Preface

Pain is the too often neglected symptom of inflammatory bowel disease (IBD) and the dominant symptom of irritable bowel syndrome (IBS). Why is it neglected? One reason might be largely because clinicians think that they can do little to relieve abdominal pain without affecting bowel function, but it could also be because pain is subjective, invisible and variable. Physicians often opt to treat symptoms or conditions that they can see or measure since objective, measurable outcomes give reassurance about the therapeutic benefit of any intervention. Perhaps the axiom of Axel Munthe, a Swedish physician working at the Saltpêtrière in Paris just over a century ago ('Your pain is my hurt') should be recalled. Louis Pasteur should also be remembered:

*'Je ne te demande pas quelle est ta race ou ta religion
Mais quelle est ta souffrance'*

Every clinical gastroenterologist caring for patients with IBD knows that some have symptoms that can only be attributed to intestinal dysmotility or hypersensitivity. There is not only an overlap in the symptoms of IBD and IBS, but some patients have both. These patients' symptoms are often refractory to standard treatments for IBD. Regrettably the mechanisms, approach to, and management of such symptoms are little discussed. To redress this imbalance, the Falk Foundation invited us to organise a meeting on the interface between IBS and IBD, which was held in Glasgow, UK, on the 11–12 September 2009. The meeting was a stunning success as it explored science beyond traditional boundaries with an internationally acclaimed faculty. The programme covered basic science, with a theme of translation into practice, experimental medicine and, above all, good practical guidance for thoughtful, practising clinicians.

The papers in this book follow the organisation of the conference: there were seven topics:

- Functional and inflammatory pain in GI disorders
- Pharmacology of current therapy: pain and inflammation
- The overlap between IBS and IBD
- Microbes in IBS and IBD
- Microbial therapy in IBS and IBD
- Novel therapy for IBS and IBD
- Unusual inflammatory disorders

The first section considers visceral and somatic pain pathways and reasons why they differ, as well as the emotional response to pain. The localisation of visceral pain is less precise than it is for other types of deep pain. This is due to the fact that visceral organs are sparsely innervated and the afferent nerves show extensive ramification of their processes within the spinal dorsal horn, synapsing with second-order neurones which receive input from large areas of the abdominal wall. Visceral pain is thus referred diffusely to superficial regions causing somatic hyperalgesia. Such symptoms are familiar to experienced clinicians as long as they hear what patients frequently describe. Clinicians are also familiar with psychological predisposing, precipitating and maintaining factors in patients with chronic pain. A multi-dimensional assessment of patients with pain needs to take into account factors such as specific feelings (emotions), thoughts (cognitions) and behavioural response, as well as pain coping strategies, recognising the role of 'catastrophising' in certain patients.

The section on pharmacology of pain and inflammation addresses the molecular mechanisms at both a peripheral and central level. A multitude of molecular nociceptors are responsible for the hypersensitivity of afferent neurones. Persistent increases in the sensory gain may result from changes in the expression, composition

or biophysical properties of transmitters, receptors or ion channels and survival of afferent neurones. Emerging targets of therapeutic relevance include distinct members of the transient receptor potential channel family (TRPV1, TRPV4, TRPA1), acid-sensing ion channels, protease-activated receptors (PAR1/2), corticotropin-releasing factor receptors and sensory neurone-specific sodium channels. Inflammation is driven and regulated by critical cytokine-mediated signalling pathways which augment intestinal T cell resistance against apoptosis. This, in turn, is a pivotal process in the pathogenesis of IBD. New therapies aim to restore mucosal T cell homeostasis.

The overlap between IBS and IBD is then explored. Recent studies indicate that the colonic mucosa in IBS shows an increase in inflammatory cells, although this 'inflammation' is quantitatively less than in IBD and of a different nature with a predominance of mast cells. Low-grade mucosal inflammation throughout the colon and including the terminal ileum can be seen for many months after an attack of acute gastroenteritis and is a feature of post-infective IBS. Stress in both animals and humans can activate mast cells, which (by increasing gut permeability) may allow activation of the systemic immune system.

The role of stress in provoking relapse in patients with IBD is covered, including the results from a prospective observational study in Canada. Some of these factors may also contribute to the placebo response in clinical trials, so there is an excellent paper on this neglected topic. Treatment with a placebo is, of course, not the same as no treatment at all.

Microbes in the gut are the topic of the next section, since these are important in both IBS and IBD. The gut is sterile at birth, but it is rapidly colonised by faecal and vaginal bacteria of maternal origin. Over the succeeding weeks, months and years, a complex microbiota develops that plays a major role in host physiology. The large intestine is an intricate ecosystem that contains a complex microbiota composed of several hundred different types of bacteria. The growth and metabolism of microbial communities in the large intestine are determined by many factors, such as diet, environment, anatomic structure of the digestive tract, disease, immunity, host genetics, drugs and ageing. This complexity is only beginning to be explored. The microbiota and therapeutic potential of pre- and probiotics in both IBS and IBD are discussed in detail, as well as the often overlooked topic of yeasts. Yeasts are overlooked because they are common commensals and difficult to culture. It is nevertheless well recognised that Crohn's disease (CD) is associated with antibodies against yeast oligomannosides (ASCA). My-

colological investigation of families with multiple cases of CD shows that patients with CD and their healthy relatives are colonized with *Candida albicans* more commonly than control families. In healthy relatives, *C. albicans* colonisation correlates with ASCA levels, whereas the onset of CD is independent of the *C. albicans* intestinal load. *C. albicans* colonisation in mice, however, generates ASCA, increases inflammation, histological scores and pro-inflammatory cytokine expression.

The translation of theory and molecular mechanisms into practice is the subject of the penultimate section. A randomised, double-blind, placebo-controlled pilot trial has assessed the effect of mesalazine on intestinal immune cells and symptom perception in patients with IBS. Mesalazine markedly reduced mucosal immune cells and mast cells in particular, compared to placebo. In addition, mesalazine significantly improved general well-being. This is a fascinating new therapeutic opportunity if confirmed. Novel targets are created through understanding the molecular mechanisms of inflammation and of pain, but care must be taken to target treatment to the precise condition. This is the subject of a practical essay on avoiding treating symptoms of IBS in patients with IBD by the use of potent antibodies against TNF. The message is simple: look for objective evidence of inflammation before starting or changing anti-TNF therapy.

The book ends with a diversionary and useful series of papers on other inflammatory intestinal disorders, including microscopic colitis (not so unusual, perhaps), eosinophilic oesophagitis and mastocytosis. These are state of the art essays. They conclude a book that crosses boundaries and will serve as a reference for both clinicians and basic scientists interested in IBD and IBS. It was a pleasure to create the meeting, develop the programme and learn from specialists in different fields. This gives us an opportunity to record our thanks to the authors and speakers at an exceptional meeting, as well as to Falk for supporting the meeting without trying to influence the content in any way. Although inflammation may be a feature common to both IBD and IBS, the two conditions differ by more than the degree of inflammation. The one (IBS) may be regarded as a central disorder with a peripheral component that may sometimes be inflammatory. The other (IBD) is primarily a peripheral inflammatory disorder, that may sometimes have a central component. Both peripheral and central components of either condition need treatment in an individual patient.

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