The irritable infection

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John Marshall is an Associate Professor of Medicine in the Division of Gastroenterology at McMaster University in Hamilton, Ontario. He has a research interest in postinfectious gastrointestinal disorders. His involvement with the Walkerton Health Study and other initiatives has helped to define the epidemiology and natural history of postinfectious irritable bowel syndrome (IBS). With his collaborators, Dr. Marshall is now determining whether infection and predisposition to postinfectious IBS predict future risk of inflammatory bowel disease (IBD).

PA: Many clinic patients will tell us that all of their gastrointestinal problems started after a trip to the Caribbean or Mexico.

JM: I agree that it is a common scenario. Traveller’s diarrhea is common, and usually does not last more than a few days. However, an unfortunate few find that Montezuma follows them home, and that it takes months, or even years, for their bowel’s to return to normal. This is the phenomenon we call postinfectious IBS. It has been estimated that up to 30% of IBS cases begin after an infection (1).

PA: Stool culture tests are performed after this history is obtained. Since the colon is normally full of a large number of bacteria, what are we measuring?

JM: That is a good question. It is worth it to look for a persistent parasitic infection, but most of the bacterial pathogens associated with traveller’s diarrhea are long gone by the time patients see us in the clinic. Postinfectious IBS seems to be a “hit-and-run” phenomenon, wherein a change in physiology persists despite the clearance of the infecting pathogen. Interestingly, we have found that viral gastroenteritis is followed by a faster recovery of bowel function than bacterial dysentery (2).

PA: It used to be more common to culture the duodenal content or to use breath testing to assess for bacterial overgrowth. A trial of an antibiotic such as metronidazole may be given. If it leads to improvement, what is the conclusion?

JM: Bacterial overgrowth should always be considered in the differential diagnosis of IBS, and is probably underrecognized. However, most clinicians would consider overgrowth and IBS to be distinct diagnoses. The idea that the symptoms of postinfectious IBS are caused by small bowel overgrowth or changes in colonic flora is intriguing, but unproven. Clinical laboratory stool assays use selective culture media, chemical tests and serotyping to identify specific known pathogens and eliminate workup of normal flora. Without controlled trials, however, I think the empirical use of antibiotics in patients without a diagnosis of overgrowth or infection with a known pathogen remains speculative and could even be detrimental.

PA: Can a transient infection in the colon lead to long-term physiological changes in the bowel?

JM: We do know from numerous epidemiological studies that transient infection leads to persistent symptoms in 10% to 30% of patients (3). The challenge is to explain the pathophysiology behind those symptoms. We and others have shown that some patients with IBS have increased intestinal permeability (4). Increased permeability could allow luminal antigens to activate an immune response in the submucosa that alters neuromuscular function. Indeed, a Swedish study (5) that obtained full-thickness, small bowel biopsies from patients with severe IBS found inflammatory changes in the myenteric plexus. Although endoscopic biopsies appear normal on routine histology, more advanced techniques can demonstrate similar immune activation in the mucosa. Changes in enterochromaffin cell numbers and circulating serotonin levels have also been reported in patients with postinfectious IBS (6). It is unlikely that all patients with postinfectious IBS share a common pathophysiology. We need better tools to detect changes in specific patients and target therapy accordingly.

PA: What did we learn about this topic from the study of the contamination of public water supplies in Walkerton, Ontario, in 2000?

JM: The outbreak of gastroenteritis that resulted from contamination of the municipal water supply was an awful human tragedy. However, it also provided a unique opportunity to study the long-term effects of waterborne gastroenteritis in a large, well-defined cohort. The Walkerton Health Study established a study clinic in Walkerton in 2002 and invited local

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residents to attend annual structured interviews. When we assessed participants that year, IBS was much more common among those with a documented history of acute illness during the outbreak than among those who had remained well (36% versus 10%, respectively; \( P<0.001 \)) (7). We also found that younger people, women and those who had suffered a more severe acute infection were at higher risk for postinfectious IBS. Fortunately, our long-term follow-up has shown that approximately one-half of the subjects with postinfectious IBS had improved when they were reassessed four years later. This is the largest and longest study of postinfectious IBS ever undertaken, and we remain grateful to the citizens of Walkerton for their support and participation.

**PA:** Can you treat these problems by giving more bacteria, such as probiotic therapy?

**JM:** That is an excellent idea, and one that I think has great merit. A lot of good, basic scientific research and some early clinical trials suggest that probiotics can influence gut function and improve symptoms. If probiotics work for postinfectious IBS, my hope for the future is that we will be able to tailor them to target individual patients’ pathophysiology and flora profile. However, I think our understanding of probiotic therapy remains rudimentary, and it is premature to endorse their routine use in patients with postinfectious IBS.

**PA:** Can transient infections in the bowel lead to chronic IBD?

**JM:** The textbook answer is that acute enteric infection does not lead to IBD. However, this concept remains the subject of active basic and clinical research. We have been intrigued by the observation that postinfectious IBS has been associated with changes in permeability and a failure to down-regulate enteric inflammation. Similar events have been invoked in the early pathogenesis of Crohn’s disease, and it is possible that the same people who develop postinfectious IBS are at increased future risk for more overt inflammatory disorders such as IBD. We are studying the Walkerton population to determine whether their incidence of IBD exceeds what would otherwise be expected. We have also undertaken a genetic analysis to identify genes that might influence the risk for IBS and IBD after enteric infection.

**REFERENCES**
