Old Herborn University Seminar Monograph 27:
Persisting consequences of intestinal infection.
Editors: Peter J. Heidt, Dennis Lang, Mark Riddle, Richard Walker, and Volker Rusch.
Old Herborn University Foundation, Herborn-Dill, Germany: 107-111 (2014).

THE ROLES OF PATHOGENIC AND COMMENSAL BACTERIA IN THE INTESTINAL AND BEHAVIOURAL MANIFESTATIONS OF FUNCTIONAL GI DISORDERS

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SUMMARY

This paper reviews clinical and animal-based studies linking pathogenic microbes to the onset of functional GI disorders, and commensal microbes to the maintenance of these chronic disorders. The review will focus on post-infectious irritable bowel syndrome (PI-IBS). The link between acute gastroenteritis and PI-IBS is now well established on the basis of clinical studies. Risk factors include the severity of acute infection, pre-existing psychiatric morbidity and age <60. Host genetic determinants point to susceptibility loci in bacterial recognition, cytokine secretion and intestinal barrier function. Low-grade colonic inflammation is evident PI-IBS as well as a subset of IBS patients without prior gastroenteritis. Risk factors for IBS include infection, stress and antibiotic usage and are known to disrupt the intestinal microbiota. Recent work has shown that destabilization of the microbiota alters gut physiology, brain chemistry and behaviour in animals. Thus a vicious cycle is established in which the initial perturbation of the microbiota results in altered colonic function and the resulting change in the colonic environment selects for different bacteria. This microbial centred model of IBS accommodates key features of IBS including chronicity, variability in symptom expression, and psychiatric co-morbidity. Growing evidence of the therapeutic benefit of microbiome-directed therapies, including pre- and probiotics and as well as selected antibiotics, for this common condition, also support this model.

FUNCTIONAL GI DISORDERS

Functional gastrointestinal disorders are chronic abdominal symptom complexes for which there is no discernible underlying structural abnormality. The most common functional disorder is the Irritable Bowel Syndrome (IBS) that is characterized by abdominal pain or discomfort and altered bowel habit and is generally considered to reflect dysfunction of the gut-brain axis (*Camilleri* and *Di Lorenzo*, 2012). Up to 80% of patients exhibit behavioural changes that include anxiety, depression or somatization. There are no biomarkers and despite the availability of diagnostic criteria, the diagnosis is often made by exclusion of other pathologies. In the absence of an underlying cause, there is no cure and treatment is invariably symptom-based and of limited

efficacy. Together, these factors account for the very high socio-economic burden of IBS (*Maxion-Bergemann* et al., 2006).

It is now well established that acute enteric infection precedes the onset of chronic symptoms in a subset of IBS patients. It is estimated that between 5 and 32% of patients with acute gastroenteritis develop post-infectious IBS (PI-IBS). Bacterial infection with *Campylobacter, Shigella, Salmonella* or *Escherichia coli,* parasitic or viral infections have been associated with the development of PI-IBS. Risk factors include the existence of psychological disorders at the time of infection, the severity of infection and host genetic factors (for review, see: *Thabane* and *Marshall*, 2009). The latter includes polymorphisms in genes that encode bacterial recognition, cytokine secretion and the integrity of the intestinal epithelium (*Villani* et al., 2006). There is evidence of low-grade inflammation (without tissue destruction) in the colonic mucosa of PI-IBS patients and this may arise from inefficient down-regulation of the acute inflammatory response to the acute gastroenteritis (*Gwee* et al., 2003). Studies in an animal model of acute parasitic infection provide proof of concept that transient infection can induce persistent gut dysfunction that can be reversed by anti-inflammatory therapy (*Barbara* et al., 2001). A recent study showed that PI-IBS may last for at least 8 years post-infection but the factors that maintain gut dysfunction in the long term are poorly understood (*Marshall* et al., 2010). Attention now focuses on changes in the intestinal microbiota as a driver of immune activation, low-grade inflammation and symptom generation in IBS.

Factors known to trigger the onset of IBS include infection, stress and antibiotic usage (*Villareal* et al., 2012). Each of these factors has been shown to induce changes in the microbial composition of the gut. Antibiotics induce a transient disruption of the intestinal microbiota, but in some cases the effect may be long lasting (*Jernberg* et al., 2010). Stress has also been shown to disrupt the microbial community of the gut in animal models (*Bailley* et al., 2010, 2011). Acute gastroenteritis produces changes in the intestinal microbiota in humans (*Nelson* et al., 2010).

Disruption of the intestinal microbiota results in changes in gut function reminiscent of that found in IBS. For example, antibiotic-induced perturbation of the intestinal microbiota in mice resulted in a small increase in inflammatory activity in the gut mucosa and an increased response to visceral distension, interpreted to reflect hyperalgesia (*Verdu* et al., 2006). Similarly, disruption of the intestinal microbiota by antibiotics results in changes in gut transit mediated by Toll-like receptor-4 TLR-4 (*Anitha* et al., 2012). Thus, disruption of the intestinal microbiota changes the physiology and the physic-chemical properties of the colon; these changes in turn generate different selection pressures on the microbial community, resulting in further destabilization of the microbiota. As illustrated in Figure 1, the resulting vicious cycle produces inter-related changes in the microbial composition of the gut and in gut physiology, resulting in chronic dysfunction and symptom generation (*Collins* and *Bercik*, 2009). This model is supported by clinical observations showing (a) variation in symptom expression over time in IBS patients (*Mearin* et al., 2004) and (b) temporal instability of the intestinal microbiome in IBS patients (*Maukonen* et al., 2005; *Matto* et al., 2006). Interestingly, a recent study showed that duodenal instillation of faecal bacteria from healthy subjects delayed the development of

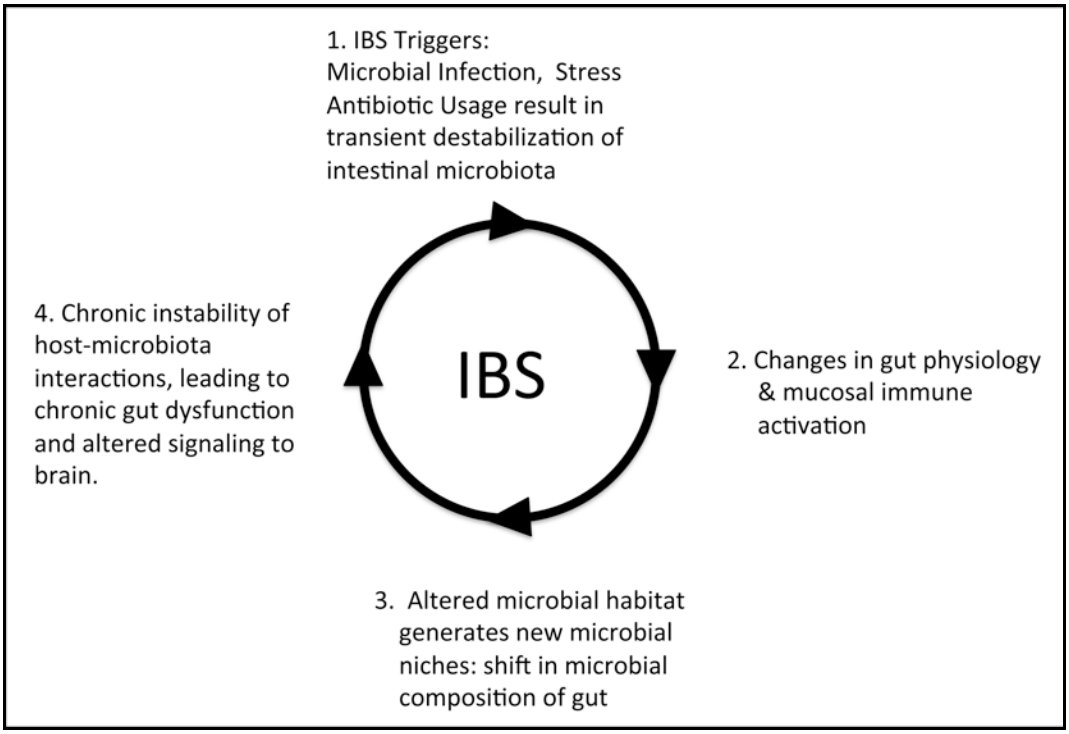

Figure 1: Schematic representation of a microbial centred model of IBS. Pathogenic microbes and other triggers cause an initial destabilization of the microbiota that creates a vicious and self sustaining cycle of host-microbial imbalance, resulting in chronic gut dysfunction and altered behaviour – IBS.

IBS symptoms in patients recovering from Giardia infection (*Morken* et al., 2009), supporting the notion that infection-induced destabilization of the microbiota plays a critical role in the expression of PI-IBS.

Up to 80% of IBS patients exhibit psychiatric co-morbidities that include anxiety and depression (*North* et al., 2007). Recent studies have shown that the intestinal microbiota influences brain chemistry and behaviour. Germ-free mice show less anxiety than colonized mice (*Neufeld* et al., 2011) and antibiotic-induced disruption of the intestinal microbiota resulted in changes in brain chemistry and behaviour (*Bercik* et al., 2011). Taken together these observations support the integration of the intestinal microbiome into the gut-brain axis, thereby providing a basis for considering the role of commensal bacteria in both the gastrointestinal and behavioural manifestations of IBS (*Collins* et al., 2012). The applicability of these animal-based studies to man is supported by the recent demonstration that probiotic bacteria alter brain activity in healthy human subjects (*Tillisch* et al., 2013).

ACKNOWLEDGEMENTS

Dr. S.M. Collins is the recipient of the GSK Chair in Gastroenterological Research and is funded by grants from the Canadian Institutes of Health Research.

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