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Editorial

Emerging evidence that irritable bowel syndrome & functional dyspepsia are microbial diseases

Conventionally, functional gastrointestinal disorders (FGIDs) as classified by the Rome IV Criteria refer to a group of chronic conditions categorized by gut symptoms that arise via multiple pathophysiological processes, conceptualized as disorders of gut-brain interactions[1]. Gastrointestinal (GI) symptoms in inflammatory bowel disease and gastric or colon cancer also arise through gut-brain interactions (no brain, no pain), so in this sense, FGIDs are not unique. Gut pathology is considered to be absent in the FGIDs, and the underlying aetiology is accepted to be unknown[1]. However, emerging evidence is challenging the current paradigm there is no pathology and no known aetiology. In particular, a microbial pathogenesis may be more important than has been previously appreciated. While there are 33 adult and 20 paediatric FGIDs classified in Rome IV[1], among the most prevalent are the irritable bowel syndrome (IBS), characterized by abdominal pain, bowel dysfunction and often bloating and functional dyspepsia (FD), characterized by early satiety, postprandial fullness or epigastric pain[2,3]. Here we discuss the emerging evidence that microbes and inflammation play an aetiopathogenic role in IBS and FD.

Psychological co-morbidity is common in FGIDs; however, the available evidence confirms that this association is largely not explained by healthcare-seeking behaviour but instead is an intimate characteristic of the disorder in a majority of cases[4]. Recently, prospective epidemiological studies have suggested that about 50 per cent of patients with an FGID have a brain-gut-driven condition, where psychological symptoms are followed at a later time by the new onset of gut symptoms, suggesting that there may be a more dominant brain to gut pathway[5]. On the other hand, in the remaining 50 per cent of cases, gut symptoms begin first followed by new-onset psychological alterations, indicating a gut-to-brain-driven disease process rather than a primary brain disorder[5]. This is further supported by a strong link between immune activation (*e.g.* through increased tumour necrosis factor alpha levels) and the severity of psychological co-morbidities present in these disorders[2,3,5,6]. If the gut is key to the onset of many with FGIDs, identifying the disease pathways may permit treatments that target cure rather than present management which is directed at symptom control, as the gut is more accessible than the brain and the gut microenvironment can be locally manipulated.

The IBS aggregates strongly in families suggesting that genes and environment both play a role[2]. A genetic mutation in the sodium channel gene has been identified in IBS with particular relevance to constipation and may explain about two per cent of cases with IBS[7]. However, twin data point to the environment being dominant, not only in dyspepsia but also in IBS[8]. One environmental gut cause of FGIDs is well established, namely food-borne infections, which may affect one in six people annually[9]. IBS can arise *de novo* after bacterial enteritis[2]. While post-infectious IBS (PI-IBS) has been well recognized, post-infectious FD has also been observed[10]. A meta-analysis concluded that PI-IBS may occur after bacterial, protozoal or parasitic enteritis, and the risk is increased in people with psychological distress and female gender, if antibiotics are used to treat the infection, with protozoal or parasitic disease, and if there is more severe enteritis[9]. Emerging evidence suggests that PI-IBS may be much more common than is generally appreciated based on cytotoxic lethal binding toxin antibody levels (a marker of previous bacterial enteritis) in IBS with diarrhoea[11]. A modelling study suggested that based on the attack rate of gastroenteritis and risk of IBS, nearly 10 per cent of the US population will be affected, closely matching the community prevalence of IBS

documented in multiple population-based surveys[12]. It has become apparent incident FD may also arise after bacterial enteritis, and up to one-third of cases develop both IBS and FD; the odds of FD after acute enteritis is over two-fold increased[10].

Although the inflammation may heal after acute infection, low-grade chronic intestinal inflammation with immune activation is documented to occur in a subset of FGID cases. In IBS, increased ileocolonic mast cells have been observed in subsets although the literature is mixed and clearly many IBS cases have no detectable increase in mast cells[13].

In FD, duodenal eosinophilia (typically more than 22 eosinophils per 5 high-power fields in the second portion of the duodenum being the diagnostic cut-off) has been consistently documented to be associated with early satiety and postprandial fullness[13] (Figure). Further, circulating small intestinal homing T-cells have been observed in IBS and FD, implicating

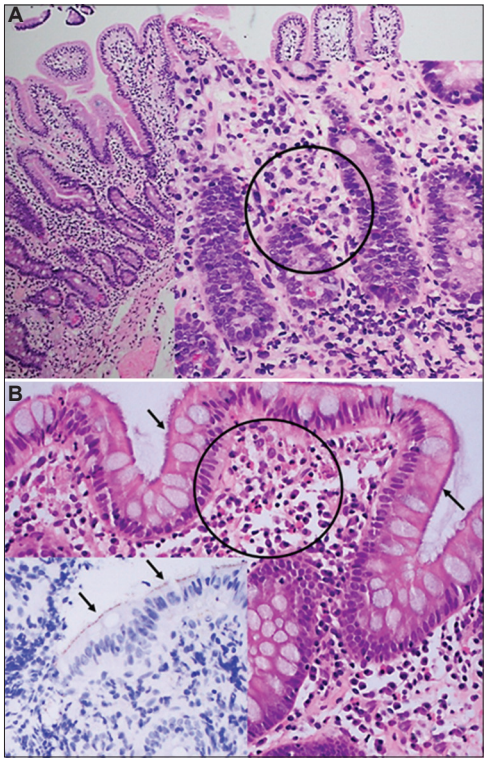

Figure. Abnormal histopathology on haematoxylin and eosin staining of duodenum and colon biopsies in functional gastrointestinal disorders: (**A**) Duodenal biopsy showing eosinophilia in functional dyspepsia (×20). Haematoxylin and eosin stain showing clusters of eosinophils, circled (×40). (**B**) Biopsy of sigmoid colon with spirochaetosis, hazy blue 'fringe' (arrows) and clusters of subepithelial eosinophils (circled) in an irritable bowel syndrome case (×40). Haematoxylin and eosin stain inset (×40) showing immunocytochemistry for *Spirochaetes* on surface of epithelium (arrows).

ongoing low-grade intestinal inflammation in the disease process[13]. It has therefore, been postulated that the extent of initial acute intestinal inflammation after infection may sensitize the intestine and determine the disease phenotype; enteritis localized to the upper small intestine may be more likely to lead to FD, while more distal enteritis or enterocolitis may lead to IBS[2]. After intestinal infection, tropical sprue may develop based on small intestinal biopsy evaluation, and it is possible that some cases of PI-IBS actually arise from a subtle malabsorption syndrome; the prevalence of tropical sprue in IBS is currently unknown[14].

What are the intestinal microenvironmental abnormalities that can lead to chronic gut symptoms either after acute infection or following other insults? One candidate is the presence of abnormal amounts of colonic bacteria in the small intestine presumably because local intestinal stasis arises, termed (vaguely) small intestinal bacterial overgrowth (SIBO). Conventionally, SIBO has been diagnosed based on culture of duodenal aspirates (a difficult technique to perform without specimen contamination) with a cut-off of more than 10^5 coliforms on culture[15]. However, it has been argued that more than 10^3 coliforms in the duodenum are abnormal in health and this should be the cut-off applied for SIBO[15]. An alternative approach has used lactulose or glucose hydrogen breath testing to indirectly identify increased coliforms in the upper small intestine, where an early rise in hydrogen excretion indicates bacterial breakdown of the sugar substrate (rather than a hydrogen rise later as normally occurs when the substrate reaches the caecum)[15]. However, breath testing is influenced by transit time which can be altered in IBS[2,15]. Simply investigating for SIBO fails to consider all other components of the intestinal microbiome so whether SIBO is really a cause of IBS is unclear.

Alterations of the intestinal microbiome are linked to several chronic human diseases although cause and effect is not yet well established[16]. Rather than the Koch paradigm of 'one organism, one disease', current research has focussed on identifying gut dysbiosis in disease including IBS and more recently FD. Most of the microbiome work in IBS has concentrated on dysbiosis in stool; a major limitation as it seems more likely that the mucosal-associated microbiome (MAM) will be key to any gut microenvironmental dysfunction or systemic immune activation[13]. Studies of the colonic MAM have described changes in IBS, but a consistent microbial signature has not been identified[17]. In FD,

our work has shown that the duodenal microbiome differs from that in health[18].

Supporting the microbial hypothesis for IBS and FD, the non-absorbable antibiotic rifaximin has been shown to improve symptoms in those with IBS-diarrhoea or mixed bowel habit, but the gain over placebo while consistent in the phase III trials is modest[19]. Further, the mechanism of action is unknown although rifaximin may modestly decrease stool microbial richness. A trial in Gulf War Veterans did not show any benefit of rifaximin on SIBO[20]. In one randomized trial, rifaximin was found superior to placebo in improving symptoms of FD although the mechanism of action was uncertain[21]. Postulating correcting colonic dysbiosis may improve IBS; faecal microbial transplant (FMT) has been trialed. The largest trial to date in 52 patients observed despite altering the stool microbiome with FMT, greater symptom improvement on placebo occurred versus the active intervention. Further research in IBS subgroups is needed before drawing definitive conclusions[22].

Focusing on changes in intestinal ecology alone in FGIDs may be limiting and misleading. We know that chronic peptic ulceration and gastric cancer are caused by a single organism, *Helicobacter pylori*, even though the gastric microbiome is greatly perturbed in the presence of this chronic infection[23]. We, for example, have identified a chronic colonic bacterial infection, colonic spirochetosis, in two per cent of individuals in Sweden[24] (Figure). Further, the bacteria are associated with subtle colonic pathology previously missed (increased colonic eosinophils) but now confirmed in two independent studies[24,25], and with an over 3-fold increased risk of IBS with diarrhoea, an association overlooked in previous studies which mistakenly concluded colonic spirochetosis as a commensal[24,25]. If colonic spirochetosis proves to be a cause of IBS and diarrhoea, then cure of this subset may be achievable, a hypothesis we are actively pursuing. *Blastocystis* is another candidate organism that may account for a small subset with IBS, but randomized controlled trials are needed to confirm multiple observational reports; on the other hand, *Dientamoeba fragilis* is probably a commensal[26].

In conclusion, acute and chronic infections, and alterations in the gut microbial environment may be important in the pathogenesis of IBS and FD. Currently, FGIDs are diagnosed by applying symptom criteria (Rome IV)[1], but we speculate that lumping Rome criteria positive cases together in clinical trials is misleading as demonstrated by the small benefit over placebo of all currently FDA-approved therapies for IBS (around 10%); identical symptom complexes may arise from very different gut-brain or brain-gut disease processes, including probably through microbial-driven pathways[2,3]. Peptic ulcer is not primarily a disease of stress or abnormal gut-brain interactions or a disturbed microbiome; most commonly, it is a bacterial disease. If microbes also play a causal or initiating role in FGIDs such as IBS or FD as seems increasingly likely, the term functional is a misnomer and will be discarded.

***Conflicts of Interest*:** None.

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