Irritable bowel syndrome – a microbial perspective

Irritable bowel syndrome is a commonly occurring symptom complex of unknown cause. The condition is characterised by gastrointestinal problems, but is often accompanied by functional disorders in several organ systems. Disruption of the intestinal flora may be a causal factor, and this possibility should be further researched, not least as a basis for treatment.

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Irritable bowel syndrome is the most common functional gastrointestinal disorder and occurs in approximately 10% of the population (1). The condition is characterised by pain, flatulence and disturbances in bowel movements. It was first described in a scientific journal in 1818 (2). The diagnosis is based on a combination of exclusion and inclusion criteria: organic diseases must be ruled out through adequate investigation (3), and internationally accepted symptom criteria have been drawn up which must be fulfilled in order to make the diagnosis (Box 1) (4).

The cause of irritable bowel syndrome is unknown, but since the condition was discussed in the Journal of the Norwegian Medical Association in 2002 (5), there has been a significant development in how its pathophysiology is viewed (6). In this article we will point to possible microbial mechanisms behind the symptoms.

A strategic position
The pathophysiology of irritable bowel syndrome is obviously complex, but there has long been a suspicion that aberrations in one or more of the control systems of the gastrointestinal tract are involved in the development of symptoms. One of the most widespread explanations is a disruption to the interaction between the brain and the intestine (7).

Already in the 1800s the American military doctor William Beaumont (1785–1853) described how mood affected the digestion of the Canadian fur-trapper Alexis St. Martin (1794–1880), who had developed a gastrointestinal fistula following a gunshot wound to his stomach (8).

Modern stress research has since discovered a number of signal pathways from the central nervous system to the gastrointestinal tract, both neural (the autonomic nervous system) and humoral (the hypothalamic-pituitary-adrenal axis). There is little doubt that activity in this brain-gut axis affects the behaviour of the intestine. The gastrointestinal tract is, however, largely autonomous thanks to extensive indigenous control systems: the enteric nervous system, the enteroendocrine system and the intestinal immune system. These components interact with one another and transmit information to the brain as nerve impulses, hormones and cytokines. Signals from the intestine thereby affect the brain’s function, perhaps especially the activity of the limbic system (9), but we currently know little about the consequences of this.

The intestinal flora is in close contact with the control systems of the gastric wall, and this position enables a microbial effect on the host, including the central nervous system (10). From such a perspective, disruptions to the intestinal flora can be thought to explain a number of symptoms, both intestinal and extraintestinal. But do we have evidence to support the claim that microbial mechanisms are involved in the pathophysiology of irritable bowel syndrome?

In the following we will seek to elucidate this question by highlighting two crucial clinical points: that the symptoms can occur after infections of the gastrointestinal tract and that they are often exacerbated by the intake of certain foods.

Post-infectious problems
The recognition that irritable bowel syndrome may occur following infections is relatively new, although the phenomenon was described as far back as the 1950s (11). Long-term gastrointestinal problems may develop after viral, bacterial and parasitic forms of gastroenteritis (12). This so-called post-infectious subgroup of irritable bowel syndrome constitutes an estimated 10% of the total number of cases (13). From a research point of view this is an attractive entity for study because the infection may be regarded as a kind of intervention in a natural experiment.

Post-infectious irritable bowel syndrome appears to be a clearly microbial condition, but the mechanisms behind the symptoms are unknown. Hitherto the research has largely focused on immunological factors, and a number of aberrations have been described in cell numbers and cytokine levels in intestinal biopsies and blood tests from patients with long-term gastrointestinal problems following various infections (14). There have been far fewer efforts to study the importance of the intestinal flora. This ought to be studied, since infectious forms of gastroenteritis not only affect the host, but also the host’s microbes (15, 16).

In 2004 there was a major outbreak of gastroenteritis in Bergen, which turned out to be caused by polluted drinking water, in which the parasite Giardia lamblia was detected. It is estimated that around 2 500 patients were treated for giardiasis (17). The parasite was detected in the faecal samples of 1 252 patients. Three years later these patients were asked to complete a questionnaire (18). Of the 817 who responded, 46.1% reported symptoms consistent with irritable bowel syndrome, 46.1% reported symptoms consistent with irritable bowel syndrome, and 28.6% had symptoms consistent with both.

Five years later, those who reported chronic fatigue were offered a thorough cross-disciplinary assessment. Of the 53 who attended for this assessment, 22 were diagnosed with chronic fatigue syndrome (19). The possibility that an infection that essentially restricts itself to upper sections of the small intestine may trigger such severe systemic symptoms is a completely new aspect.

Immunological mechanisms may be involved, and Hausken and collaborators have recently described an increased number of CD20-positive cells in duodenal biopsies from patients who have suffered from Giardia infection (20). Interestingly, this is the same cell population that is inhibited...
by rituximab, an antibody that may have positive effects in the treatment of chronic fatigue syndrome (21). Disruption of the intestinal flora is another possible explanation (22).

Fermentative dyspepsia revisited
A number of studies have investigated the composition of the intestinal flora using advanced molecular biological methods, and this is consistently thought to be altered in patients with irritable bowel syndrome compared with healthy persons (23). However, the findings are relatively subtle and disappointingly inconsistent, and it is unclear whether the changes detected are primary or secondary to disruption of the intestinal function. In any case, from a pathophysiological perspective such studies of the structure of the intestinal flora provide relatively limited information – it is far more important to investigate what the microbes do than who they are.

The main function of the intestinal flora is to break down nutrients which the host is unable to digest itself (24). Food substances that are poorly absorbed in the small intestine, primarily low-digestible carbohydrates, continue to the colon, where they undergo microbial fermentation. Intriguingly, it is precisely this type of food that often gives rise to symptoms in patients with irritable bowel syndrome (25). This hypersensitivity to food has long been neglected, but is now being taken seriously, exemplified by the fact that the renowned American Journal of Gastroenterology recently dedicated an entire issue to a review of the disorder (26).

Intake of food with a high FODMAP content (fermentable oligosaccharides, disaccharides, monosaccharides and polyols) appears to play a central role in the development of symptoms (27). The Norwegian Directorate of Health now recommends that people with irritable bowel syndrome reduce their intake of these types of carbohydrates, which are found in large quantities in, for example, apples, fruit juice, wheat, broccoli, beans, milk and honey (28).

Interestingly, similar advice was given in the early 1900s in the treatment of fermentative dyspepsia (29). This diagnosis is no longer used, but it is worth noting that this old designation for irritable bowel syndrome expresses an essential aspect of the condition’s pathophysiology, namely that fermentation processes seem to be involved. We still know little about why fermentation provokes symptoms in people with irritable bowel syndrome (30), but we suspect that microbial metabolites may play a significant role (31). Perhaps this can explain both the gastrointestinal problems and the associated health symptoms (32)?

Final comments
Microbial mechanisms appear, therefore, to be involved in the pathophysiology of irritable bowel syndrome. Until now, this has mainly been investigated using descriptive studies of the composition of the intestinal flora and testing of different types of antibiotics and probiotics (33). We must take on board that intestinal flora is an active metabolic organ and place much greater emphasis on studying the functions of the microbes.

Attempts to change the intestinal flora with antibiotics and probiotics are an interesting therapeutic principle for irritable bowel syndrome, but we do not yet have a full picture of their mechanisms of action and long-term effects, and this type of therapy can sometimes have unfavourable effects (34, 35).

**BOX 1**

Diagnosis of irritable bowel syndrome according to the Rome III criteria (4). The patient must have suffered from recurrent abdominal pain or discomfort for more than six months. In addition the symptoms must have been present for at least three days per month for three months. At the same time at least two of the following factors must be present:

Symptoms improve with defaecation
Onset of symptoms associated with a change in frequency of stool
Onset of symptoms associated with a change in consistency of stool