

Review

Postinfectious Irritable Bowel Syndrome: A Long-Term Consequence of Bacterial Gastroenteritis[†]

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ABSTRACT

Irritable bowel syndrome (IBS) is a commonly diagnosed disease characterized by gastrointestinal symptoms that may be associated with psychological illness and emotional problems. The prevalence rate worldwide for IBS ranges from 10 to 20% and is higher for women than for men. IBS imposes a substantial financial burden on both patients and employers because of increased medical costs and decreased work productivity. Recent studies indicate that inflammatory processes involving the gastrointestinal tract are strongly correlated with IBS. Acute bacterial gastroenteritis has been linked with the onset of symptoms in approximately 15% of patients diagnosed with IBS; these cases have been called postinfectious IBS. Organisms commonly associated with postinfectious IBS include the foodborne pathogens *Campylobacter*, *Escherichia coli*, *Salmonella*, and *Shigella*. The pathologic changes associated with postinfectious IBS are likely due to inflammatory reactions induced by the infecting organisms. Postinfectious IBS should be recognized as a potential long-term consequence of foodborne gastroenteritis.

Irritable bowel syndrome (IBS; also called spastic, irritable, or nervous colon) is the most common gastroenterological disorder seen by gastroenterologists and is one of the most common conditions observed by primary care physicians in developed countries (48). All age groups are affected. IBS is not life threatening and does not predispose patients to more serious conditions; however, the disease significantly impairs the quality of life and imposes a high health-care cost on the afflicted individuals (70). The syndrome is characterized by lower abdominal pain or discomfort, a feeling of abdominal distension, and altered bowel habits; however, there is great variability in the presentation of these symptoms (25).

Acute bacterial gastroenteritis has been correlated with the onset of IBS symptoms in some patients, and this association has given rise to the concept of postinfectious IBS (PI-IBS) (25, 60). The pathophysiology of IBS and PI-IBS, their socioeconomic impact, and the role of enteric pathogens in the induction of IBS are discussed in this review.

GENERAL ASPECTS OF IBS

IBS is a functional gastrointestinal disorder defined by the presence of particular symptoms without an identifiable biochemical or structural pathology. However, Talley (69) suggested that this definition is not correct and that functional gastrointestinal disorders occur after infection or inflammation. These disorders may be associated with psy-

chological and emotional problems such as anxiety or depression (35, 58). Other functional gastrointestinal disorders include functional diarrhea (frequent or urgent diarrhea without abdominal pain) and functional (non-ulcer) dyspepsia (recurrent or persistent pain or discomfort that is located in the upper abdomen and is associated with early satiety, fullness, bloating, and nausea) (54, 58). IBS should not be confused with inflammatory bowel disease, which is the descriptive term used for ulcerative colitis and Crohn's disease (3), because the pathophysiology of these diseases is different from that of IBS.

Clinical features of IBS. IBS is defined clinically according to the Rome II criteria (Table 1). The main features of IBS are recurrent abdominal pain with a clear relationship to changes in bowel movement frequency or stool consistency with relief of the pain by defecation (66). Diagnosis is complicated because the symptoms and their severity vary greatly among patients and also may vary in the same patient over time. Individuals may experience different symptoms during each episode of IBS, and they may have alternating periods of IBS with predominant symptoms of constipation (C-IBS) and diarrhea (D-IBS) (25). In addition to the gastrointestinal symptoms, patients frequently report psychological illness, lassitude, poor sleep, fibromyalgia, headache, backache, frequent urination, dysmenorrhea, and dyspareunia (35, 66). More than 40% of IBS patients avoid normal activities, certain types of food, work, and leisure activities, and most patients report a decreased quality of life (27). The symptoms of IBS characteristically wax and wane, and the patient may suffer the illness for months or years.

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TABLE 1. Rome II symptom criteria for IBS^a

Abdominal pain or discomfort (often described as crampy) for at least 12 weeks (not necessarily consecutive) in the preceding 12 months associated with two of the following:

1. Pain or discomfort is relieved by defecation
2. Onset is associated with a change in stool frequency
3. Onset is associated with a change in the form or characteristics of the stool

Symptoms that cumulatively lend support to an IBS diagnosis:

1. Abnormal bowel movements (more than three per day or fewer than three per week)
2. Abnormal stool form (lumpy to hard or loose to watery)
3. Abnormal stool passage (straining, urgency, or feeling of incomplete evacuation)
4. Passage of mucus during bowel movement
5. Bloating or feeling of abdominal distension

^a Adapted from Gilkin (25) and Talley and Spiller (70).

Epidemiology of IBS. The prevalence (percentage of the population affected) of IBS in adults in the United States is 10 to 20% (25, 48, 62). The prevalence in the United Kingdom is 9 to 12% (35, 66), and the mean prevalence of IBS in European countries and in North America is 12.6% (range, 4.0 to 21.6%) (51). Cremonini and Talley (16) found that the mean IBS prevalence for Australia, North America, and Europe was 8.9% (range, 1.1 to 22.0%). Studies in a number of Asian countries indicated a mean IBS prevalence of 7.3% (range, 0.8 to 14%) (16). The incidence (rate of occurrence in a population) of IBS in Europe and North America is two or three affected individuals per 1,000 persons per year (16). Mortality is estimated at 0.03 deaths per 100,000 persons per year (2). IBS is a worldwide problem and is present in every country where it has been investigated (36, 66). The syndrome is diagnosed two to three times more frequently in women than in men, and age and race have an inconsistent impact on the prevalence of IBS symptoms (5, 35, 62). In the United States, IBS results in 1.5 to 3.5 million physician visits each year (25, 48); however, not all IBS victims seek medical care. Jones et al. (35) stated that approximately half of British IBS victims seek medical care compared with only 15 to 25% in the United States (10, 62).

Impact and cost of IBS. In a study comparing 720 employees with IBS and 1,056 employees without IBS in a U.S. company, Dean et al. (20) found a 3.5-fold reduction in work productivity in employees with IBS compared with those without IBS. The reduced work productivity due to gastrointestinal symptoms was approximately 15.8 days/year for employees without IBS and 54.8 days/year for employees with the illness (20). Absenteeism was low in all employees, but the absentee rate was 4.3-fold higher in employees with IBS compared with those without IBS (20). The greatest loss in total productivity in employees with IBS, therefore, was due to impairment during working hours rather than due to absence from work. Thus, the economic loss sustained by employers due to decreased productivity by employees with IBS can be substantial. Em-

ployees with IBS had a 3.3-fold reduction in regular activities such as housework, shopping, childcare, exercising, and studying compared with employees without IBS (20).

For 1998, the estimated total direct costs due to IBS in the United States (including hospital inpatient, outpatient, and emergency room services, physician office visits, and drugs) was \$1.6 billion; in addition, the average IBS patient missed 13.4 days of work, resulting in an estimated productivity loss of \$19.2 billion (2). Longstreth et al. (38) studied patients who received flexible sigmoidoscopy in the year 2000 at a health maintenance organization. Those patients with IBS had significantly more outpatient visits (medical, surgery, and emergency), were hospitalized more often, and required more outpatient prescriptions and IBS-related prescriptions than did non-IBS patients. During a period of 1 year, the mean total cost incurred by an IBS patient was \$3,729.04 compared with \$2,607.12 for a non-IBS patient (38).

Maxion-Bergemann et al. (42) reviewed the direct and indirect costs incurred by IBS patients in the United States and the United Kingdom. They determined that the total direct costs (medically associated costs) ranged from \$348 to \$8,750 (in 2002 dollars) and the total indirect costs (loss in productivity) ranged from \$355 to \$3,344. The average number of work days missed ranged from 8.5 to 21.6. IBS is an expensive disease both in terms of productivity losses and medical expenses.

Pathophysiology of IBS. Patients who consult a physician concerning IBS symptoms are more likely to experience depression, anxiety, somatization (conversion of anxiety into physical symptoms), abuse (physical or sexual), phobia, hypochondriasis, obsessive-compulsive disorder, and stress than are members of the general population (7, 39, 41, 54). However, Quigley (60) suggested that the role of psychosocial factors in IBS is exaggerated because those IBS patients with these problems are generally more likely to seek health care than are those IBS patients without them.

Multiple factors have been proposed to account for the symptom complex displayed by IBS patients. The disorder involves dysregulation of the enteric and central nervous systems, leading to aberrations in gut motility and visceral sensation modulated by psychosocial and environmental factors (18, 39). The neurotransmitter serotonin (5-hydroxytryptamine [5-HT]) and its receptors (5-HT₃ and 5-HT₄) play an important role in gut function (17, 39). Approximately 90% of the body's serotonin is contained within the gastrointestinal tract in enterochromaffin cells (7, 19). Serotonin is synthesized by these cells, stored in specific secretory vesicles, and secreted in a calcium-dependent manner (61). Serotonin is implicated in several major actions of the gut: mediation of gastrointestinal motility and transit, mediation of intestinal secretion, and modulation of visceral sensation perception through the activation of 5-HT receptors distributed on enteric nerves and sensory afferents (7, 19). Serotonin has been implicated in a number of psychiatric disorders, including anxiety and depression (17). There appears to be a genetic component in IBS, specifi-

TABLE 2. Comparison of the concentrations of serotonin and 5-hydroxyindoleacetic acid (5-HIAA) in platelet-depleted plasma from fasting and fed healthy volunteers and D-IBS and C-IBS patients^a

Treatment group	n	Serotonin concn (nmol/liter)		5-HIAA concn (nmol/liter)	
		Fasting	After meal	Fasting	After meal
Healthy volunteers	35 (29 female)	21.3	28.5	27.0	31.1
D-IBS patients	55 (50 female)	27.4	41.6	25.7	35.16
C-IBS patients	29 (26 female)	22.4	18.7	17.5	16.2

^a Modified from Atkinson et al. (6).

cally a clustering of IBS in families. Twin studies have revealed an increased frequency of IBS in monozygotic twins compared with dizygotic twins (57).

Almost all the blood serotonin is present in platelets. Although platelets do not synthesize serotonin, they do take up serotonin released by enterochromaffin cells. Using platelet-depleted plasma, Atkinson et al. (6) compared the mean plasma concentrations of serotonin and its metabolic product 5-hydroxyindoleacetic acid (5-HIAA) in healthy volunteers, D-IBS patients, and C-IBS patients under fasting and fed conditions (Table 2). Under fasting conditions, D-IBS patients had significantly greater plasma serotonin concentrations than did healthy controls or C-IBS patients. The ingestion of food increased the plasma concentrations of serotonin and of 5-HIAA in both healthy volunteers and D-IBS patients, whereas food did not increase the concentrations of serotonin or 5-HIAA in C-IBS patients (Table 2). The concentrations of 5-HIAA were significantly lower in fasting C-IBS patients than in fasting controls or D-IBS patients (Table 2), and the concentration of 5-HIAA was similar in both fasting and fed C-IBS patients (Table 2). Thus, plasma serotonin concentrations are correlated with IBS symptoms; elevated concentrations are linked to D-IBS, and reduced concentrations are linked to C-IBS.

Activation of 5-HT₃ or 5-HT₄ receptors by serotonin augments gastrointestinal transit (17). Antagonism of these receptors with 5-HT₃ or 5-HT₄ antagonists delays gastrointestinal transit and relieves diarrheic symptoms (17, 31, 68). 5-HT₄ agonists have some effectiveness in relieving the symptoms of IBS constipation (31, 68). The fact that 5-HT₃ or 5-HT₄ receptor antagonists improve symptoms in D-IBS patients and 5-HT₄ receptor agonists improve symptoms in C-IBS patients suggests an excess or deficiency of serotonin in D-IBS or C-IBS patients, respectively (31, 68).

Treatment of IBS. Because of the lack of a single etiology, functional gastrointestinal disorders such as IBS are notoriously difficult to treat; thus, therapy is directed toward alleviating symptoms. A number of therapeutic approaches have been tried, including dietary changes, antispasmodic agents, antidiarrheal agents, antidepressant and anti-anxiety medications, psychotherapy, serotonin receptor antagonists and agonists, and probiotics (4, 18, 27, 31, 56,

62). Because IBS symptoms are quite variable within and between individuals, successful treatment generally involves multiple strategies, and each IBS patient must be treated on an individual basis. 5-HT receptor-modulating agents show promise for treating IBS (4, 31, 45). A number of 5-HT₃ antagonists and 5-HT₄ agonists are being studied in clinical trials (45).

PI-IBS

The main features of PI-IBS are similar to those of non-PI-IBS. PI-IBS has been defined as exhibiting acute onset Rome II IBS symptoms (Table 1) that develop after the individual experiences a gastrointestinal infection with two or more of the following characteristics: fever, vomiting, diarrhea, or a stool culture positive for an infectious agent (65).

In 1962, Chaudhary and Truelove (13) studied 130 patients with IBS and found that 34 (26.2%) of the patients could date their IBS symptoms to a point in time following an attack of bacillary or amebic dysentery. The patients with postdysentery IBS had a more favorable prognosis than did those IBS patients without such a history. At the close of the study, 20 (62.5%) of 32 postdysentery IBS patients were free of IBS symptoms, whereas only 27 (27.8%) of the 97 IBS patients with no history of dysentery were symptom free (13).

Table 3 lists a number of studies on the prevalence of PI-IBS. The mean prevalence of PI-IBS is 15.0% (range, 3.4 to 31.6%). The prevalence of IBS in an uninfected population was determined in only seven of the studies. The mean prevalence of IBS in the uninfected populations was 3.1% (range, 0.7 to 10.1%). Thus, the probability of developing IBS symptoms following bacterial gastroenteritis was several times that of an uninfected population. Halvorson et al. (32) studied the risk of IBS following infectious gastroenteritis and found that the prevalence of IBS as a sequela to bacterial gastroenteritis was 9.8% compared with 1.2% for uninfected control groups. The pooled risk estimates indicated that there was a sevenfold increase in the risk of developing IBS in patients with infective gastroenteritis as compared with control groups. Prevention of bacterial gastroenteritis would decrease the incidence of PI-IBS (32). Although microorganisms were not isolated in all of the outbreaks listed in Table 3, species of *Campylobacter*, *Salmonella*, and/or *Shigella* were the most common agents identified in some of the outbreaks.

Risk factors for PI-IBS. Risk factors for the development of PI-IBS include female gender, younger age, severity of the initial gastrointestinal insult, toxigenicity (virulence) of the infecting bacteria, duration of the enteritis, and adverse psychological factors (7, 64). Neal et al. (53) determined that being female and the duration of the preceding infectious diarrhea were the most important risk factors for developing IBS after a gastroenteritis infection. Females were 3.4-fold more susceptible to PI-IBS than were males. The longer the individual suffered from infectious gastroenteritis, the greater the chance for developing PI-IBS. There was a 2.9-fold increase in developing IBS if the

TABLE 3. Prevalence of postinfectious irritable bowel syndrome

1. **United Kingdom.** Two foodborne outbreaks of *Salmonella* Enteritidis (phage type 4) infection resulted in 38 cases; 33 of these patients had positive stool cultures. The patients were 13 males and 25 females with a median age of 40 years. At 12 months, 12 (31.6%) of the 38 patients (10 females) had IBS. During the outbreak, these 12 patients had stool samples that were positive for *Salmonella* (44). Five years later, 9 of 11 of the IBS patients still had altered bowel function (43).
2. **United Kingdom.** Three months after an attack of acute gastroenteritis, 22 (29.3%) of 75 patients had IBS symptoms (mean age of the IBS patients was 34 years, and 17 were female). These symptoms persisted for 6 months in 20 of the IBS patients. Nine of 12 patients still had IBS symptoms at 12 months (29).
3. **United Kingdom.** Six months after a bacterial gastrointestinal attack, 23 (6.6%) of 347 individuals showed signs of IBS. The inciting organisms were identified as *Campylobacter*, *Salmonella*, or *Shigella* species (53). After 6 years, 6 of 14 patients had recovered but 8 of 14 patients still had IBS symptoms (52).
4. **United Kingdom.** Of 94 patients who had acute gastroenteritis, 22 (23.4%; 14 females) developed IBS symptoms. *Salmonella*, *Campylobacter*, or *Shigella* were isolated from 12 of these 22 IBS patients (30).
5. **United Kingdom.** Three hundred three patients were evaluated for IBS symptoms for 1 year after they had a bout of gastroenteritis: 54.0% of patients were infected with *Campylobacter*, 37.4% were infected with *Salmonella*, and 8.5% were infected with other organisms. IBS was confirmed in 12 (4.0%) of these 303 patients. In a similar study in a gastroenteritis-free general population, 2,027 (0.35%) of 575,169 individuals were diagnosed with IBS (24).
6. **United Kingdom.** At 6 months after infection with *Campylobacter jejuni*, 17 (9.0%) of 188 individuals had IBS symptoms (71).
7. **United Kingdom.** The prevalence of IBS was 16.7% (18 of 108) for 108 patients 6 months after they reported a bacterial gastroenteritis attack that was confirmed by stool samples positive for *Campylobacter* (83.4% of the patients), *Salmonella* (14.1%), or *Shigella* (1.6%). In a control population of 206 individuals that did not have gastroenteritis, 4 individuals presented with IBS (1.9%) at 6 months (59).
8. **United Kingdom.** Of 747 individuals with a stool sample positive for *C. jejuni* or *Campylobacter coli*, 103 (13.8%) had IBS symptoms at 3 months (22).
9. **Canada and United States.** Traveler's diarrhea was diagnosed in 48 (44%) of 109 individuals traveling outside the United States or Canada. IBS was detected in 2 (4.2%) of these 48 individuals at 12 weeks after their return, whereas only 1 (1.6%) of the 61 individuals without traveler's diarrhea showed signs of IBS (33).
10. **Canada.** An outbreak of gastroenteritis due to *Escherichia coli* O157:H7 and *C. jejuni* contamination of a municipal water system included 1,368 patients. IBS was present in 30.5% of these patients. There were 71 cases of IBS (10.1%) in 701 individuals without gastroenteritis. The mean age of the gastroenteritis patients was 45.2 years, and 55.6% were women (41).
11. **Canada.** Gastroenteritis was diagnosed in 207 individuals: 119 patients were infected with *Campylobacter*, 38 with *Salmonella*, and 50 with *Giardia*. Seven patients (five with *Campylobacter*, one with *Salmonella*, and one with *Giardia*) contracted IBS, for a prevalence of IBS of 3.4% in the infected population (9).
12. **China.** In 235 patients (mean age, 40.7 years; male:female ratio, 1:1.3) diagnosed with a *Shigella* infection, 24 (10.2%) had IBS symptoms. In a closely matched control group, 2 (0.8%) of 243 had IBS (73).
13. **United States.** Of 40 students who contracted diarrhea while traveling in Mexico, 7 (17.5%) had IBS symptoms 6 months later, after returning to the United States. Enterotoxigenic *E. coli*, enteroaggregative *E. coli* (EAEC), *Shigella*, or *Cryptosporidium* were isolated from 25 of these students. Two of patients with IBS had been infected with EAEC and one had been infected with *Shigella*; no pathogen was isolated from the other IBS patients (55).
14. **Spain.** The prevalence of IBS in a Spanish population 1 year after a foodborne outbreak of *Salmonella* Enteritidis infection was 10.0% of 271 individuals compared with 0.7% of 335 individuals in the infection-free control population. The mean age of the infected individuals was 48.5 years (range, 18 to 93 years), and 55.3% were women. The controls were similar in age (mean age, 49.8 years) and sex (57.5% were women) (46).
15. **Korea.** Twelve months after infection with *Shigella sonnei*, 15 (14.9%) of 101 patients had IBS symptoms (male:female ratio, 1:2.5; mean age, 33.5 years; age range, 22 to 58 years). In an uninfected control population, 6 (5.9%) of 102 individuals had IBS at 12 months (male:female ratio, 1:2; mean age, 32.0 years; age range, 20 to 59 years) (34).

duration of gastroenteritis was 8 to 14 days, a 6.5-fold increase if the duration was 15 to 21 days, and a 11.4-fold increase if the diarrhea lasted >22 days (53). The age group most susceptible to PI-IBS was 19 to 44 years, whereas individuals 45 to >60 years of age were less susceptible (53). Similarly, Wang et al. (73) and Ji et al. (34) found that the longer the duration of infectious diarrhea, the greater the chance of developing PI-IBS; however, these workers also found that age and sex had no effect on the development of PI-IBS.

In a long-term study, Neal et al. (52) found that 6 years after diagnosis of IBS, symptoms persisted in those patients with a history of treatment for anxiety and/or depression. Most of these IBS patients were female (22 of 27; 81.5%),

and depression and/or anxiety interfered with recovery from IBS symptoms. Six years after diagnosis of IBS, 4 (30.8%) of 13 non-PI-IBS patients had recovered normal bowel habits; however, 6 (42.9%) of 14 patients with PI-IBS had recovered (52). Thus, the data of Neal et al. (52) suggest a better prognosis for PI-IBS patients than for IBS patients who had not suffered a preceding gastroenteritis infection. Spiller (65) suggested that PI-IBS is a benign disease and that 50% of the patients recover within 6 years.

Dunlop et al. (23) found that patients with IBS, both PI-IBS and non-PI-IBS, had a higher likelihood of a history of treatment for anxiety or depression compared with controls without IBS; however, significantly fewer patients with PI-IBS had a history of treatment for anxiety or de-

TABLE 4. Comparison of colonic transit time, peak serotonin concentrations after feeding, and platelet serotonin concentrations in PI-IBS patients, C-IBS patients, and healthy controls^a

Parameter studied	PI-IBS patients	C-IBS patients	Healthy controls
<i>n</i>	15 (7 female)	15 (15 female)	15 (10 female)
Colonic transit time (h)	26.7	49.4	34.1
Peak serotonin after feeding (nmol/liter)			
All patients	71.7	31.2	43.6
Women only	99.0	31.2	40.9
Platelet serotonin (ng per 10 platelets)			
All patients	484.1	652.0	598.0
Women only	440.1	652.0	626.4

^a Modified from Dunlop et al. (21).

pression compared with non-PI-IBS patients. Observing patients who had acute gastroenteritis, Gwee et al. (29, 30) found that those patients who developed PI-IBS had higher scores for a number of psychological characteristics than did those individuals with gastroenteritis but who did not develop PI-IBS. In a study of patients with *Campylobacter*-induced enteritis, Dunlop et al. (22) found that those patients with PI-IBS had higher scores for anxiety, depression, fatigue, decreased normal activities, and decreased emotional function than did enteritis patients who had recovered and did not contract PI-IBS.

When *Campylobacter jejuni* strains isolated from 93 patients with gastroenteritis were tested against HEp-2 cells (human larynx epidermoid carcinoma), 50 of the 93 isolates induced cytotoxic changes in these cells (elongation or rounding). Bowel changes reminiscent of PI-IBS occurred in 11 patients, and only 2 of these patients were infected with *C. jejuni* strains lacking cytotoxic activity (71). In vitro toxicity of the *C. jejuni* strains isolated from patients may be related to the induction of PI-IBS, and production of a toxin by *C. jejuni* may be a risk factor for PI-IBS.

Role of serotonin in PI-IBS. Dunlop et al. (21), using platelet-poor plasma, studied the peak plasma serotonin concentrations after a meal in PI-IBS patients, C-IBS patients, and healthy volunteers (Table 4). PI-IBS patients had a 2.3-fold increase in peak serotonin concentrations after a meal compared with C-IBS patients. The mean peak serotonin concentration in female PI-IBS patients was higher than that of male patients. The decreased serotonin concentrations in the C-IBS patients were correlated with the increased colonic transit time in these patients (Table 4); serotonin is known to stimulate gastric secretion and peristalsis. In addition, the accelerated colonic transit time for PI-IBS patients was correlated with increased serotonin concentrations. The concentration of serotonin within platelets was significantly reduced in PI-IBS patients compared with C-IBS patients and controls (Table 4).

ROLE OF INFLAMMATION IN IBS AND PI-IBS

There is a link between prior gastroenteritis, inflammation, IBS, and PI-IBS. An increase in the number of

chronic inflammatory cells, enterochromaffin cells, and T lymphocytes was demonstrated in rectal biopsy specimens from patients with PI-IBS (30, 67). An increase in gut permeability was also seen in the PI-IBS patients (67). Gwee et al. (28) found that the expression of rectal mucosal interleukin 1 β (IL-1 β) was increased in patients with PI-IBS, whereas patients who recovered from enteritis and who did not contract PI-IBS had IL-1 β concentrations similar to those of normal controls. IL-1 β expression was approximately twofold higher in PI-IBS patients than in non-PI-IBS patients (73). IL-1 is a mediator of host inflammatory responses (1). Because a number of gastroenteritis-inducing microorganisms are associated with PI-IBS, host inflammatory responses to enteric infection rather than the infecting microorganism per se probably is the determining factor in the alteration of the colonic physiology leading to PI-IBS (15). Patients who develop IBS after a bout of gastroenteritis are unable to down-regulate intestinal inflammation induced by the infecting organism.

Inflammation is also important in non-PI-IBS. Chadwick et al. (11) examined colonic biopsies from IBS patients and found that there was an increased number of activated immunocompetent cells (intraepithelial lymphocytes, CD3⁺ and CD25⁺ cells, neutrophils, mast cells, and natural killer cells), indicating that the mucosal immune system has a role in IBS. Barbara et al. (8) found that IBS patients (34 of 44; 77.3%) had a 2.8-fold increase in the number of mast cells in colonic mucosa compared with healthy controls, and there was a significant increase in mast cell degranulation with release of tryptase (a protease) and histamine. The increase in mast cells was approximately 1.5-fold higher in females than in males. Barbara et al. (8) also found that the severity and frequency of abdominal pain of IBS was correlated with how close the activated mast cells were to the gut wall nerve endings. Inflammation induced by the release of tryptase and histamine probably is involved in the pain symptoms of IBS (8).

Gonsalkorale et al. (26) found that approximately 25% of 230 IBS patients and 450 controls were genetically predisposed to produce low concentrations of the anti-inflammatory cytokine IL-10. IBS patients, with a reduced capacity to produce IL-10, have a compromised ability to down-regulate inflammatory responses (26). The mean concentration of IL-10 released from peripheral blood mononuclear cells (PBMCs) isolated from IBS patients was 575 pg/ml compared with 968 pg/ml from healthy controls, and the concentration of the proinflammatory cytokine IL-12 released from the PBMCs of IBS patients was 15 pg/ml compared with 6 pg/ml for controls (56). The IL-10:IL-12 ratio for IBS patients was significantly lower than that for healthy controls. The reduced IL-10:IL-12 ratio in IBS patients indicates that the immune response is skewed toward a proinflammatory Th1 profile (56). Spiller (63) pointed out that the balance between the anti-inflammatory cytokine IL-10 and the proinflammatory cytokine IL-12 in the gut mucosa determines T-cell responses, including cell-mediated immunity (Th1-type cells that produce proinflammatory cytokines) and humoral-mediated immunity (Th2-type cells that produce anti-inflammatory cytokines). IL-10 limits the

immune response and minimizes damage to the gastric mucosa by inhibiting secretion of proinflammatory cytokines. Thus, the decreased secretion of IL-10 by some IBS patients is an important factor leading to the inflammation that induces IBS. When O'Mahony et al. (56) administered a *Bifidobacterium infantis* probiotic preparation to IBS patients, their decreased IL-10:IL-12 ratio normalized to the ratio found in control individuals. The probiotic was probably acting as an immunomodulator to bring the ratio back to normal (37).

van der Veek et al. (72) demonstrated that tumor necrosis factor α (TNF- α) is an important proinflammatory cytokine involved in IBS. The combination of a high producer genotype for TNF- α plus a low producer genotype for IL-10 was three times more prevalent in IBS patients than in healthy controls (72). The high TNF- α plus low IL-10 genotype was equally represented in PI-IBS and non-PI-IBS patients. However, the high TNF- α plus low IL-10 genotype was more prevalent in D-IBS patients (7 of 35; 20.0%) than in C-IBS patients (1 of 27; 3.7%) or patients with alternating diarrhea and constipation (1 of 34; 2.9%) (72). These results indicate that the imbalance between the proinflammatory TNF- α and anti-inflammatory IL-10 favors enhanced inflammation and that TNF- α is associated with diarrhea in IBS.

Serotonin is released in high concentrations at sites of inflammation (49); thus, serotonin exerts a proinflammatory effect on the immune system. Serotonin increases mesenteric microvascular permeability, which facilitates the influx of lymphocytes and other inflammatory cells into intestinal tissue (47). Serotonin receptors are located on various immune cells such as B cells, T cells, monocytes, and macrophages (50). Immune functions in which serotonin is involved include activation of T cells and killer cells, responses tied to delayed-type hypersensitivity, and induction of chemotactic factors that generate infiltrates containing a variety of immune cells (50).

Inflammation is an important factor in the induction of PI-IBS. However, inflammatory processes also are involved in some cases of non-PI-IBS. It is not clear whether inflammation is a general phenomenon in non-PI-IBS or whether it occurs only in a subset of those patients.

PERSPECTIVES

The chance that a patient will develop PI-IBS is increased when the gastroenteritis is severe and of long duration. The virulence of the infecting bacteria, i.e., the ability to cause changes in the gut mucosa and induce inflammation, probably plays a role in induction of PI-IBS. Females are two to three times more likely to develop IBS and PI-IBS than are males. The risk of development of IBS or PI-IBS is elevated in patients with high degrees of anxiety, depression, or other psychological disorders.

The driving forces behind the persistent debilitating symptoms of IBS remain unclear. However, recent investigations of IBS patients, especially PI-IBS patients, indicate that inflammation of the gut mucosa is accompanied by an influx of immune cells such as T cells, mast cells, neutrophils, and natural killer cells. There is also an increase in

inflammatory mediators such as histamine, serotonin, and cytokines. Thus, inflammatory processes probably are responsible for the pathophysiology of IBS. In addition, certain individuals probably are genetically more susceptible to the syndrome because of their inability to down-regulate inflammatory immune responses or may have other physiological defects leading to altered serotonin profiles.

In a number of studies, serotonin and cytokines have been involved in the pathophysiology of IBS and PI-IBS. However, there is little information on the possible interrelationship between cytokines and serotonin in the induction and maintenance of IBS. Chaitidis et al. (12) reported that IL-4 and IL-13 up-regulated the expression of monoamine oxidase A, an enzyme involved in the decomposition of serotonin. Serotonin also can have an effect on cytokine production. Cloëz-Tayarani et al. (14) found decreased production of TNF- α and increased production of IL-1 β in response to serotonin in *E. coli* lipopolysaccharide-stimulated PBMCs. Although it has not been demonstrated, cytokine-serotonin interactions probably are involved in inflammatory processes leading to the symptoms seen in IBS and PI-IBS patients.

A microbial gastroenteritis infection can be the trigger of PI-IBS. Identified outbreak organisms associated with PI-IBS (Table 3) included *C. coli*, *C. jejuni*, *E. coli* O157:H7, enteroaggregative *E. coli*, *Salmonella* Enteritidis, and *S. sonnei*; in some outbreaks, the organisms were merely identified as *Campylobacter*, *Salmonella*, or *Shigella*. Any severe gastroenteritis attack (either sporadic or part of an outbreak) probably can provoke PI-IBS in susceptible individuals. Therefore, PI-IBS should be considered as a long-term consequence of foodborne illness because the gastroenteritis-inducing microorganisms leading to PI-IBS are common foodborne pathogens.

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