP approach. *J Gastroenterol Hepatol* **25**, 252–258.

55. Shepherd SJ, Parker FC, Muir JG et al. (2008) Dietary triggers of abdominal symptoms in patients with irritable bowel syndrome: randomized placebo-controlled evidence. Clin Gastroenterol Hepatol 6, 765–771.

56. De Giorgio R, Volta U & Gibson PR (2016) Sensitivity to wheat, gluten and FODMAPs in IBS: facts or fiction? Gut 65, 169–178.

57. O'Keeffe M & Lomer MC (2017) Who should deliver the low FODMAP diet and what educational methods are optimal: a review. J Gastroenterol Hepatol 32, Suppl. 1, 23–26.

58. Whigham L, Joyce T, Harper G et al. (2015) Clinical effectiveness and economic costs of group versus one-to-one education for short-chain fermentable carbohydrate restriction (low FODMAP diet) in the management of irritable bowel syndrome. J Hum Nutr Diet 28, 687–696.

59. Karajeh MA, Hurlstone DP, Patel TM et al. (2005) Chefs' knowledge of coeliac disease (compared to the public): a questionnaire survey from the United Kingdom. Clin Nutr 24, 206–210.

60. Sverker A, Hensing G & Hallert C (2005) 'Controlled by food'- lived experiences of coeliac disease. J Hum Nutr Diet 18, 171–180.

61. Aziz I, Karajeh MA, Zilkha J et al. (2014) Change in awareness of gluten-related disorders among chefs and the general public in the UK: a 10-year follow-up study. Eur J Gastroenterol Hepatol 26, 1228–1233.

62. Tanpowpong P, Ingham TR, Lampshire PK et al. (2012) Coeliac disease and gluten avoidance in New Zealand children. Arch Dis Child 97, 12–16.

63. Choung RS, Unalp-Arida A, Ruhl CE et al. (2016) Less hidden celiac disease but increased gluten avoidance without a diagnosis in the united states: findings from the national health and nutrition examination surveys from 2009 to 2014. Mayo Clin Proc 92, 30–38.

64. Cooper BT, Holmes GK, Ferguson R et al. (1976) Proceedings: chronic diarrhoea and gluten sensitivity. Gut 17, 398.

65. Ellis A & Linaker BD. (1978) Non-coeliac gluten sensitivity? Lancet 1, 1358–1359.

66. Staudacher HM, Lomer MC, Anderson JL et al. (2012) Fermentable carbohydrate restriction reduces luminal bifidobacteria and gastrointestinal symptoms in patients with irritable bowel syndrome. J Nutr 142, 1510–1518.

67. Böhn L, Störsrud S, Liljebo T et al. (2015) Diet low in FODMAPs reduces symptoms of irritable bowel syndrome as well as traditional dietary advice: a randomized controlled trial. Gastroenterology 149, 1399–1407.

68. O'Keeffe M, Jansen C, Martin L et al. (2018) Long-term impact of the low-FODMAP diet on gastrointestinal symptoms, dietary intake, patient acceptability, and healthcare utilization in irritable bowel syndrome. Neurogastroenterol Motil 30 [Epublication ahead of print version].

69. Wild D, Robins GG, Burley VJ et al. (2010) Evidence of high sugar intake, and low fibre and mineral intake, in the gluten-free diet. Aliment Pharmacol Ther 32, 573–581.

70. Ferrara P, Cicala M, Tiberi E et al. (2009) High fat consumption in children with celiac disease. Acta Gastroenterol Belg 72, 296–300.

71. Halmos EP, Christophersen CT, Bird AR et al. (2015) Diets that differ in their FODMAP content alter the colonic luminal microenvironment. Gut 64, 93–100.

72. Staudacher HM, Lomer MCE, Farquharson FM et al. (2017) Diet Low in FODMAPs reduces symptoms in patients with irritable bowel syndrome and probiotic restores bifidobacterium species: a randomized controlled trial. Gastroenterology 153, 936–947.

73. De Palma G, Nadal I, Collado MC et al. (2009) Effects of a gluten-free diet on gut microbiota and immune function in healthy adult human subjects. Br J Nutr 102, 1154–1160.

74. Biesiekierski JR, Peters SL, Newnham ED et al. (2013) No effects of gluten in patients with self-reported non-celiac gluten sensitivity after dietary reduction of fermentable, poorly absorbed, short-chain carbohydrates. Gastroenterology 145, 320–328.

75. Shahbazkhani B, Sadeghi A, Malekzadeh R et al. (2015) Non-celiac gluten sensitivity has narrowed the spectrum of irritable bowel syndrome: a double-blind randomized placebo-controlled trial. Nutrients 7, 4542–4554.

76. Zanwar VG, Pawar SV, Gambhire PA et al. (2016) Symptomatic improvement with gluten restriction in irritable bowel syndrome: a prospective, randomized, double blinded placebo controlled trial. Intest Res 14, 343–350.

77. Pedersen N, Andersen NN, Végh Z et al. (2014) Ehealth: low FODMAP diet vs Lactobacillus rhamnosus GG in irritable bowel syndrome. World J Gastroenterol 20, 16215–16226.

78. Halmos EP, Power VA, Shepherd SJ et al. (2014) A diet low in FODMAPs reduces symptoms of irritable bowel syndrome. Gastroenterology 146, 67–75.

79. Eswaran SL, Chey WD, Han-Markey T et al. (2016) A randomized controlled trial comparing the low FODMAP diet vs. modified NICE guidelines in US adults with IBS-D. Am J Gastroenterol 111, 1824–1832.

80. McIntosh K, Reed DE, Schneider T et al. (2017) FODMAPs alter symptoms and the metabolome of patients with IBS: a randomised controlled trial. Gut 66, 1241–1251.

81. Harvie RM, Chisholm AW, Bisanz JE et al. (2017) Long-term irritable bowel syndrome symptom control with reintroduction of selected FODMAPs. World J Gastroenterol 23, 4632–4643.

82. Hustoft TN, Hausken T, Ystad SO et al. (2017) Effects of varying dietary content of fermentable short-chain carbohydrates on symptoms, fecal microenvironment, and cytokine profiles in patients with irritable bowel syndrome. Neurogastroenterol Motil 29 [Epublication ahead of print version].