

# **Current Thinking About IBS:**

**An Educational Review of  
Irritable Bowel Syndrome**

**Section 1:  
Epidemiologic Perspectives  
on IBS**

# Earliest Descriptions of Symptoms Defining IBS

- **1849: Cumming<sup>1</sup>**
  - “The bowels are at one time constipated, at another lax, in the same person. How the disease has two such different symptoms I do not profess to explain. . . .”
- **Other Historical Terms**
  - Mucous colitis
  - Colonic spasm
  - Neurogenic mucous colitis
  - Irritable colon
  - Unstable colon
  - Nervous colon
  - Spastic colon
  - Nervous colitis
  - Spastic colitis
- **1962: Chaudhary and Truelove<sup>2</sup>**  
Irritable colon syndrome
- **1966: DeLor<sup>3</sup>**  
Irritable bowel syndrome (IBS)

References: 1. Cumming. *Lond Med Gazette*. 1849;NS9:969-973. 2. Chaudhary and Truelove. *Q J Med*. 1962;31:307-322. 3. DeLor. *Am J Gastroenterol*. 1967;47:427-434.

Physicians have been aware of the symptoms of irritable bowel syndrome (IBS) for well over a century. The first reports in medical journals of patients with functional abdominal symptoms appeared in the early 19th century. In 1849, Cumming aptly described IBS when he stated, “The bowels are at one time constipated, at another lax, in the same person. How the disease has two such different symptoms, I do not profess to explain...”<sup>1</sup> Throughout the 19th and into the 20th century, some of the other terms used to describe IBS were neurogenic mucous colitis,<sup>2</sup> spastic colon,<sup>3</sup> and irritable colon syndrome.<sup>4</sup>

However, it was not until just over 30 years ago that the term irritable bowel syndrome was coined. In 1966, DeLor referred to the irritable bowel syndrome, defining it as a functional enteropathy, characterized by one or a combination of symptoms, including abdominal pain, diarrhea, constipation, dyschezia, and passage of mucus in the stool.<sup>5</sup>

## References:

1. Cumming W. Electro-galvanism in a peculiar affection of the mucous membrane of the bowels. *Lond Med Gazette*. 1849;NS9:969-973.
2. Bockus HL, Bank J, Wilkinson SA. Neurogenic mucous colitis. *Am J Med Sci*. 1928;176:813-829.
3. Ryle JA. Chronic spasmodic affections of the colon and the diseases which they simulate. *Lancet*. 1928;215:1115-1119.
4. Chaudhary NA, Truelove SC. The irritable colon syndrome. *Q J Med*. 1962;31:307-322.
5. DeLor CJ. The irritable bowel syndrome. *Am J Gastroenterol*. 1967;47:427-434.

## Historical Perspective

- Long dismissed as a psychosomatic condition<sup>1</sup>
  - No clear etiology
  - Affects predominantly women (~70% of sufferers are women)<sup>2</sup>
  - Condition not fatal
- Attitudes now changing
- Incidence and prevalence not extensively monitored in past

References: 1. Maxwell et al. *Lancet*. 1997;350:1691-1695. 2. Sandler. *Gastroenterology*. 1990;99:409-415.

IBS was long dismissed as a psychosomatic condition.<sup>1</sup> It has no clear etiology or pathophysiology, affects mainly women, and is not fatal.<sup>2</sup> However, attitudes are changing as physicians learn more about the pathophysiology of IBS.

The incidence and prevalence of IBS have not been extensively monitored, so it is difficult to discern historical trends. In addition, only a small proportion of IBS sufferers seek treatment,<sup>3</sup> and diagnosis of the condition is difficult.<sup>4</sup>

### References:

1. Maxwell PR, Mendall MA, Kumar D. Irritable bowel syndrome. *Lancet*. 1997;350:1691-1695.
2. Sandler RS. Epidemiology of irritable bowel syndrome in the United States. *Gastroenterology*. 1990;99:409-415.
3. Drossman DA, Thompson WG. The irritable bowel syndrome: review and a graduated multicomponent treatment approach. *Ann Intern Med*. 1992;116(pt 1):1009-1016.
4. Paterson WG, Thompson WG, Vanner SJ, et al. Recommendations for the management of irritable bowel syndrome in family practice. *Can Med Assoc J*. 1999;161:154-160.

## Current Definition

IBS is defined as “a functional bowel disorder in which abdominal pain is associated with defecation or a change in bowel habits, with features of disordered defecation and distention.”

Reference: Thompson et al. *Gut*. 1999;45(suppl 2):1143-1147.

The Rome II multinational consensus document on functional gastrointestinal (GI) disorders has defined IBS as “a functional bowel disorder in which abdominal pain is associated with defecation or a change in bowel habits, with features of disordered defecation and distention.”

**Reference:**

Thompson WG, Longstreth GF, Drossman DA, Heaton KW, Irvine EJ, Müller-Lissner SA. Functional bowel disorders and functional abdominal pain. *Gut*. 1999;45(suppl 2):1143-1147.

## Key Facts About IBS

- Up to 20% of the US population report symptoms consistent with IBS<sup>1</sup>
- The most common GI diagnosis among gastroenterology practices in the US<sup>2</sup>
- One of the top 10 reasons for PCP visits<sup>3</sup>
- Affects predominantly females (~70% of sufferers)<sup>4</sup>
- The most common functional bowel disorder<sup>5</sup>

References: 1. Camilleri and Choi. *Aliment Pharmacol Ther.* 1997;11:13-15. 2. Everhart and Renault. *Gastroenterology.* 1991;100:998-1005. 3. Drossman et al. *Dig Dis Sci.* 1993;38:1569-1580. 4. Sandler. *Gastroenterology.* 1990;99:409-415. 5. Thompson et al. *Gastroenterol Int.* 1992;5:75-91.

Prevalence estimates from surveys among American adults suggest that up to 20% of the population report symptoms consistent with IBS.<sup>1</sup> These surveys have shown that, in general, female patients outnumber male patients 3:1.<sup>2</sup>

IBS is the most common functional bowel disorder,<sup>3</sup> the most common GI diagnosis among US gastroenterology practices,<sup>4</sup> and one of the top 10 reasons for primary care physician visits.<sup>5</sup>

Estimates of prevalence of IBS are diverse, however. This is likely to be a consequence of the differences between epidemiologic studies (ie, the use of different diagnostic criteria, selected populations, and the source of the data).<sup>2</sup>

### References:

1. Camilleri M, Choi M-G. Review article: irritable bowel syndrome. *Aliment Pharmacol Ther.* 1997;11:3-15.
2. Everhart JE, Renault PF. Irritable bowel syndrome in office-based practice in the United States. *Gastroenterology.* 1991;100:998-1005.
3. Thompson WG, Creed F, Drossman DA, Heaton KW, Mazzacca G. Functional bowel disease and functional abdominal pain. *Gastroenterol Int.* 1992;5:75-91.
4. Sandler RS. Epidemiology of irritable bowel syndrome in the United States. *Gastroenterology.* 1990;99:409-415.
5. Drossman DA, Li Z, Andruzzi E, et al. US householder survey of functional gastrointestinal disorders—prevalence, sociodemography, and health impact. *Dig Dis Sci.* 1993;38:1569-1580.

## Key Facts About IBS (cont'd)

- Symptoms can range from mild and intermittent to severe and continuous<sup>1</sup>
- Can significantly disrupt daily life<sup>2</sup>
- Can have negative impact on quality of life<sup>2</sup>
- Current treatment options<sup>3</sup>
  - Dietary modification
  - Fiber supplements
  - Pharmacologic agents
  - Psychotherapy

References: 1. Lembo et al. *Clinical Gastroenterology and Hepatology*. 2005;3:717-725. 2. Hahn et al. *Digestion*. 1999;60:77-81. 3. Drossman. *Aliment Pharmacol Ther*. 1999;13(suppl 2):3-14.

IBS can cause great discomfort and can affect an individual for many years. The symptoms can be either persistent or recurrent and may vary over time.<sup>1</sup> Patients suffer from altered bowel habits accompanied by pain or discomfort, which can significantly disrupt their daily lives.<sup>2</sup>

Current treatment options include

- Dietary restrictions—avoiding fatty foods or lactose<sup>3</sup>
- Supplementing diet with fiber<sup>3,4</sup>
- Pharmacologic agents—antidiarrheals,<sup>3</sup> laxatives,<sup>3</sup> antispasmodics,<sup>3</sup> tricyclic antidepressants, and SSRIs<sup>4</sup>
- Psychotherapy—hypnotherapy, relaxation exercises, psychological treatment<sup>3,4</sup>

Success of current treatment options in addressing multiple symptoms of IBS has been limited.<sup>5</sup>

### References:

1. Lembo et al. *Clinical Gastroenterology and Hepatology*. 2005;3:717-725.
2. Hahn BA, Yan S, Strassels S. Impact of irritable bowel syndrome on quality of life and resource use in the United States and United Kingdom. *Digestion*. 1999;60:77-81.
3. Drossman DA. Review article: an integrated approach to the irritable bowel syndrome. *Aliment Pharmacol Ther*. 1999;13(suppl 2):3-14.
4. American Gastroenterological Association. Medical position statement: irritable bowel syndrome. *Gastroenterology*. 1997;112:2118-2119.
5. Klein KB. Controlled treatment trials in the irritable bowel syndrome: a critique. *Gastroenterology*. 1988;95:232-241.

## US Population Statistics

- IBS Up to 20%
- Diarrhea-predominant 5%-10%
- Female/male ratio 80:20

Reference: Drossman et al. *Gastroenterology*. 1997;112:2120-2137.

IBS is a common disorder affecting up to 20% of the US population in epidemiologic surveys.<sup>1</sup> The diarrhea-predominant form affects 5-10% of the US population, representing 25 to 50% of IBS patients.<sup>1</sup> Women are more commonly affected by the disorder. These data provide an insight into why IBS is the most common diagnosis in US gastroenterology practices and one of the top 10 reasons for primary care physician visits.

### Reference:

1. Drossman DA, Whitehead WE, Camilleri M. Irritable bowel syndrome: a technical review for practice guideline development. *Gastroenterology*. 1997;112:2120-2137.

## IBS Versus Other Important Disease States

- US prevalence of IBS up to 20%<sup>1</sup>
- US prevalence rates for other common diseases<sup>2</sup>
  - Diabetes 3%
  - Asthma 4%
  - Heart disease 8%
  - Hypertension 11%

References: 1. Camilleri and Choi. *Aliment Pharmacol Ther.* 1997;11:3-15. 2. Adams and Benson. *Vital Health Stat 10.* 1991:83. DHHS publication (PHS) 92-1509.

When compared with prevalence rates of other common diseases, IBS ranks the highest and has nearly twice the rate of hypertension, the next most prevalent disease state.<sup>1</sup> Although it is not a life-threatening disease, it is important to note the dramatic impact that IBS can have on the quality of life of those who are affected.

### Reference:

1. Adams PF, Benson V. Current estimates from the National Health Interview Survey, 1990. *Vital Health Stat 10.* Hyattsville, Md: US Dept of Health and Human Services, Public Health Service, Centers for Disease Control, National Center for Health Statistics; 1991:83. DHHS publication (PHS) 92-1509.

## IBS Subtypes

- Constipation predominant
- Diarrhea predominant
- Alternator (alternating bouts of diarrhea and constipation)

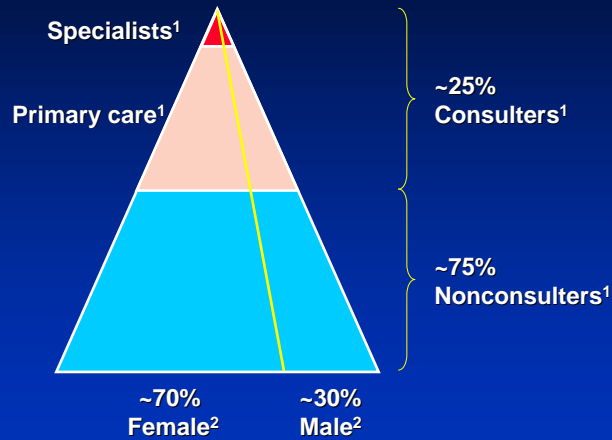
Reference: Talley et al. *Gastroenterology*. 1991;101:927-934.

A person who suffers from IBS typically suffers from diarrhea, constipation, or an alternation of both.<sup>1</sup> In the Olmsted County study, there were equal prevalence rates of constipation-predominant IBS, diarrhea-predominant IBS, and IBS with alternating bowel movements (5.2%).<sup>2</sup> With regard to diarrhea and constipation, it was found that some patients with diarrhea-predominant IBS have accelerated transit in the small bowel and colon, while others with constipation-predominant IBS have delayed transit.<sup>3</sup>

### References:

1. Dancy CP, Backhouse S. Towards a better understanding of patients with irritable bowel disease. *J Adv Nurs*. 1993;18:1443-1450.
2. Talley NJ, Zinsmeister AR, Van Dyke C, Melton LJ 3rd. Epidemiology of colonic symptoms and the irritable bowel syndrome. *Gastroenterology*. 1991;101:927-934.
3. Drossman DA. Review article: an integrated approach to the irritable bowel syndrome. *Aliment Pharmacol Ther*. 1999;13(suppl 2):3-14.

## IBS Consultation Pattern



References: 1. Drossman and Thompson. *Ann Intern Med.* 1992;116(pt 1):1009-1016. 2. Sandler. *Gastroenterology.* 1990;99:409-415.

Although IBS affects up to one fifth of the population, only 25% seek medical advice. It is unclear why the other 75% do not consult their physicians.<sup>1</sup> Some patients may have received unsatisfactory treatment in the past,<sup>1</sup> or simply may have learned to live with their condition and accept their current quality of life.<sup>2</sup>

### References:

1. Drossman DA, Thompson WG. The irritable bowel syndrome: review and a graduated multicomponent treatment approach. *Ann Intern Med.* 1992;116(pt 1):1009-1016.
2. Wells NEJ, Hahn BA, Whorwell PJ. Clinical economics review: irritable bowel syndrome. *Aliment Pharmacol Ther.* 1997;11:1019-1030.

## Direct Medical Costs Associated With IBS

- IBS results annually in an estimated
  - \$2 billion in direct medical costs<sup>1</sup>
  - \$20 billion in indirect costs<sup>1</sup>
  - 3.5 million physician visits<sup>2</sup>
  - 2.2 million prescriptions<sup>2</sup>
- IBS sufferers incur 74% more direct healthcare costs than non-IBS sufferers<sup>3</sup>
- IBS patients have more physician visits for both GI and non-GI complaints<sup>4</sup>

References: 1. Camilleri M. *Gastroenterology*. 2001;120:652-668. 2. Everhart et al. *Gastroenterology*. 1991;100:998-1005. 3. Talley et al. *Gastroenterology*. 1995;109:1736-1741. 4. Drossman et al. *Dig Dis Sci*. 1993;38:1569-1580.

In the United States, IBS accounts for an estimated 3.5 million physician visits per year and an estimated 2.2 million prescriptions.<sup>1</sup>

The high prevalence of IBS contributes to substantial national and medical costs estimated at close to \$2 billion in 1998.<sup>2</sup> Unnecessary diagnostic tests, inappropriate management, and unnecessary surgery account for some of the costs.<sup>3</sup> Significant among these is the cost associated with absenteeism and lost productivity due to the inability to work. Although it is difficult to estimate with precision, this has been calculated at approximately \$20 billion in 1998.<sup>2</sup>

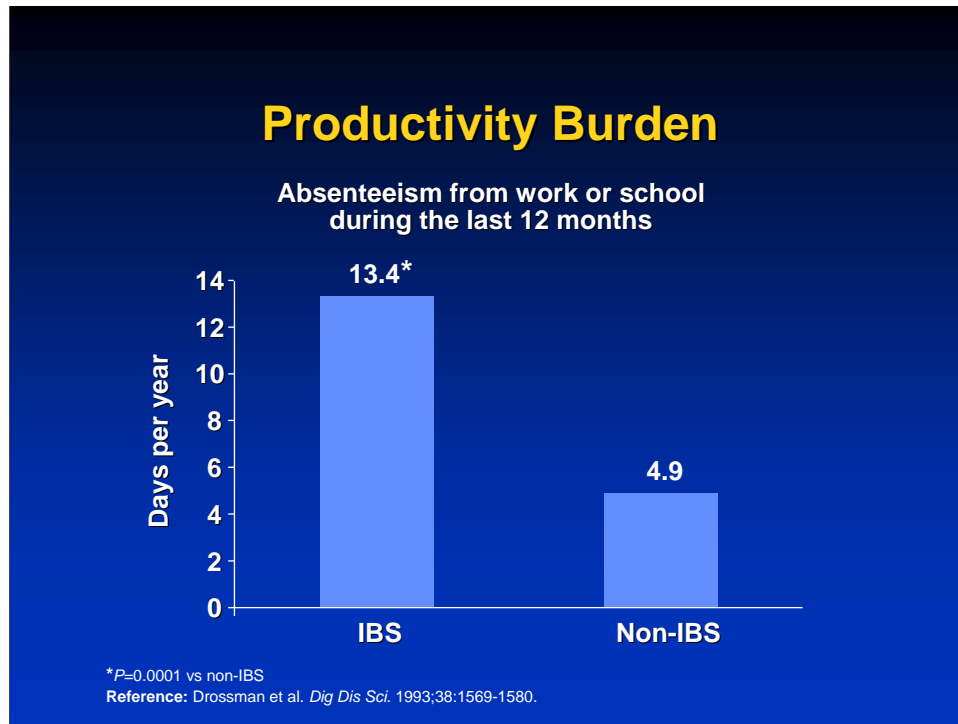
A community survey assessing the direct medical costs of IBS in the United States over a period of 1 year classified respondents (n=2,960) as<sup>4</sup>

- Subjects with symptoms compatible with IBS (abdominal pain more than 6 times in the prior year in combination with any 2 or more of the Manning criteria)
- Control subjects (no GI symptoms in the prior year)
- Subjects with some GI symptoms (abdominal pain or disturbed defecation in the prior year who failed to meet the criteria for IBS)

They found that direct 1-year medical charges for a patient with IBS were, on average, \$742 (based on charges in 1992), compared with \$429 for one without IBS, and \$614 for a person with some GI symptoms. Extrapolation of these findings to the US white population, based on 1992 costs, showed an annual charge of over \$8 billion resulting from IBS.<sup>4</sup>

### References:

1. Everhart JE, Renault PF. Irritable bowel syndrome in office-based practice in the United States. *Gastroenterology*. 1991;100:998-1005.
2. Camilleri M. Management of the irritable bowel syndrome. *Gastroenterology*. 2001;120:652-668.
3. Drossman DA, Whitehead WE, Camilleri M. Irritable bowel syndrome: a technical review for practice guideline development. *Gastroenterology*. 1997;112:2120-2137.
4. Talley NJ, Gabriel SE, Harmsen WS, Zinsmeister AR, Evans RW. Medical costs in community subjects with irritable bowel syndrome. *Gastroenterology*. 1995;109:1736-1741.



Symptoms of IBS and the resulting diminished quality of life have an impact on productivity. The impact of productivity is measured not only in terms of how businesses are affected by the high rate of absenteeism, but also by the impact of consultants on the healthcare system.

The purpose of the US Householder Survey reported here was to provide national data for the United States on the frequency and sociodemographic features of functional GI disorders and their relationship to absenteeism from work or school and healthcare use. A random sample of US householders was surveyed.

The survey showed that patients with IBS had missed about 3 times as many days from work or school in the previous year because of illness compared with those with no evidence of functional GI disorder (mean values: 13.4 days vs 4.9 days;  $P=0.0001$ ). In addition, a higher proportion of those with IBS reported that they currently were too sick to work or to go to school compared with those without IBS (11.3% vs 4.2%).

There is also an impact on health care systems and productivity. Persons with IBS were significantly more likely to see physicians for complaints unrelated to the GI tract (3.9/year vs 1.8/year;  $P=0.0001$ ), as well as for GI complaints (1.6/year vs 0.1/year;  $P=0.0001$ ), than were persons with no evidence of functional GI disorders.

**Reference:**

Drossman DA, Li Z, Andruzzi E, et al. US householder survey of functional gastrointestinal disorders—prevalence, sociodemography, and health impact. *Dig Dis Sci.* 1993;38:1569-1580.

## Impact on Work Due to IBS

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Patients with some missed workdays	30%
Average number missed workdays*	1.7
Patients who cut back some days	46%
Average number days cut back*	3

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\*Over the previous 4 weeks.

Adapted from Hahn et al. *Digestion*. 1999;60:77-81.

In a point-in-time postal survey of a random sample of 500 members of the International Foundation for Functional Gastrointestinal Disorders in the United States (65% response rate), Hahn et al questioned patients about major changes in their work due to IBS.

On average, patients lost nearly 2 days of work and cut back on their workday 3 days a month due to their IBS.

### Reference:

Hahn BA, Yan S, Strassels S. Impact of irritable bowel syndrome on quality of life and resource use in the United States and United Kingdom. *Digestion*. 1999;60:77-81.

## Impact on Work Due to IBS (cont'd)

### Patients who ever experienced change due to IBS\*

– Turned down promotion/advancement	16%
– Worked fewer hours	15%
– Changed to working at home	12%
– Lost a job or quit work	12%
– Changed jobs for health reasons	9%
– Changed schedule	8%

\*Patients could respond to any of the items listed.

Adapted from Hahn et al. *Digestion*. 1999;60:77-81.

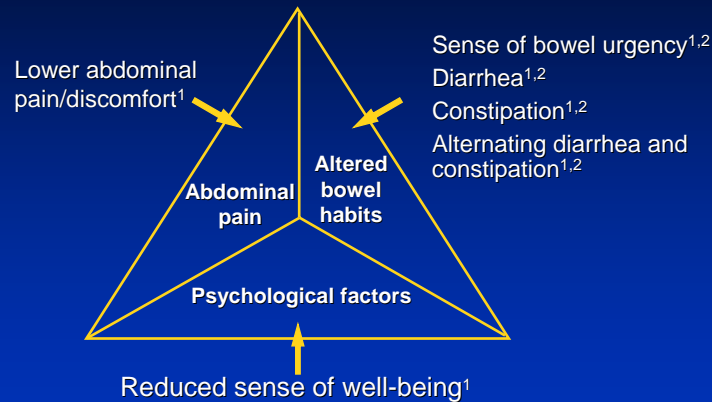
In this survey, a substantial percentage of patients had dramatic changes in their work routines due to IBS. Approximately 12% changed to working at home, and another 8% changed their work schedule due to IBS. Larger percentages lost a job or quit work, turned down a promotion, or worked fewer hours as a result of their condition.

The economic consequences of such changes are clearly far-reaching and show the potentially high impact of IBS on both the patient and the employer. Patients obviously may pay a price by turning down promotions, changing jobs, and/or having to work from home, and in many cases suffer financial losses. Businesses also share in the economic burden when the rate of absenteeism increases and productivity decreases.

### Reference:

Hahn BA, Yan S, Strassels S. Impact of irritable bowel syndrome on quality of life and resource use in the United States and United Kingdom. *Digestion*. 1999;60:77-81.

## IBS Symptoms Reduce Quality of Life



References: 1. Drossman. *Aliment Pharmacol Ther.* 1999;13(suppl 2):3-14. 2. Thompson et al. *Gut.* 1999;45 (suppl 2):1143-1147. 3. Hahn et al. *Digestion.* 1999;60:77-81.

IBS is a symptom complex in which lower abdominal pain or discomfort, altered bowel habits, and psychological factors may reduce a patient's quality of life.<sup>1,2</sup>

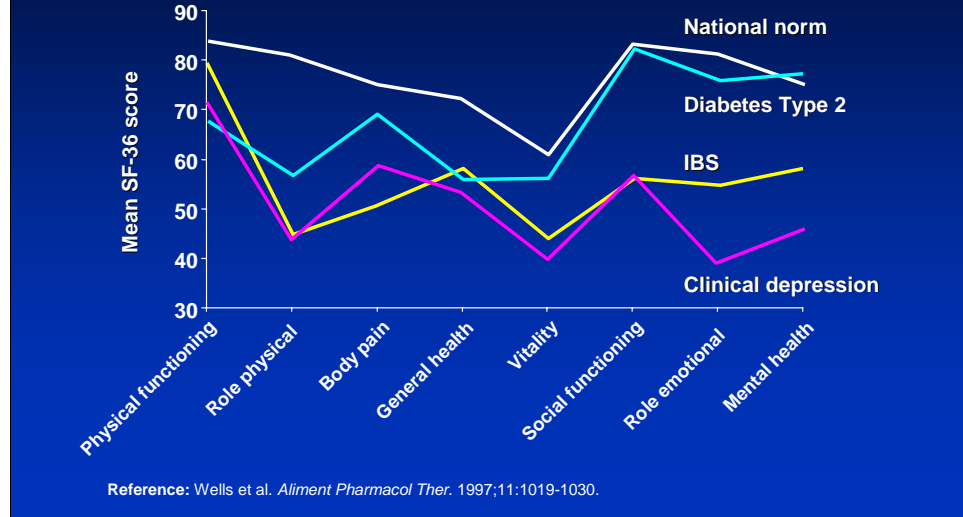
The burden of an illness can be examined in terms of impact on quality of life. There is growing recognition among physicians and healthcare providers that a patient's well-being is a critical component of health, encompassing physical functioning, mental health, social interaction, and overall quality of life.<sup>1,3</sup>

Although IBS is not life threatening, patients frequently report a restricted lifestyle that has been adapted to cope with their condition. These coping mechanisms have costs in terms of time lost from work, job opportunities, psychological consequences, and limited social interaction with family and friends.<sup>3</sup>

### References:

1. Hahn BA, Yan S, Strassels S. Impact of irritable bowel syndrome on quality of life and resource use in the United States and United Kingdom. *Digestion.* 1999;60:77-81.
2. Drossman DA. Review article: an integrated approach to the irritable bowel syndrome. *Aliment Pharmacol Ther.* 1999;13(suppl 2):3-14.
3. Wells NEJ, Hahn BA, Whorwell PJ. Clinical economics review: irritable bowel syndrome. *Aliment Pharmacol Ther.* 1997;11:1019-1030.

## Impact of IBS on Quality of Life Compared With Other Conditions



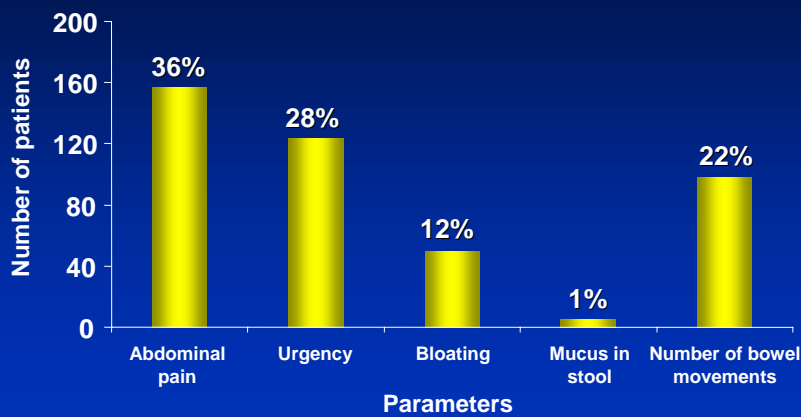
Despite the benign reputation of IBS, it is increasingly recognized that patients with IBS have worse health-related quality of life than national norms. As shown in the above graph, health-related quality of life in patients with IBS is worst for most domains when compared with both normal patients and patients with Type 2 diabetes.<sup>1</sup> Moreover, IBS patients have a health-related quality of life generally comparable to patients suffering from clinical depression, a well-recognized and very serious functional disorder.<sup>1</sup> In fact, vitality and social functioning are equally impaired in both conditions.

Such factors as physical functioning, mental health, and interaction with family and friends are key contributors to a patient's sense of well-being and health.<sup>1</sup> Studies have shown that IBS can affect sleep,<sup>2</sup> employment,<sup>3</sup> sexual function, leisure, and travel,<sup>4</sup> and can cause depression and anxiety.<sup>2</sup>

### References:

1. Wells NEJ, Hahn BA, Whorwell PJ. Clinical economics review: irritable bowel syndrome. *Aliment Pharmacol Ther.* 1997;11:1019-1030.
2. Sjödin I, Svedlund J. Psychological aspects of non-ulcer dyspepsia: a psychosomatic view focusing on a comparison between the irritable bowel syndrome and peptic ulcer disease. *Scand J Gastroenterol.* 1985;20(suppl 109):51-58.
3. Hahn BA, Yan S, Strassels S. Impact of irritable bowel syndrome on quality of life and resource use in the United States and United Kingdom. *Digestion.* 1999;60:77-81.
4. Dancy CP, Backhouse S. Towards a better understanding of patients with irritable bowel syndrome. *J Adv Nurs.* 1993;18:1443-1450.

## Bothersome Symptoms of IBS in Nonconstipated Female Patients



Reference: Camilleri et al. *Arch Intern Med.* 2001;161(14):1733-1740.

IBS is characterized by abdominal pain and discomfort, changes in stool frequency and consistency, urgency to defecate, bloating, and mucus in the stool. The results of a survey that sought to evaluate the relative importance of these various symptoms in female nonconstipated IBS patients participating in two 18-week clinical studies were reported by Camilleri et al.

On 3 random days, approximately 6 weeks apart, patients were asked, "When your IBS is active, which of the following symptoms bothers you the most?" Possible answers, of which only one could be selected, included abdominal pain, urgency to defecate, bloating, mucus in stool, and number of bowel movements. Patients consistently reported that abdominal pain and urgency were the 2 most bothersome symptoms.

### Reference:

Camilleri M, Chey WY, Mayer EA, et al. A randomized controlled clinical trial of the serotonin type 3 receptor antagonist alosetron in women with diarrhea-predominant irritable bowel syndrome. *Arch Intern Med.* 2001;161(14):1733-1740.

## Epidemiologic Perspectives on IBS: Summary

- IBS is “a functional bowel disorder in which abdominal pain is associated with defecation or a change in bowel habits, with features of disordered defecation and distention.”<sup>1</sup>
- Up to 20% of the US population, predominantly female (~70% of sufferers), report symptoms consistent with IBS<sup>2,3</sup>
- IBS is the most common functional bowel disorder<sup>4</sup> and most common diagnosis among GI practices in the US<sup>3</sup>
- IBS patients suffer from either diarrhea-predominant IBS, constipation-predominant IBS, or an alternation of both<sup>5</sup>

References: 1. Thompson et al. *Gut*. 1999;45(suppl 2):1143-1147. 2. Camilleri and Choi. *Aliment Pharmacol Ther*. 1997;11:3-15. 3. Sandler. *Gastroenterology*. 1990;99:409-415. 4. Thompson et al. *Gastroenterol Int*. 1992;5:75-91. 5. Dancy and Backhouse. *J Adv Nurs*. 1993;18:1443-1450.

The Rome II multinational consensus document on functional GI disorders defined IBS as “a functional bowel disorder in which abdominal pain is associated with defecation or a change in bowel habits, with features of disordered defecation and distention.”<sup>1</sup>

It is estimated that up to 20% of the US population report symptoms consistent with IBS.<sup>2</sup> Women outnumber men 3:1.<sup>3</sup>

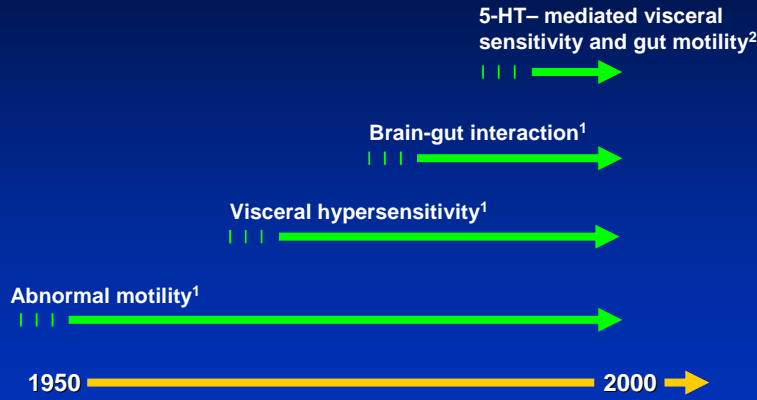
IBS is the most common functional bowel disorder,<sup>4</sup> the most common GI diagnosis among US gastroenterology practices,<sup>3</sup> and one of the top 10 reasons for primary care physician visits. A person who suffers from IBS typically suffers from diarrhea, constipation, or an alternation of both.<sup>5</sup>

### References:

1. Thompson WG, Longstreth GF, Drossman DA, Heaton KW, Irvine EJ, Müller-Lissner SA. Functional bowel disorders and functional abdominal pain. *Gut*. 1999;45(suppl 2):1143-1147.
2. Camilleri M, Choi M-G. Review article: irritable bowel syndrome. *Aliment Pharmacol Ther*. 1997;11:3-15.
3. Sandler RS. Epidemiology of irritable bowel syndrome in the United States. *Gastroenterology*. 1990;99:409-415.
4. Thompson WG, Creed F, Drossman DA, Heaton KW, Mazzacca G. Functional bowel disease and functional abdominal pain. *Gastroenterol Int*. 1992;5:75-91.
5. Dancy CP, Backhouse S. Towards a better understanding of patients with irritable bowel disease. *J Adv Nurs*. 1993;18:1443-1450.

## **Section 2: Pathophysiology of IBS**

# Evolution of Mechanistic Hypotheses in IBS



References: 1. Drossman DA. *Aliment Pharmacol Ther.* 1999;13(suppl 2):3-14. 2. Prior and Read. *Aliment Pharmacol Ther.* 1993;7:175-180.

The recognition of the importance of brain-gut interaction in determining abnormal intestinal functioning in IBS has arisen gradually over several decades.<sup>1</sup> Observations in the 1950s of heightened bowel motility in patients with irritable colon suggested that abnormal motility underlies IBS symptoms.<sup>2</sup> Later observations showing that patients with IBS have lower visceral pain thresholds than healthy subjects suggested that visceral hypersensitivity is also important in explaining the clinical manifestations of IBS.<sup>3,4</sup> As knowledge increased about the intricate interrelatedness of the brain and the gut, researchers realized that the abnormal motility and visceral hypersensitivity in IBS are determined by reciprocal interactions between gut and brain.<sup>1</sup>

During the last decade, chemical mediators of brain-gut interaction (ie, bradykinin, tachykinins, calcitonin gene-related peptide [CGRP], vasoactive intestinal polypeptide [VIP], substance P, and serotonin [5-HT]) have begun to be identified. 5-HT, a neurotransmitter in both the central nervous system (CNS) and the enteric nervous system (ENS), is a key mediator of visceral hypersensitivity and heightened bowel motility in patients with IBS.<sup>5</sup>

## References:

1. Drossman DA. Review article: an integrated approach to the irritable bowel syndrome. *Aliment Pharmacol Ther.* 1999;13(suppl 2):3-14.
2. Almy TP. Experimental studies on the irritable colon. *Am J Med.* 1951;10:60-67.
3. Ritchie J. Pain from distension of the pelvic colon by inflating a balloon in the irritable colon syndrome. *Gut.* 1973;14:125-132.
4. Whitehead WE, Engel BT, Schuster MM. Irritable bowel syndrome: Physiological and psychological differences between diarrhea-predominant and constipation-predominant patients. *Dig Dis Sci.* 1980;25:404-413.
5. Prior A, Read NW. Reduction of rectal sensitivity and post-prandial motility by granisetron, a 5-HT<sub>3</sub>-receptor antagonist, in patients with irritable bowel syndrome. *Aliment Pharmacol Ther.* 1993;7:175-180.

## Evolution of Research on the Pathophysiology of IBS

- **Abnormal gut motility**
  - Helps identify IBS
  - Not sufficient to explain symptoms of abdominal pain
- **Visceral hypersensitivity**
  - Influenced by but independent of abnormal motility and psychological disturbance
  - Inflammatory mediators in mucosa consistent with visceral sensitivity in patients with diarrhea-predominant IBS

Reference: Drossman. *Aliment Pharmacol Ther.* 1999;13(suppl 2):3-14.

From the 1950s through the early 1980s, enhanced gut motility was thought to be the basis for IBS symptoms.<sup>1</sup> Much of the research addressed the effects of experimental stress, meals, peptides, pain, and other stimuli on the motor response of the colon.<sup>2</sup> Pretreatment with an anticholinergic agent reduced postprandial sigmoid motility, and this finding led to the widespread use of anticholinergic medication in IBS to reduce meal-stimulated cramps and diarrhea. With regard to diarrhea, it was found that some patients with diarrhea-predominant IBS have accelerated transit in the small bowel and colon.<sup>1</sup> Beginning in the 1970s, efforts were also made to identify specific markers of motility for IBS. The early evidence for a characteristic 3-cycle/minute myoelectric pattern was not supported in later studies.<sup>1</sup> In the 1980s, studies identified abnormal nonperistaltic phase II contraction of the proximal and distal small bowel that were somewhat specific for IBS,<sup>2</sup> but these contractions were associated with patient reports of pain less than half of the time. So although these motility patterns helped to identify IBS, they were not sufficient to explain patients' symptoms of abdominal pain.<sup>1</sup>

The failure of dysmotility to explain symptoms of pain eventually led to studies of "visceral hypersensitivity" in IBS. It was found that with balloon distention studies of the ileum and colorectum, patients with IBS experience awareness of distention and pain at pressures and volumes that are significantly lower than in control subjects. The fact that IBS patients have normal or even increased thresholds for pain stimulation of somatic neuroreceptors indicates that the hypersensitivity is relatively specific for the viscera. The mechanism of visceral hypersensitivity is under investigation. It has been proposed that multiple factors (ie, genetic, inflammation, motility, local nerve mechanical irritation, psychological factors) alter neuroreceptors and afferent spinal neural function and CNS modulation of afferent input in a fashion that produces long-term sensitization of pathways involved in the transmission of visceral sensation. Evidence that a subset of patients with diarrhea-predominant IBS have inflammatory mediators in their mucosa would be consistent with the visceral sensitivity hypothesis.<sup>1</sup>

### References:

1. Drossman DA. Review article: an integrated approach to the irritable bowel syndrome. *Aliment Pharmacol Ther.* 1999;13(suppl 2):3-14.
2. Drossman DA, Whitehead WE, Camilleri M. Irritable bowel syndrome: a technical review for practice guideline development. *Gastroenterology.* 1997;112:2120-2137.

## Evolution of Research on the Pathophysiology of IBS (cont'd)

- Brain-gut interaction
  - Modulating effect of CNS on ENS regulation of motility
  - Numerous brain-gut neurotransmitters (ie, enkephalins, nitric oxide [NO], tachykinins, CGRP, cholecystokinin [CCK], 5-HT)

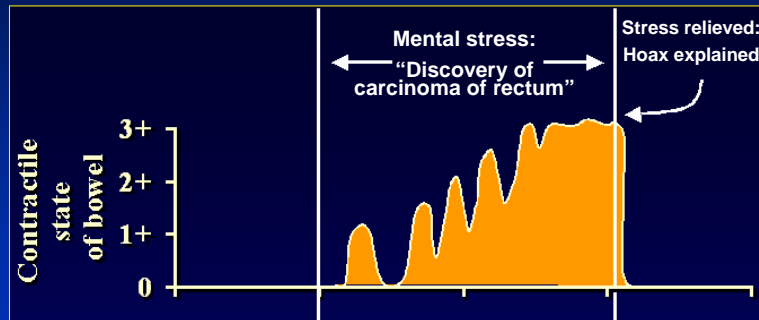
Reference: Drossman. *Aliment Pharmacol Ther.* 1999;13(suppl 2):3-14.

CNS centers modulate peripheral intestinal motor or sensory activity. An evolving theory is that normal gastrointestinal function results from an integration of intestinal motor, sensory, autonomic, and CNS activities, and that gastrointestinal symptoms may relate to dysregulation of these systems. These domains interact through bidirectional parallel circuits (“brain-gut axis”), which link visceral afferent sensation and intestinal motor function with higher cortical centers that modulate and modify their activity. Thus, extrinsic (ie, vision, smell) or enteroceptive (ie, emotion, thought) sources of information have, by the nature of their neural connections from higher centers, the capability to affect gastrointestinal sensation, motility, and secretion. Conversely, nociceptive input reciprocally affects central pain perception, mood, and behavior. Based on these findings, it appears that physiological and psychological factors cause pain and other bowel symptoms.

### Reference:

Drossman DA. Review article: an integrated approach to the irritable bowel syndrome. *Aliment Pharmacol Ther.* 1999;13(suppl 2):3-14.

## Early Demonstration of Brain-Gut Interaction in Stress



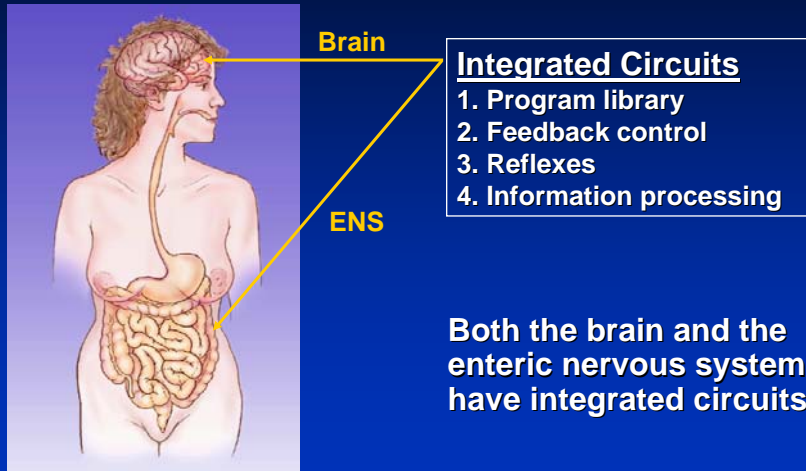
Adapted from Almy. *Am J Med.* January 1951;10:60-67.

To provide a historical context, Dr. Thomas P. Almy and colleagues were the first to show an early demonstration of brain-gut interaction.<sup>1,2</sup> They sought to determine the relationship between emotional states and gut functioning. A 22-year-old medical student volunteered to participate in an experiment that he was told would require a preliminary proctoscopy. After a 10-minute observation period, during which the volunteer's colon became relaxed and unengorged, the volunteer was led to believe that the proctoscopic evaluation had revealed evidence of a rectal carcinoma. Upon receiving this news, the volunteer expressed concern, and the contractile state of his bowel increased markedly. Occlusive spasm and engorgement developed. The volunteer was then informed that the discovery of the carcinoma was a hoax. Colonic motility and engorgement suddenly returned to normal. By demonstrating that emotional states can alter gut functioning, these data aptly demonstrate the physiological integration between brain and gut.

### References:

1. Almy TP. Experimental studies on the irritable colon. *Am J Med.* 1951;10:60-67.
2. Hasler WL, Owyang C. Irritable bowel syndrome. In: Yamada T, Alpers DH, Owyang C, Laine L, Powell DW, eds. *Textbook of Gastroenterology*. 3rd ed. New York: Lippincott. 1999;84(2):1884-1909.

## The Enteric Nervous System Functions as a “Brain-in-the-Gut”



Reference: Wood et al. *Gut*. 1999;45(suppl II):II6-II16.

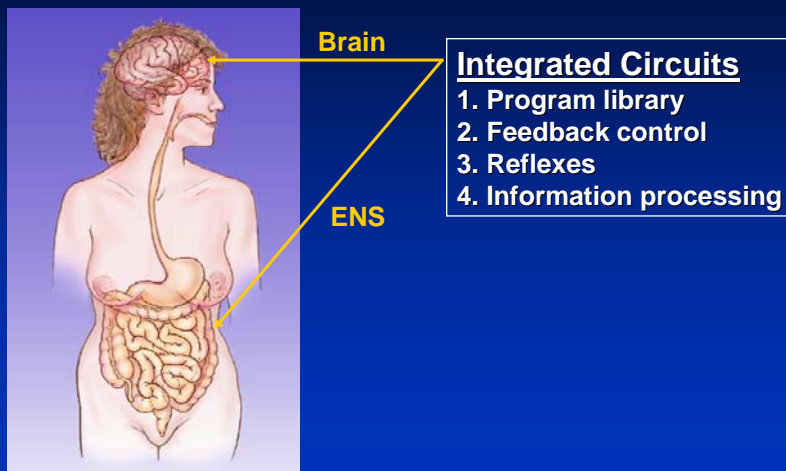
Gut function is largely controlled by the enteric nervous system (ENS). The ENS is the gut's neural network that regulates gut sensation and motor activity. Similar to the central nervous system (CNS), the ENS contains independent local circuits that mediate stimulus processing and behavior. The ENS is a local minibrain within which is stored a library of programs for different patterns of gut behavior. The ENS contains integrated local circuits that mediate 1) motor and secretory programs (program library); 2) feedback control; 3) reflexes; and 4) sensory information processing.<sup>1</sup> The ENS can therefore function independently of the brain to mediate gut activity and has been characterized as a “brain-in-the-gut.”<sup>2,3</sup>

Although some enteric functions are controlled largely by the enteric brain, the integrated circuits between the ENS and the CNS render them interdependent.

### References:

1. Wood JD, Alpers DH, Andrews PLR. Fundamentals of neurogastroenterology. *Gut*. 1999;45(suppl II):II6-II16.
2. Gershon MD, Kirchgessner AL, Wade PR. Functional anatomy of the enteric nervous system. In: Johnson LR, ed. *Physiology of the Gastrointestinal Tract*. 3rd ed. New York: Raven Press; 1994:381-422.
3. Goyal RK, Hirano I. The enteric nervous system. *N Engl J Med*. 1996;334:1106-1115.

## Dysregulation of the Brain-Gut Axis in IBS



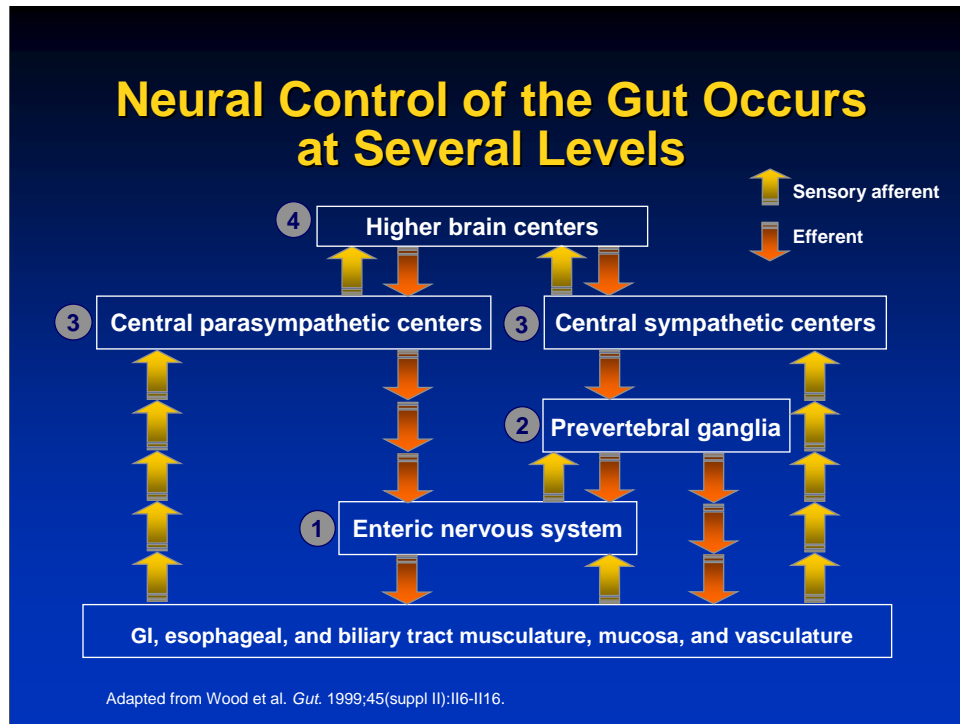
Reference: Wood et al. *Gut*. 1999;45(suppl II):II6-II16.

Although the exact cause of IBS is unknown, according to current thinking, IBS is a manifestation of dysregulation in the brain-gut (or CNS-ENS) axis.<sup>1</sup> The functioning of the GI tract is determined by reciprocal interactions between the brain and the gut.<sup>2</sup> The CNS and the ENS constitute 2 poles of the brain-gut axis that link gut visceral sensation and motor function with brain centers that modulate gut sensation, motility, and secretion. The brain-gut axis is a system of integrated circuits that allows gut activity to influence that of the brain, and brain activity to influence that of the gut. For example, changes in mood can affect GI motility and/or secretory function by virtue of neural connections between the brain and the gut. Likewise, painful sensations in the gut can affect brain activity.

The symptoms that occur in IBS are hypothesized to arise from dysregulation within the neural circuitry of the brain-gut axis.<sup>1</sup>

### References:

1. Drossman DA. The functional gastrointestinal disorders and the Rome II process. In: Drossman DA, Corazziari E, Talley NJ, Thompson WG, Whitehead WE, eds. *Rome II: The Functional Gastrointestinal Disorders: Diagnosis, Pathophysiology, and Treatment: A Multinational Consensus*. 2nd ed. McLean, VA: Degnon Associates; 2000:1-29.
2. Drossman DA. Review article: an integrated approach to the irritable bowel syndrome. *Aliment Pharmacol Ther*. 1999;13(suppl 2):3-14.



Experts agree that neural control of the gut occurs at several physiological levels in addition to that of the ENS.

The first level of neural control is the ENS, the “brain-in-the-gut” that contains local neural circuitry for storing and executing motor and secretory programs for gut activities such as emesis and digestion.<sup>1,2</sup> The second level is that of the prevertebral sympathetic ganglia, where information from the spinal cord is relayed to the gut.<sup>1</sup> The third level comprises the central parasympathetic and sympathetic centers,<sup>1</sup> which transmit information primarily via the vagus nerve (of the parasympathetic system) and splanchnic nerve (of the sympathetic system) from the gut to higher brain centers, as well as from higher brain centers to the gut.<sup>3</sup> The fourth level constitutes higher brain centers, which interpret afferent sensory information from the gut and send signals to level 3, where they are integrated with incoming sensory information for moment-to-moment integration of gut motor and secretory programs.<sup>1</sup>

### References:

1. Wood JD, Alpers DH, Andrews PLR. Fundamentals of neurogastroenterology. *Gut*. 1999;45(suppl II):II6-II16.
2. Gershon MD, Kirchgessner AL, Wade PR. Functional anatomy of the enteric nervous system. In: Johnson LR, ed. *Physiology of the Gastrointestinal Tract*. 3rd ed. New York: Raven Press; 1994:381-422.
3. Goyal RK, Hirano I. The enteric nervous system. *N Engl J Med*. 1996;334:1106-1115.

# IBS: Dysregulation of Chemical Signaling<sup>1</sup>

CNS-ENS dysregulation contributes to

- Visceral hypersensitivity<sup>2</sup>
- Abnormal colonic motility<sup>2</sup>

References: 1. Wood et al. *Gut*. 1999;45(suppl II):II6-II16. 2. Drossman. In: Drossman et al, eds. *Rome II: The Functional Gastrointestinal Disorders: Diagnosis, Pathophysiology, and Treatment: A Multinational Consensus*. 2nd ed. 2000:1-29.

IBS can be characterized as a dysregulation of chemical signaling at 1 or more of these levels of neural organization of the gut.<sup>1</sup> The resulting CNS-ENS dysregulation contributes to visceral hypersensitivity and abnormal colonic motility, which are 2 of the hallmarks of functional GI disorders.<sup>2</sup>

Leading experts now consider visceral hypersensitivity as well as abnormal motility and secretion to be manifestations of brain-gut dysregulation in functional GI disorders.<sup>2</sup> Although the exact cause of this dysregulation is not known, the roles of serotonergic signaling and signaling involving other neurotransmitters (ie, bradykinin, tachykinins, CGRP, VIP, substance P) are currently being investigated.<sup>2,3</sup>

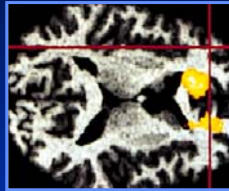
## References:

1. Wood JD, Alpers DH, Andrews PLR. Fundamentals of neurogastroenterology. *Gut*. 1999;45(suppl II):II6-II16.
2. Drossman DA. The functional gastrointestinal disorders and the Rome II process. In: Drossman DA, Corazziari E, Talley NJ, Thompson WG, Whitehead WE, eds. *Rome II: The Functional Gastrointestinal Disorders: Diagnosis, Pathophysiology, and Treatment: A Multinational Consensus*. 2nd ed. McLean, VA: Degnon Associates; 2000:1-29.
3. Gershon MD. Review article: roles played by 5-hydroxytryptamine in the physiology of the bowel. *Aliment Pharmacol Ther*. 1999;13(suppl 2):15-30.

## Patients With IBS Show Differences in Brain Activity in the Prefrontal Cortex

PET scans taken during anticipation of painful rectal distention

Healthy



Normal:  
No left dorsolateral  
prefrontal activation

IBS



Abnormal:  
Left dorsolateral  
prefrontal activation

Reference: Silverman et al. *Gastroenterology*. 1997;112:64-72. PET scans reproduced with permission.

Brain-gut interaction studies provide direct evidence for differences in brain processing of information from the gut in patients with IBS. In a 1997 positron emission tomography (PET) study, brain activity in patients with IBS and healthy subjects was monitored during application of nonpainful, painful, and simulated rectal pressure produced by inflation of a latex balloon in the rectum. Results from the study show that the left dorsolateral prefrontal cortex was significantly activated during anticipation of painful rectal pressure in patients with IBS, but not in healthy subjects.<sup>1</sup>

This study provides a direct demonstration of abnormal cortical activity associated with processing of visceral information in patients with IBS.<sup>1</sup> The study findings are consistent with the hypothesis that patients with IBS abnormally process pain information.<sup>2</sup> Like the early study of the carcinoma hoax,<sup>3</sup> this PET study illustrates the interactions in the brain-gut axis.<sup>1</sup>

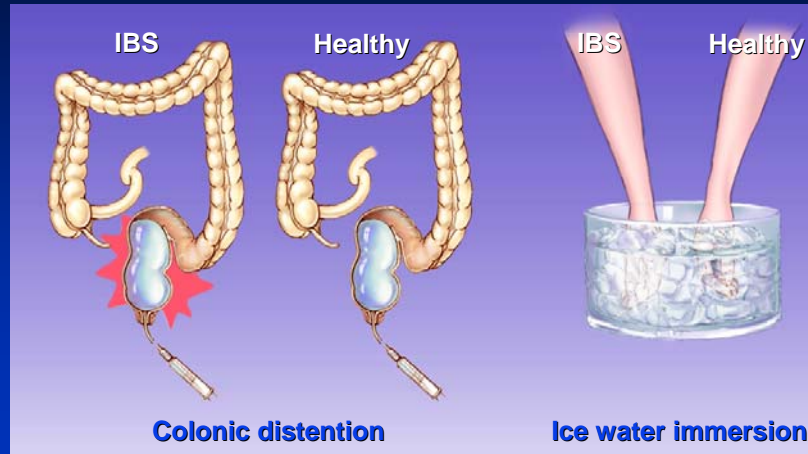
### Supplementary Information:

This study employed PET with <sup>15</sup>O-water. This radiotracer shows patterns of regional cerebral blood flow, thought to reflect regional neuronal activity. Painful and nonpainful rectal stimuli were delivered via a latex balloon catheter inserted in each subject's rectum before imaging sessions. The study was conducted in 6 patients with IBS and 6 healthy subjects.<sup>1</sup>

### References:

1. Silverman DHS, Munakata JA, Ennes H, Mandelkern MA, Hoh CK, Mayer EA. Regional cerebral activity in normal and pathological perception of visceral pain. *Gastroenterology*. 1997;112:64-72.
2. Drossman DA. Review article: an integrated approach to the irritable bowel syndrome. *Aliment Pharmacol Ther*. 1999;13(suppl 2):3-14.
3. Almy TP. Experimental studies on the irritable colon. *Am J Med*. 1951;10:60-67.

## Lower Visceral, But Not Somatic, Pain Thresholds in IBS



Reference: Whitehead et al. *Gastroenterology*. 1990;98:1187-1192.

One of the hallmarks of the brain-gut dysregulation in IBS is visceral hypersensitivity.<sup>1</sup> Chronic or recurrent pain is associated with IBS as well as other functional GI disorders.<sup>2</sup> In fact, abdominal pain is the hallmark symptom of IBS. Asked which of the main IBS symptoms bothered them the most, more than one third of female nonconstipated patients with IBS in a controlled clinical trial cited abdominal pain (36%). Urgency was the second most frequently cited symptom, considered most bothersome by 28% of patients.<sup>3</sup>

Another study compared pain thresholds of patients with IBS (n=16) with those of healthy subjects (n=18) for both visceral pain and somatic pain. Visceral pain was produced by rectal balloon distention; somatic pain was produced by immersion of the hand into ice water.<sup>4</sup>

Patients with IBS had significantly lower pain thresholds than did healthy subjects in response to colonic distention.<sup>4</sup> This result is consistent with the finding from a 1980 study,<sup>5</sup> in which pain thresholds of 25 patients with IBS and 20 healthy subjects were tested by exposing them to stepwise increases in colonic distention caused by inflation of a rectosigmoid balloon. Through the range of distention pressures, patients with IBS were more likely than healthy subjects to report pain. In contrast, the pain thresholds of patients with IBS in response to immersion of the hand in ice water did not differ from those of healthy subjects.<sup>4</sup> That is, patients with IBS exhibited normal somatic pain thresholds but abnormal visceral pain thresholds.

These findings suggest that patients with IBS may experience hypersensitivity in the gut only, whereas they may have normal tolerance thresholds to acute somatic pain. This finding is consistent with the existence of visceral hypersensitivity in IBS.<sup>4</sup>

### References:

1. Drossman DA. Review article: an integrated approach to the irritable bowel syndrome. *Aliment Pharmacol Ther*. 1999;13(suppl 2):3-14.
2. Drossman DA. The functional gastrointestinal disorders and the Rome II process. In: Drossman DA, Corazziari E, Talley NJ, Thompson WG, Whitehead WE, eds. *Rome II: The Functional Gastrointestinal Disorders: Diagnosis, Pathophysiology, and Treatment: A Multinational Consensus*. 2nd ed. McLean, VA: Degnon Associates; 2000:1-29.
3. Camilleri M, Chey WY, Mayer EA, et al. A randomized controlled clinical trial of the serotonin type 3 receptor antagonist alosetron in women with diarrhea-predominant irritable bowel syndrome. *Arch Intern Med*. 2001;161(14):1733-1740.
4. Whitehead WE, Holtkotter B, Enck P, et al. Tolerance for rectosigmoid distention in irritable bowel syndrome. *Gastroenterology*. 1990;98:1187-1192.
5. Whitehead WE, Engel BT, Schuster MM. Irritable bowel syndrome: physiological and psychological differences between diarrhea-predominant and constipation-predominant patients. *Dig Dis Sci*. 1980;25:404-413.

## Abnormal Colonic Motility

- More frequent giant propagating contractions<sup>1</sup>
- Stronger giant propagating contractions
- Shorter or longer colonic transit time<sup>2</sup>

References: 1. Kellow and Phillips. *Gastroenterology*. 1987;92:1885-1893. 2. Drossman. *Aliment Pharmacol Ther*. 1999;13(suppl 2):3-14.

In addition to visceral hypersensitivity, another hallmark of IBS<sup>1</sup> and other functional GI disorders<sup>2</sup> is abnormal colonic motility. Studies have shown that the abnormal colonic motility in IBS is manifested in a number of ways: more frequent giant propagating contractions,<sup>3</sup> stronger giant propagating contractions, and shorter<sup>1</sup> or longer<sup>1</sup> colonic transit time.

Intestinal power propulsion is a kind of motility that accomplishes mass movement of intraluminal material.<sup>4</sup> It is also a protective response to the presence of irritating agents in the intestinal lumen. As a motility pattern programmed by the ENS, it can be recorded with manometric sensors as long-lasting, giant contractions of the circular muscle that propagate for extended distances along the intestine. Power propulsion rapidly strips the lumen clean as it travels along extended lengths of intestine.<sup>4</sup> Abdominal cramping sensations and diarrhea are associated with this motor program.

Giant propagating contractions, which reflect the occurrence of power propulsion, are more common in patients with IBS than in individuals without IBS; abnormal giant propagating contractions are a cardinal manifestation of the abnormal colonic motility in IBS.<sup>5</sup>

### References:

1. Drossman DA. Review article: an integrated approach to the irritable bowel syndrome. *Aliment Pharmacol Ther*. 1999;13(suppl 2):3-14.
2. Drossman DA. The functional gastrointestinal disorders and the Rome II process. In: Drossman DA, Corazziari E, Talley NJ, Thompson WG, Whitehead WE, eds. *Rome II: The Functional Gastrointestinal Disorders: Diagnosis, Pathophysiology, and Treatment: A Multinational Consensus*. 2nd ed. McLean, VA: Degnon Associates; 2000:1-29.
3. Kellow JE, Phillips SF. Altered small bowel motility in irritable bowel syndrome is correlated with symptoms. *Gastroenterology*. 1987;92:1885-1893.
4. Wood JD, Alpers DH, Andrews PLR. Fundamentals of neurogastroenterology: basic science. In: Drossman DA, Corazziari E, Talley NJ, Thompson WG, Whitehead WE, eds. *Rome II: The Functional Gastrointestinal Disorders: Diagnosis, Pathophysiology, and Treatment: A Multinational Consensus*. 2nd ed. McLean, VA: Degnon Associates; 2000:31-90.
5. Kellow JE, Phillips SF. Altered small bowel motility in irritable bowel syndrome is correlated with symptoms. *Gastroenterology*. 1987;92:1885-1893.

## Selected Mediators of Motility and Visceral Hypersensitivity

- Mediators of motility
  - Serotonin
  - Enkephalins
  - Acetylcholine (ACh)
  - ATP
  - Motilin
  - Nitric oxide (NO)
  - Somatostatin
  - Substance P
  - Vasoactive intestinal polypeptide (VIP)
- Mediators of visceral hypersensitivity
  - Serotonin
  - Bradykinin
  - Tachykinins
  - Cholecystokinin (CCK)
  - Calcitonin gene-related peptide (CGRP)
  - Neurotropins

Reference: Drossman. *Aliment Pharmacol Ther.* 1999;13(suppl 2):3-14.

The numerous neurotransmitters found both in the brain and the gut are the messengers that affect the enteric nervous system regulation of motility. The enkephalins, substance P, NO, serotonin, CCK, and others have varied and integrated effects on pain control, GI motility, emotional behavior, and immunity.

### Reference:

Drossman DA. Review article: an integrated approach to the irritable bowel syndrome. *Aliment Pharmacol Ther.* 1999;13(suppl 2):3-14.

## Dysregulation of Chemical Signaling<sup>1</sup> in IBS

- Visceral hypersensitivity and abnormal colonic motility reflect disordered CNS-ENS interactions, which may be attributed to a dysregulation of chemical signaling<sup>1</sup>
- Intrinsic primary afferent neurones are key mediators of defensive and pathological intestinal functions
  - Disturbed intestinal functions caused by mechanical or chemical stimuli at NK<sub>3</sub> receptor level<sup>2,3</sup>
- Serotonin (5-HT) is a chemical signal that plays an important role in IBS<sup>4</sup>

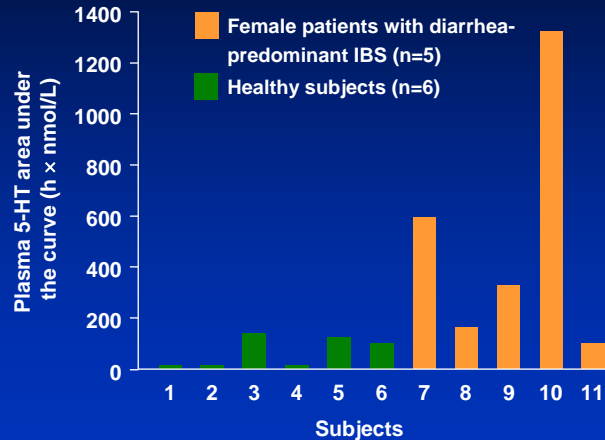
References: 1. Drossman. *Aliment Pharmacol Ther.* 1999;13(suppl 2):3-14. 2. Neunlist et al. *J Physiol.* 1999;517(suppl 2):533. 3. Alex et al. *Neurosci.* 2001;104:263. 4. Gershon. *Aliment Pharmacol Ther.* 1999;13(suppl 2):15-30.

Abnormal motility and visceral hypersensitivity reflect disordered CNS-ENS interactions, which, evidence suggests, are attributed to a dysregulation in chemical signaling,<sup>1</sup> possibly at multiple levels of gut neural control.<sup>2</sup> The chemical signal implicated as being important in IBS is serotonin (5-HT).<sup>3</sup>

### References:

1. Drossman DA. Review article: an integrated approach to the irritable bowel syndrome. *Aliment Pharmacol Ther.* 1999;13(suppl 2):3-14.
2. Wood JD, Alpers DH, Andrews PLR. Fundamentals of neurogastroenterology. *Gut.* 1999;45(suppl II):II6-II16.
3. Gershon MD. Review article: roles played by 5-hydroxytryptamine in the physiology of the bowel. *Aliment Pharmacol Ther.* 1999;13(suppl 2):15-30.

## Plasma 5-HT Levels Are Elevated After a Meal in Patients With IBS



Adapted from Bearcroft et al. *Gut*. 1998;42:42-46.

Evidence consistent with a role for 5-HT in IBS comes from the observation that plasma levels of 5-HT are more elevated after a meal in female patients with diarrhea-predominant IBS than they are in healthy subjects. In a pilot study measuring the plasma 5-HT areas under the curve for 6 healthy subjects and 5 female patients with diarrhea-predominant IBS, the area under the curve for 5-HT was significantly greater for patients with IBS (median=317 h x nmol/L) than for healthy subjects (median=51 h x nmol/L).

Furthermore, the duration of the 5-HT peak in plasma was 3 times longer in patients with IBS (median=3 h) than in healthy subjects (median=1 h;  $P<0.05$ ).

### Supplementary Information:

In this study, female patients with diarrhea-predominant IBS (n=5) and healthy subjects (n=6) were given a high-carbohydrate meal after an overnight fast. Blood samples were taken before the meal and for 4 hours after the meal. Plasma 5-HT was measured using reversed-phase high-performance liquid chromatography.

### Reference:

Bearcroft CP, Perrett D, Farthing MJG. Postprandial plasma 5-hydroxytryptamine in diarrhoea predominant irritable bowel syndrome: a pilot study. *Gut*. 1998;42:42-46.

## Ninety-Five Percent of 5-HT Is Found in the GI Tract

CNS: 5%



GI Tract: 95%<sup>1</sup>

- Enterochromaffin cells<sup>1</sup>
- Mast cells<sup>2</sup>
- Neurons<sup>1</sup>

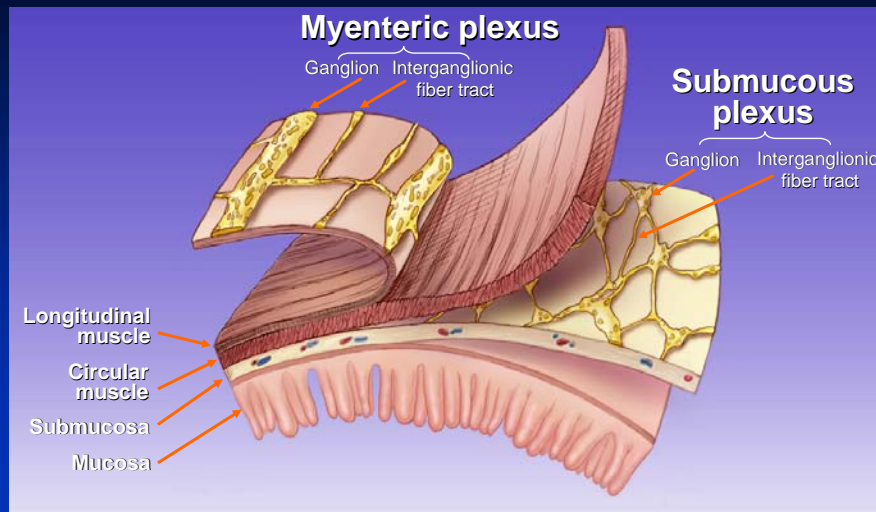
References: 1. Gershon. *Aliment Pharmacol Ther.* 1999;13(suppl 2):15-30. 2. Wood. *Pharmacology.* 1993;47(suppl 1):7-13.

That 5-HT plays a significant role in gut functioning should not be surprising: 95% of the body's 5-HT is synthesized and stored in the gut.<sup>1</sup> Most of the gut 5-HT is found in enterochromaffin cells that line the intestinal lumen,<sup>1</sup> but intestinal mast cells<sup>2</sup> and neurons<sup>1</sup> also contain and release 5-HT.

### References:

1. Gershon MD. Review article: roles played by 5-hydroxytryptamine in the physiology of the bowel. *Aliment Pharmacol Ther.* 1999;13(suppl 2):15-30.
2. Wood JD. Neuro-immunophysiology of colon function. *Pharmacology.* 1993;47(suppl 1):7-13.

# Enteric Nervous System



Adapted from Wood et al. In: Drossman et al, eds. *Rome II: The Functional Gastrointestinal Disorders: Diagnosis, Pathophysiology, and Treatment: A Multinational Consensus*. 2nd ed. 2000:31-90.

5-HT-mediated synaptic transmission and paracrine signaling occur in the ENS, which is embedded within the walls of the digestive tract. The ENS consists of ganglia, primary interganglionic fiber tracts, and secondary and tertiary fiber projections to the effector systems (ie, musculature, glands, and blood vessels). Two ganglionated plexuses are the most obvious constituents of the ENS. The myenteric plexus (Auerbach's plexus) is located between the longitudinal and circular muscle layers of most of the digestive tract. The submucous plexus (Meissner's plexus) is situated in the submucosal region between the circular muscle and mucosa. The submucous plexus is most prominent as a ganglionated network in the small and large intestine.

Motor neurons to the musculature are in the myenteric plexus. Motor innervation of the secretory epithelium of the intestinal crypts originates in the submucous plexus. Neurons in the submucosal ganglia extend fibers into the myenteric plexus and also receive input from axons projecting from the myenteric plexus. The interconnections link the 2 networks into a functionally integrated nervous system.

Structure, function, and neurochemistry of enteric ganglia differ significantly from ganglia of the sympathetic and parasympathetic divisions of the autonomic nervous system. Unlike other autonomic ganglia, which function mainly as relay-distribution centers for signals transmitted from the brain and spinal cord, enteric ganglia form an interconnected nervous system with mechanisms for integration and processing of information like those found in the brain and spinal cord. For this reason, the ENS is sometimes called the "brain-in-the-gut."

## Reference:

Wood JD, Alpers DH, Andrews PLR. Fundamentals of neurogastroenterology: basic science. In: Drossman DA, Corazziari E, Talley NJ, Thompson WG, Whitehead WE, eds. *Rome II: The Functional Gastrointestinal Disorders: Diagnosis, Pathophysiology, and Treatment: A Multinational Consensus*. 2nd ed. McLean, VA: Degnon Associates; 2000:31-90.

## 5-HT Release From Enterochromaffin Cells Initiates the Peristaltic Reflex<sup>1,2</sup>

Mechanical or chemical stimulation

Mucosa

Mucosal enterochromaffin cell

5-HT

5-HT receptors on enteric neurons and sensory afferents in the ENS

References: 1. Gershon. *Hosp Pract.* 1999;34:31-52. 2. Gershon. *Aliment Pharmacol Ther.* 1999;13(suppl 2):15-30.

It has been hypothesized that 5-HT released from enterochromaffin cells in response to mechanical or chemical stimulation initiates the peristaltic reflex by stimulating submucosal sensory neurons that contain 5-HT receptors. These submucosal cells, in turn, stimulate neurons in the myenteric plexus, with consequent initiation of the peristaltic reflex.<sup>1,2</sup> The proposed role of 5-HT in the gut is associated with increased GI motility.<sup>3</sup>

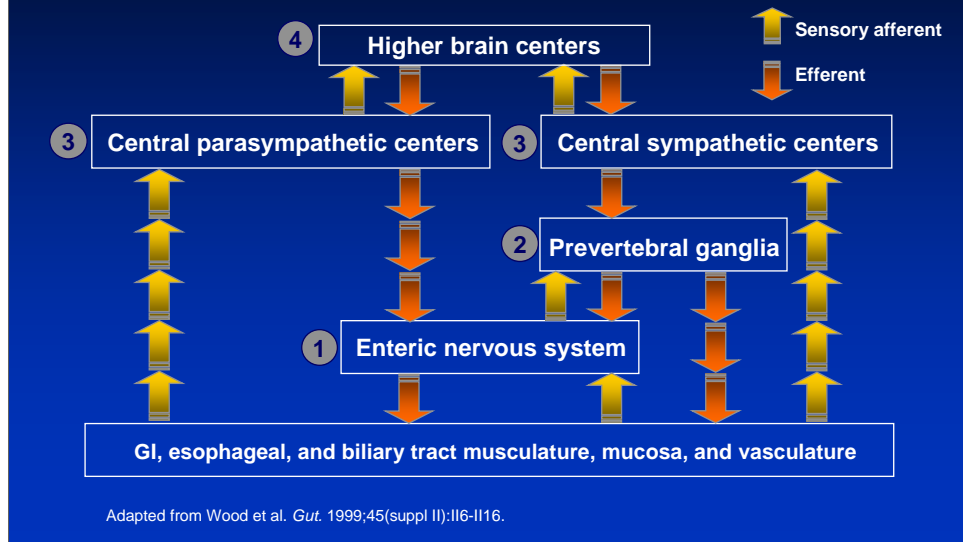
Evidence supporting the hypothesis that 5-HT release from enterochromaffin cells stimulates the peristaltic reflex derives from the observations that<sup>1</sup>

- 5-HT stimulates the peristaltic reflex when it is applied to the mucosal surface of the bowel
- 5-HT is released when the peristaltic reflex is initiated
- Removal of 5-HT weakens the peristaltic reflex.

### References:

1. Gershon MD. The enteric nervous system: a second brain. *Hosp Pract.* 1999;34:31-52.
2. Gershon MD. Review article: roles played by 5-hydroxytryptamine in the physiology of the bowel. *Aliment Pharmacol Ther.* 1999;13(suppl 2):15-30.
3. Talley NJ. Review article: 5-hydroxytryptamine agonists and antagonists in the modulation of gastrointestinal motility and sensation: clinical implications. *Aliment Pharmacol Ther.* 1992;6:273-289.

## 5-HT Is Involved at Multiple Levels in Neural Control of the Gut



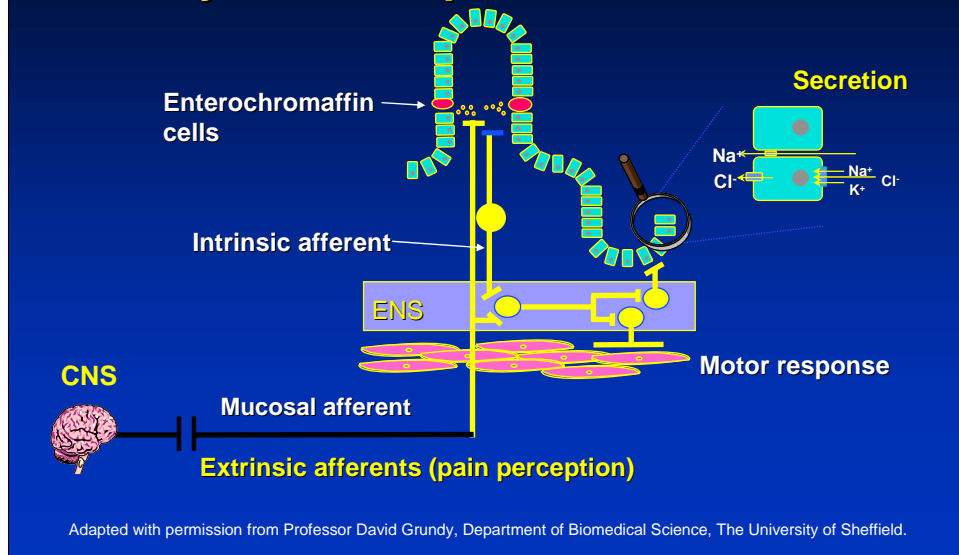
It has been shown that 5-HT is involved at most levels in the bidirectional communication occurring along the brain-gut axis.

First, 5-HT released from enterochromaffin cells in response to mechanical or chemical stimulation activates intrinsic enteric neurons. 5-HT is also involved in information transfer to and from the CNS via interaction with the (parasympathetic) vagus nerve and the (sympathetic) splanchnic nerve.<sup>1,2</sup>

### References:

1. Gershon MD. Review article: roles played by 5-hydroxytryptamine in the physiology of the bowel. *Aliment Pharmacol Ther*. 1999;13(suppl 2):15-30.
2. Wood JD, Alpers DH, Andrews PLR. Fundamentals of neurogastroenterology. *Gut*. 1999;45(suppl II):II6-II16.

## Some IBS Symptoms May Be Mediated by 5-HT Receptors in the Colon



It is plausible that pain and possibly other symptoms experienced by patients with IBS may be initiated by the release of 5-HT from enterochromaffin cells. Chemical or mechanical stimulation of the intestinal lumen is thought to cause enterochromaffin cells to secrete 5-HT. The 5-HT released from enterochromaffin cells is hypothesized to 1) stimulate extrinsic afferent pathways involved in pain perception by the CNS and 2) stimulate intrinsic afferent neurons involved in triggering intestinal motor responses.<sup>1</sup>

Immunocytochemical studies of the distribution of 5-HT receptors in the intestinal mucosa provide strong evidence to support the notion that these receptors are present on the terminals of extrinsic sensory nerves. The immunoreactivity of 5-HT receptors is abundant on subepithelial nerve fibers that encircle intestinal crypts and extend into villi.<sup>2</sup> In many instances, the involvement of 5-HT in normal gut function, as well as the abnormal gut function in IBS, could be attributed to activity at specific receptor subtypes.

### References:

1. Gershon MD. 5-HT (serotonin) physiology and related drugs. *Curr Opin Gastroenterol.* 2000;16:113-120.
2. Gershon MD. Review article: roles played by 5-hydroxytryptamine in the physiology of the bowel. *Aliment Pharmacol Ther.* 1999;13(suppl 2):15-30.

## Pathophysiology of IBS: Summary

- The ENS functions as a “brain-in-the-gut”<sup>1-3</sup>
- Dysregulation in the brain-gut axis contributes to visceral hypersensitivity and abnormal colonic motility in IBS<sup>4</sup>
- IBS can be characterized as a dysregulation of chemical signaling in the brain-gut axis<sup>3</sup>
- Various mediators of motility and visceral hypersensitivity (ie, 5-HT, NKs, NO, CGRP, CCK)<sup>5</sup>
- 5-HT is thought to play an important role in IBS<sup>6</sup>
- IBS symptoms may be initiated by stimulation of 5-HT receptors by 5-HT released from enterochromaffin cells<sup>7</sup>

**References:** 1. Goyal and Hirano. *N Engl J Med.* 1996;334:1106-1115. 2. Gershon et al. In: Johnson LR, ed. *Physiology of the Gastrointestinal Tract.* 3rd ed. 1994:381-422. 3. Wood et al. *Gut.* 1999;45(suppl II):II6-II16. 4. Drossman et al, eds. *Rome II: The Functional Gastrointestinal Disorders: Diagnosis, Pathophysiology, and Treatment: A Multinational Consensus.* 2nd ed. 2000:1-29. 5. Drossman. *Aliment Pharmacol Ther.* 1999;13(suppl 2):3-14. 6. Gershon. *Aliment Pharmacol Ther.* 1999;13(suppl 2):15-30. 7. Gershon. *Curr Opin Gastroenterol.* 2000;16:113-120.

Gut function is largely controlled by the enteric nervous system (ENS). The ENS is the gut's neural network that regulates gut sensation and motor activity. Similar to the central nervous system (CNS), the ENS contains independent local circuits that mediate stimulus processing and behavior. The ENS is a local minibrain within which is stored a library of programs for different patterns of gut behavior. The ENS contains integrated local circuits that mediate 1) motor and secretory programs (program library); 2) feedback control; 3) reflexes; and 4) sensory information processing.<sup>1</sup> The ENS can therefore function independently of the brain to mediate gut activity and has been characterized as a “brain-in-the-gut.”<sup>2,3</sup> Although the exact cause of IBS is unknown, according to current thinking, IBS is a manifestation of dysregulation in the brain-gut (or CNS-ENS) axis.<sup>4</sup>

The numerous neurotransmitters found both in the brain and the gut are the messengers that affect the enteric nervous system regulation of motility. The enkephalins, substance P, NO, 5-HT, CCK, and others have varied and integrated effects on pain control, GI motility, emotional behavior, and immunity.<sup>5</sup> It is plausible that pain and possibly other symptoms experienced by patients with IBS may be initiated by the release of 5-HT from enterochromaffin cells. Chemical or mechanical stimulation of the intestinal lumen is thought to cause enterochromaffin cells to secrete 5-HT. The 5-HT released from enterochromaffin cells is hypothesized to 1) stimulate extrinsic afferent pathways involved in pain perception by the CNS and 2) stimulate intrinsic afferent neurons involved in triggering intestinal motor responses.<sup>6</sup>

### References:

1. Wood JD, Alpers DH, Andrews PLR. Fundamentals of neurogastroenterology. *Gut.* 1999;45(suppl II):II6-II16.
2. Gershon MD, Kirchgessner AL, Wade PR. Functional anatomy of the enteric nervous system. In: Johnson LR, ed. *Physiology of the Gastrointestinal Tract.* 3rd ed. New York: Raven Press; 1994:381-422.
3. Goyal RK, Hirano I. The enteric nervous system. *N Engl J Med.* 1996;334:1106-1115.
4. Drossman DA. The functional gastrointestinal disorders and the Rome II process. In: Drossman DA, Corazziari E, Talley NJ, Thompson WG, Whitehead WE, eds. *Rome II: The Functional Gastrointestinal Disorders: Diagnosis, Pathophysiology, and Treatment: A Multinational Consensus.* 2nd ed. McLean, VA: Degnon Associates; 2000:1-29.
5. Drossman DA. Review article: an integrated approach to the irritable bowel syndrome. *Aliment Pharmacol Ther.* 1999;13(suppl 2):3-14.
6. Gershon MD. 5-HT (serotonin) physiology and related drugs. *Curr Opin Gastroenterol.* 2000;16:113-120.

**Section 3:  
Diagnosis and Current  
Management of IBS**

## Hallmark Symptoms of IBS

- **Chronic or recurrent GI symptoms**
  - Lower abdominal pain/discomfort
  - Altered bowel function (urgency, altered stool consistency, altered stool frequency, incomplete evacuation)
  - Bloating
- **Not explained by identifiable structural or biochemical abnormalities**

Reference: Thompson et al. *Gut*. 1999;45(suppl 2):1143-1147.

IBS is one of over 20 functional GI disorders.<sup>1</sup> It is defined as a functional bowel disorder in which abdominal pain is associated with a change in bowel habits with features of disordered defecation. Hallmark symptoms of IBS are chronic or recurrent lower abdominal pain and discomfort associated with features of altered bowel function, such as urgency, altered stool consistency, altered stool frequency, and incomplete evacuation, as well as bloating.<sup>2</sup> Although structural or biochemical abnormalities are not usually found, it is likely that these disorders relate to abnormalities of motility and/or afferent neurosensitivity as modulated by the CNS.<sup>3</sup>

### References:

1. Drossman DA, Thompson WG, Talley NJ, Funch-Jensen P, Janssens J, Whitehead WE. Identification of sub-groups of functional gastrointestinal disorders. *Gastroenterol Int*. 1990;3:159-172.
2. Thompson WG, Longstreth GF, Drossman DA, Heaton KW, Irvine EJ, Müller-Lissner SA. Functional bowel disorders and functional abdominal pain. *Gut*. 1999;45(suppl 2):1143-1147.
3. Drossman DA. Review article: an integrated approach to the irritable bowel syndrome. *Aliment Pharmacol Ther*. 1999;13(suppl 2):3-14.

## IBS Disease Severity

- Symptoms can range from mild and intermittent to severe and continuous
- No consensus definition of IBS severity currently exists

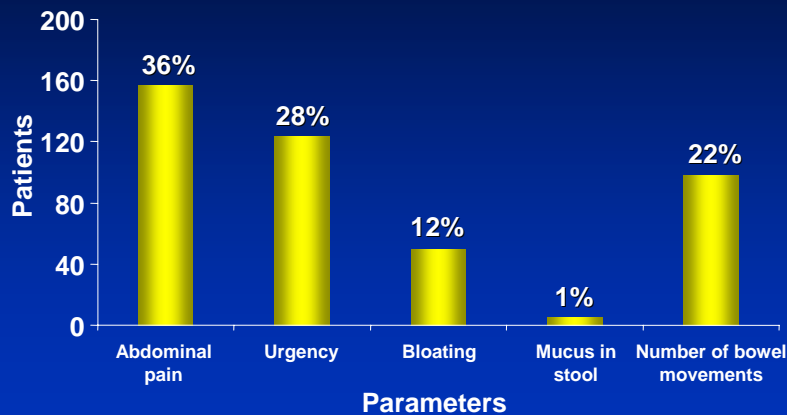
Reference: Lembo et al. *Clinical Gastroenterology and Hepatology*. 2005;3:717-725.

Symptoms can range from mild and intermittent to severe and continuous. Current guidelines related to IBS do not address severity. Measurements of IBS severity may vary depending on a number of factors, including whether the assessment is made by the patient or physician, the type of scale used, and the time of the assessment.<sup>1</sup>

**Reference:**

1. Lembo A, Ameen VZ, Drossman DA. Irritable bowel syndrome: toward an understanding of severity. *Clinical Gastroenterology and Hepatology*. 2005;3:717-725.

## Abdominal Pain as the Defining Symptom of IBS



Reference: Camilleri et al. *Arch Intern Med.* 2001;161(14):1733-1740.

In fact, abdominal pain is the hallmark symptom of IBS. Asked which of the main IBS symptoms bothered them the most, more than one third of female nonconstipated patients with IBS in a controlled clinical trial cited abdominal pain (36%). Urgency was the second most frequently cited symptom, considered most bothersome by 28% of patients.

### Supplementary Information:

On 3 arbitrary days approximately 6 weeks apart during 2 identical clinical trials enrolling nonconstipated female patients with IBS, the patients were asked, “When your IBS is active, which of the following symptoms bothers you the most?” Possible answers, of which only 1 could be selected, included 1) abdominal pain; 2) urgency; 3) bloating; 4) mucus in stool; and 5) number of bowel movements.

### Reference:

Camilleri M, Chey WY, Mayer EA, et al. A randomized controlled clinical trial of the serotonin type 3 receptor antagonist alosetron in women with diarrhea-predominant irritable bowel syndrome. *Arch Intern Med.* 2001;161(14):1733-1740.

## Diagnosis of IBS

- **AGA Practice Guidelines<sup>1</sup>**
  - Symptom-based diagnostic criteria (Rome II)<sup>2</sup> with careful history and physical exam
  - Search for organic diseases (clinical laboratory test, stool O&P, flexible sigmoidoscopy + barium enema or colonoscopy)
- **Diagnosis of IBS with initial evaluation rarely associated with missed diagnosis<sup>1</sup>**
- **Once made, diagnosis is maintained in 97% of IBS patients<sup>3</sup>**

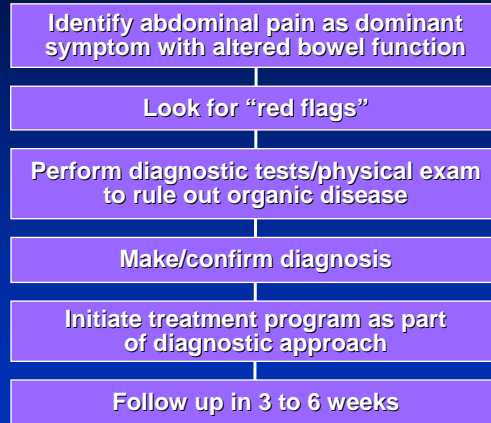
References: 1. American Gastroenterological Association. *Gastroenterology*. 1997;112:2120-2137.  
2. Thompson et al. *Gut*. 1999;45(suppl 2):1143-1147. 3. Owens et al. *Ann Intern Med*. 1995;122:107-112.

The diagnosis of IBS is made by clinical criteria that were developed by an expert panel and published as practice guidelines by the American Gastrointestinal Association.<sup>1</sup> Well-defined and easily applied symptom-based criteria (ie, Rome II criteria) in the absence of structural or gastrointestinal disease are required for diagnosis.<sup>2</sup> Following a careful examination, clinical experience indicates that a diagnosis of IBS is rarely missed, and the disorder is usually persistent in those patients who carry the diagnosis.<sup>3</sup>

### References:

1. American Gastroenterological Association. Irritable bowel syndrome: a technical review for practice guideline development. *Gastroenterology*. 1997;112:2120-2137.
2. Thompson WG, Longstreth GF, Drossman DA, Heaton KW, Irvine EJ, Müller-Lissner SA. Functional bowel disorders and functional abdominal pain. *Gut*. 1999;45(suppl 2):1143-1147.
3. Owens DM, Nelson DK, Talley NJ. The irritable bowel syndrome: long-term prognosis and the physician-patient interaction. *Ann Intern Med*. 1995;122:107-112.

## Make a Positive Diagnosis<sup>1,2</sup>



References: 1. Paterson et al. *Can Med Assoc J.* 1999;161:154-160. 2. American Gastroenterological Association. *Gastroenterology.* 1997;112:2120-2137.

Precision in diagnosing IBS has been enhanced and simplified through the use of symptom-based criteria. If a patient presents with chronic ( $\geq 12$  weeks) bowel function disorders including abdominal pain as the dominant symptom with altered bowel function, a diagnosis of IBS is quite likely. To rule out an alternative or coexisting diagnosis, look for red flags such as weight loss, rectal bleeding, or anemia. Next, order laboratory studies and perform a physical exam to confirm the absence of organic disease.<sup>1</sup> Once the diagnosis has been confirmed, initiate a treatment program and follow up in 3 to 6 weeks.<sup>2</sup>

### References:

1. Paterson WG, Thompson WG, Vanner SJ, et al. Recommendations for the management of irritable bowel syndrome in family practice. *Can Med Assoc J.* 1999;161:154-160.
2. American Gastroenterological Association. Irritable bowel syndrome: a technical review for practice guideline development. *Gastroenterology.* 1997;112:2120-2137.

## History of Diagnostic Approaches

- 1950s: Increased gut motility<sup>1</sup>
- 1970s: Specific motility markers<sup>1</sup>
- 1980 to 1999: Symptom-based criteria<sup>1</sup>
  - Manning criteria
  - Rome criteria
- 1999: Rome II criteria<sup>2</sup>

References: 1. Drossman. *Aliment Pharmacol Ther.* 1999;13(suppl 2):3-14. 2. Thompson et al. *Gut.* 1999;45(suppl 2):1143-1147.

Diagnostic approaches continue to change. In the 1950s, physicians believed increased gut motility was the underlying cause of IBS. In the 1970s, specific motility markers were used to define IBS, and in the 1980s, diagnostic criteria were developed to help doctors make more positive diagnoses. The Manning criteria, introduced in 1988, identified a number of key features that were predictive of IBS. These criteria were further refined by the Rome committee for use in clinical research and are referred to as the Rome criteria.<sup>1</sup> The Rome II criteria are a simplification of the original criteria for application to clinical practice.<sup>2</sup>

### References:

1. Drossman DA. Review article: an integrated approach to the irritable bowel syndrome. *Aliment Pharmacol Ther.* 1999;13(suppl 2):3-14.
2. Thompson WG, Longstreth GF, Drossman DA, Heaton KW, Irvine EJ, Müller-Lissner SA. Functional bowel disorders and functional abdominal pain. *Gut.* 1999;45(suppl 2):1143-1147.

## Rome II Criteria

At least 12 weeks, which need not be consecutive, in the preceding 12 months, of abdominal discomfort or pain that has 2 of 3 features

- Relieved with defecation
- Onset associated with a change in frequency of stool
- Onset associated with a change in form (appearance) of stool

Reference: Thompson et al. *Gut*. 1999;45(suppl 2):1143-1147.

By reviewing terminology and findings from clinical research, the 1998 Working Team refined the Rome criteria. The new criteria, called Rome II, define IBS as a functional bowel disorder characterized by the presence of symptoms for at least 12 weeks, not necessarily consecutive, during the preceding year. Furthermore, their definition of IBS presumes a lack of either a structural or biochemical explanation for the symptoms. By adding “onset” to relevant symptom features, they elucidated how discomfort and pain are temporally related to a change in frequency and form of stool.

**Reference:**

Thompson WG, Longstreth GF, Drossman DA, Heaton KW, Irvine EJ, Müller-Lissner SA. Functional bowel disorders and functional abdominal pain. *Gut*. 1999;45(suppl 2):1143-1147.

## “Red Flags” May Suggest an Alternative or Coexisting Diagnosis

Additional diagnostic screening needed for atypical presentations such as

- Anemia
- Fever
- Persistent diarrhea
- Rectal bleeding
- Severe constipation
- Weight loss
- Nocturnal symptoms of pain and abnormal bowel function
- Family history of GI cancer, inflammatory bowel disease, or celiac disease
- New onset of symptoms in patients 50+ years of age

Reference: Paterson et al. *Can Med Assoc J.* 1999;161:154-160.

To rule out alternative or coexisting disease, there are some red flags that may appear either during the intake or physical exam that would suggest a condition other than IBS.

### Reference:

Paterson WG, Thompson WG, Vanner SJ, et al. Recommendations for the management of irritable bowel syndrome in family practice. *Can Med Assoc J.* 1999;161:154-160.

## Diagnostic Tests: What? When? Who?

If patient has typical features of IBS

- If <50 years of age, order CBC, electrolytes, and LFTs, screen stool for occult blood, and consider sigmoidoscopy<sup>1</sup>
- If ≥50 years of age, order CBC, electrolytes, and LFTs, and perform a colonoscopy or air-contrast barium enema with sigmoidoscopy<sup>1,2</sup>

References: 1. American Gastroenterological Association. *Gastroenterology*. 1997;112:2120-2137.  
2. Paterson et al. *Can Med Assoc J*. 1999;161:154-160.

Precision in the diagnosis of IBS has been enhanced and simplified through the use of symptom-based criteria. If a patient has typical features of IBS and is less than 50 years of age, order a CBC, electrolytes, and LFTs, screen stool for occult blood, and consider sigmoidoscopy.<sup>1</sup> If the patient is 50 years of age or older, order CBC, electrolytes, and LFTs, and perform a colonoscopy or air-contrast barium enema with sigmoidoscopy.<sup>1,2</sup>

### References:

1. Paterson WG, Thompson WG, Vanner SJ, et al. Recommendations for the management of irritable bowel syndrome in family practice. *Can Med Assoc J*. 1999;161:154-160.
2. American Gastroenterological Association. Irritable bowel syndrome: a technical review for practice guideline development. *Gastroenterology*. 1997;112:2120-2137.

## Differential Diagnosis

- **Malabsorption**
  - Postgastrectomy
  - Intestinal diseases
  - Pancreatic insufficiency
- **Dietary factors**
  - Lactose intolerance
  - Caffeine/alcohol
  - Fat-containing/gas-producing food
- **Infection**
  - Bacteria
  - Parasites

Reference: Drossman. *Aliment Pharmacol Ther.* 1999;13(suppl 2):3-14.

The following categories should be considered in the differential diagnosis of recurrent abdominal discomfort and bowel dysfunction: **Malabsorptive conditions**, such as postgastrectomy, intestinal diseases (ie, sprue), or pancreatic insufficiency. These conditions may cause cramps and/or diarrhea.<sup>1</sup> **Dietary factors**, such as lactose (in lactose-intolerant patients), caffeine, alcohol, and fat-containing or gas-producing (ie, cruciferous vegetables) foods. Some foods may act as triggers and may therefore cause and/or intensify symptoms.<sup>2</sup> **Infections** due to bacteria (ie, *Campylobacter jejuni*, *Salmonella* spp) or common parasites such as *Giardia lamblia*.<sup>1</sup>

### References:

1. Drossman DA. Review article: an integrated approach to the irritable bowel syndrome. *Aliment Pharmacol Ther.* 1999;13(suppl 2):3-14.
2. American Gastroenterological Association. Irritable bowel syndrome: a technical review for practice guideline development. *Gastroenterology.* 1997;112:2120-2137.

## Differential Diagnosis (cont'd)

- Inflammatory bowel disease<sup>1</sup>
  - Crohn's disease
  - Ulcerative colitis
- Psychological disorders<sup>1</sup>
  - Panic disorder
  - Depression
  - Somatization
- Gynecological disorders<sup>2</sup>
  - eg, endometriosis/dysmenorrhea
- Miscellaneous<sup>1</sup>
  - Endocrine tumors
  - HIV and associated infections

References: 1. Drossman. *Aliment Pharmacol Ther.* 1999;13(suppl 2):3-14. 2. Moore et al. *Br J Obstet Gynaecol.* 1998;105:1322-1325.

**Inflammatory bowel disease** (IBD) such as Crohn's disease or ulcerative colitis. Symptoms of these diseases can often mimic those of IBS. For instance, patients suffering from IBD can present with symptoms such as anemia, fever, rectal bleeding, nocturnal symptoms of pain, and abnormal bowel function.<sup>1</sup> Other, less-common microscopic colitides such as collagenous colitis or mast-cell disease, can be diagnosed by colonic biopsy.<sup>2</sup> **Psychological disorders**, including panic disorder, depression, and somatization. These disorders may be associated with an increase in symptom reporting.<sup>2</sup> **Miscellaneous conditions**, including gynecological conditions such as endometriosis or dysmenorrhea,<sup>3</sup> endocrine tumors (ie, carcinoid, Zollinger-Ellison syndrome, VIPoma), and HIV disease and other associated infections.<sup>2</sup>

### References:

1. Collins SM, Piche T, Rampal P. The putative role of inflammation in the irritable bowel syndrome. *Gut.* 2001;49(6):743-745.
2. Drossman DA. Review article: an integrated approach to the irritable bowel syndrome. *Aliment Pharmacol Ther.* 1999;13(suppl 2):3-14.
3. Moore J, Barlow D, Jewell D, Kennedy S. Do gastrointestinal symptoms vary with the menstrual cycle? *Br J Obstet Gynaecol.* 1998;105:1322-1325.

## Current Management of IBS

- Establish a **positive** diagnosis<sup>1</sup>
- Reassure patient that there is no serious organic disease or alarming symptoms<sup>1</sup>

Reference: Drossman. *Aliment Pharmacol Ther.* 1999;13(suppl 2):3-14.

Patients need to be told that their symptoms of IBS are in fact real and that they are not suffering from a serious organic disease. The best time to reassure patients that they are not seriously ill and that their disorder is manageable is after the evaluation. Listening to the patient's concerns and establishing a supportive relationship is critical to establishing a successful treatment plan.<sup>1</sup>

Currently, many of the pharmacologic agents available for the treatment of IBS generally target only one symptom. Therefore, patients may need to take more than one medication to get their symptoms under control. The use of medications directed at the gut should be targeted for the predominant symptom (ie, pain, diarrhea, or constipation).<sup>2,3</sup> Tricyclic antidepressants and SSRIs are often prescribed for patients with severe or refractory pain.<sup>3</sup>

**Many of the conventional therapies prescribed for the treatment of IBS symptoms are empiric and have not, therefore, been subject to any formal FDA review and approval.**

### References:

1. Drossman DA. Review article: an integrated approach to the irritable bowel syndrome. *Aliment Pharmacol Ther.* 1999;13(suppl 2):3-14.
2. Maxwell PR, Mendall MA, Kumar D. Irritable bowel syndrome. *Lancet.* 1997;350:1691-1695.
3. Drossman DA, Thompson WG. The irritable bowel syndrome: review and a graduated multicomponent treatment approach. *Ann Intern Med.* 1992;116(pt 1):1009-1016.

## Current Management Components of IBS

- Education and reassurance
- Dietary modification and fiber
- Symptom-targeted pharmacotherapy
  - Pain and bloating: antispasmodics
  - Diarrhea and urgency: antidiarrheals
- Failure of conventional therapies may lead physicians and patients to try other approaches
  - Psychological/behavioral options
  - Psychotropics
  - Alternative approaches
- Realistic goals

Reference: Drossman. *Aliment Pharmacol Ther.* 1999;13(suppl 2):3-14.

Current conventional therapy for IBS uses a stepped approach starting with education and reassurance followed by dietary modification that may include fiber supplementation. The key to helping patients better manage their IBS is education. By explaining that the intestines overreact to a variety of stimuli such as food, hormonal changes, medication, and stress, patients can be made more aware of what may trigger an episode or intensify existing symptoms. Make it clear that stimuli can produce spasm or stretching of the gut, enhance sensitivity of nerves, or both. When this happens, the patient experiences pain, diarrhea, constipation, bloating, or a combination of any of these symptoms.<sup>1</sup> Patients need to be reassured that their symptoms are real and not life threatening. By understanding how to modify their diet to minimize their symptoms (ie, reduction in alcohol, fat, caffeine, and sorbitol), coupled with medical treatment, patients should be better equipped to manage their disease.<sup>1</sup>

**Many of the conventional therapies prescribed for the treatment of IBS symptoms are empiric and have not, therefore, been subject to any formal FDA review and approval.** The current treatment of IBS includes antispasmodics, anticholinergics, tricyclic antidepressants, SSRIs, antidiarrheals, laxatives, bulking agents, and opioids.<sup>1</sup> Some patients may seek alternative therapies, including psychotherapy.<sup>2</sup> It is also important to set realistic goals. IBS is a condition that can be managed, not cured. Patients need to know what they can expect and to what degree their quality of life can be improved.<sup>1</sup>

### References:

1. Drossman DA. Review article: an integrated approach to the irritable bowel syndrome. *Aliment Pharmacol Ther.* 1999;13(suppl 2):3-14.
2. Smart HL, Mayberry JF, Atkinson M. Alternative medicine consultations and remedies in patients with the irritable bowel syndrome. *Gut.* 1986;27:826-828.

## Conventional Prescription Treatments Used for IBS

- Laxatives and bulking agents
- Antispasmodic/anticholinergic agents
  - Dicyclomine HCl<sup>1</sup>
  - Hyoscyamine sulfate (± other anticholinergics/sedatives)<sup>2</sup>
  - Belladonna and phenobarbital<sup>1</sup>
  - Clidinium bromide with chlordiazepoxide<sup>1</sup>
- Antidiarrheal agents
  - Cholestyramine
  - Loperamide<sup>1</sup>

References: 1. *PDR® Generics™*. 1998:314, 559-561, 873-875. 2. *Physicians' Desk Reference®*. 1999:2910-2911.

Dicyclomine hydrochloride is a direct GI smooth-muscle relaxant that competitively blocks the effects of ACh at muscarinic cholinergic receptors, mediating the effects of parasympathetic postganglionic impulses, and thus relaxing the GI tract.<sup>1</sup>

Hyoscyamine sulfate, also known as atropine sulfate,<sup>2</sup> is an anticholinergic and belladonna alkaloid that competitively blocks the effect of ACh at muscarinic cholinergic receptors that mediate the effects of parasympathetic postganglionic impulses, depressing salivary secretions, relaxing the GI tracts, and inhibiting gastric acid secretion at high doses. It also blocks the effects of ACh in the CNS. It may be used alone or in conjunctions with sedatives and phenobarbital to depress motor output and produce sedation as necessary.

Clidinium bromide,<sup>1</sup> another anticholinergic, is often used in combination with chlordiazepoxide hydrochloride, an antianxiety agent that acts mainly at subcortical levels of the CNS to produce relaxation.

### References:

1. *PDR® Generics™*. 1998:314, 559-561, 873-875.
2. *Physicians' Desk Reference®*. 1999:2910-2911.

# Laxatives and Bulking Agents

## Symptomatic treatment of constipation

- Increased dietary fiber or psyllium<sup>1</sup>
- Osmotic laxatives (MgSO<sub>4</sub>, lactulose)<sup>2</sup>
- Stimulant laxatives<sup>3</sup>
- Some laxatives and bulking agents can exacerbate abdominal pain and bloating<sup>3</sup>

References: 1. American Gastroenterological Association. *Gastroenterology*. 1997;112:2120-2132. 2. Camilleri and Choi. *Aliment Pharmacol Ther*. 1997;11:3-15. 3. *Drug Facts and Comparisons*<sup>®</sup>. 1999:316-317a.

Bulking agents include various fibers, psyllium, coarse bran, polycarbophil, and ispaghula husk that often result in ease of stool passage, as well as improvement in bowel satisfaction and stool frequency.<sup>1</sup> For many patients who experience constipation, fiber is often tried.<sup>2</sup> Increased dietary fiber or psyllium decreases whole-gut transit time and intracolonic pressure, but does not reduce colonic contractile activity.<sup>3</sup> If this is not helpful, osmotic laxatives may be prescribed.<sup>4</sup> Stimulant laxatives (ie, bisacodyl, phenolphthalein) enhance intestinal motility and stimulate accumulation of water and electrolytes in the colonic lumen. These agents are effective in relieving constipation associated with IBS. In some patients, laxatives can exacerbate abdominal pain and bloating.<sup>5</sup>

## References:

1. Jailwala J, Imperiale TF, Kroenke K. Pharmacologic treatment of the irritable bowel syndrome: a systematic review of randomized, controlled trials. *Ann Intern Med*. 2000;133:136-147.
2. Camilleri M, Choi M-G. Review article: irritable bowel syndrome. *Aliment Pharmacol Ther*. 1997;11:3-15.
3. American Gastroenterological Association. Irritable bowel syndrome: a technical review for practice guideline development. *Gastroenterology*. 1997;112:2120-2137.
4. Drossman DA. Review article: an integrated approach to the irritable bowel syndrome. *Aliment Pharmacol Ther*. 1999;13(suppl 2):3-14.
5. *Drug Facts and Comparisons*<sup>®</sup>. St. Louis, MO: Facts and Comparisons; 1999:316-317a.

## Bulking Agents

- **Thirteen trials evaluated<sup>1,2</sup>**
  - Seven met high-quality criteria
  - Three showed benefit
- **Supplemental fiber<sup>1,2</sup>**
  - Accelerates colonic and oro-anal transit
  - Improves constipation with sufficient supplementation (20-30 g per day)
  - May worsen some IBS symptoms (ie, bloating and abdominal pain)
  - Limited data suggest equivocal benefits in IBS

References: 1. Cann et al. *Dig Dis Sci.* 1984;29:239-247. 2. Lucey et al. *Gut.* 1987;28:221-225.

Supplemental fiber appears to have equivocal benefits in IBS and may even worsen some of the symptoms associated with IBS, such as bloating and abdominal pain. Several studies report an apparent short-term symptomatic response to bran, but suggest that much if not all of this may be a placebo effect.<sup>1-3</sup>

### References:

1. Cann PA, Read NW, Holdsworth CD, Barends D. Role of loperamide and placebo in management of the irritable bowel syndrome. *Dig Dis Sci.* 1984;29:239-247.
2. Lucey MR, Clark ML, Lowndes J, Dawson AM. Is bran efficacious in irritable bowel syndrome? A double-blind, placebo-control, crossover study. *Gut.* 1987;28:221-225.
3. Jailwala J, Imperiale TF, Kroenke K. Pharmacologic treatment of the irritable bowel syndrome: a systematic review of randomized, controlled trials. *Ann Intern Med.* 2000;133:136-147.

## Antispasmodics/Anticholinergics

### Symptomatic treatment of abdominal pain<sup>1</sup>

- Smooth-muscle relaxants via anticholinergic effects and/or direct action on smooth muscle<sup>2</sup>

References: 1. Drossman. *Aliment Pharmacol Ther.* 1999;13(suppl 2):3-14. 2. *Drug Facts and Comparisons*®. 1999:298-298c.

IBS is a complex of symptoms, and each individual symptom typically is treated with a specific agent. For abdominal pain, the most frequently used medications are antispasmodics.<sup>1,2</sup> Antispasmodics are relaxants that affect and/or have direct action on smooth muscle by blocking the passage of impulses through the parasympathetic nerves.<sup>3</sup> In the United States, anticholinergics are widely used, especially when the pain is postprandial.<sup>2</sup>

#### References:

1. Jaiwala J, Imperiale TF, Kroenke K. Pharmacologic treatment of the irritable bowel syndrome: a systematic review of randomized, controlled trials. *Ann Intern Med.* 2000;133:136-147.
2. Drossman DA. Review article: an integrated approach to the irritable bowel syndrome. *Aliment Pharmacol Ther.* 1999;13(suppl 2):3-14.
3. *Drug Facts and Comparisons*®. St Louis, MO: Facts and Comparisons; 1999:298-298c.

## Meta-Analysis of Smooth-Muscle Relaxants in IBS

- Total of 23 randomized clinical trials of myorelaxant agents selected for meta-analysis of efficacy and tolerance in IBS
- Six drugs analyzed:
  - Cimetropium bromide (5 trials; not available in the US)
  - Hyoscine butyl bromide (3 trials)
  - Mebeverine (5 trials; not available in the US)
  - Otilium bromide (4 trials; not available in the US)
  - Pinaverium bromide (2 trials; not available in the US)
  - Trimebutine (4 trials; not available in the US)

Reference: Poynard et al. *Aliment Pharmacol Ther.* 2001;15(3):355-361.

Twenty-three (23) placebo-controlled, double-blind, randomized clinical trials, conducted between 1965 and 1998, were identified for a recent meta-analysis to update previous overviews of similar trials assessing the efficacy and tolerance of smooth-muscle relaxants in the treatment of IBS. The total number of patients included was 1888, of which 945 received an active agent and 943 a placebo. Six drugs were analyzed:

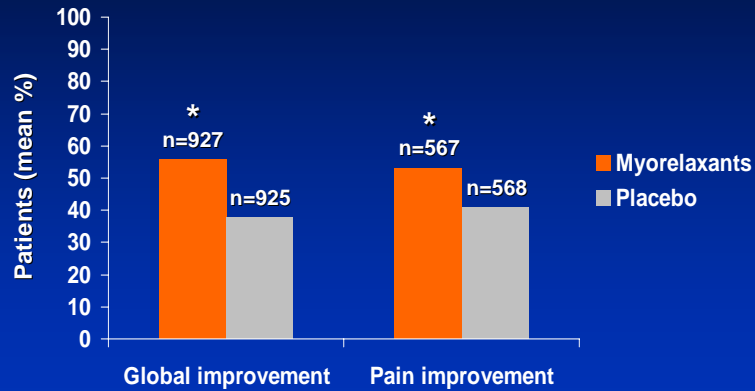
- Cimetropium bromide (5 trials; not available in the US)
- Hyoscine butyl bromide (3 trials)
- Mebeverine (5 trials; not available in the US)
- Otilium bromide (4 trials; not available in the US)
- Pinaverium bromide (2 trials; not available in the US)
- Trimebutine (4 trials; not available in the US)

The authors concluded that myorelaxants are superior to placebo in the management of IBS.<sup>1</sup> Another recent meta-analysis of 28 high-quality trials of pharmacologic agents for IBS derived similar conclusions.<sup>2</sup>

### References:

1. Poynard T, Regimbeau C, Benhamou Y. Meta-analysis of smooth muscle relaxants in the treatment of irritable bowel syndrome. *Aliment Pharmacol Ther.* 2001;15(3):355-361.
2. Jaiiwala J, Imperiale TF, Kroenke K. Pharmacologic treatment of the irritable bowel syndrome: a systematic review of randomized, controlled trials. *Ann Intern Med.* 2000;133:136-147.

## Meta-Analysis of Smooth-Muscle Relaxants in IBS (cont'd)



\* $P < 0.001$  vs placebo.

Reference: Poynard et al. *Aliment Pharmacol Ther.* 2001;15(3):355-361.

As shown in the above graph, the mean percentage of patients with global improvement was 56% in the myorelaxant group versus 38% in the placebo group (n=925), in favor of myorelaxant agents with a mean odd ratio of 2.13 ( $P < 0.001$ ; 95% CI 1.8-2.6) and a mean risk difference of 22% ( $P < 0.001$ ; 95% CI 13-32). The percentage of patients with pain improvement was respectively 53% in the myorelaxant group (n=567) and 41% in the placebo group (n=567), with a mean odd ratio of 1.65 ( $P < 0.001$ ; 95% CI 1.3-2.1) and a mean risk difference of 18% ( $P < 0.001$ ; 95% CI 7-28). There was no significant difference for adverse events.

The authors of this meta-analysis concluded that myorelaxants demonstrated a statistically significant difference versus placebo in global and pain improvement.

### Reference:

Poynard T, Regimbeau C, Benhamou Y. Meta-analysis of smooth muscle relaxants in the treatment of irritable bowel syndrome. *Aliment Pharmacol Ther.* 2001;15(3):355-361.

## Antidiarrheals

### Symptomatic treatment of diarrhea

- Increase stool consistency
- Decrease stool frequency

Reference: *Drug Facts and Comparisons*®. 1999:324b.

Antidiarrheals slow intestinal transit and enhance intestinal water and ion absorption, resulting in decreased stool frequency and increased stool consistency.<sup>1,2</sup> For diarrhea due to idiopathic bile salt malabsorption, cholestyramine may be helpful.<sup>1</sup>

#### References:

1. Drossman DA. Review article: an integrated approach to the irritable bowel syndrome. *Aliment Pharmacol Ther.* 1999;13(suppl 2):3-14.
2. *Drug Facts and Comparisons*®. St Louis, MO: Facts and Comparisons; 1999:324b.

## Loperamide for IBS With Diarrhea

- Does not cross blood-brain barrier<sup>1</sup>
  - Unlike diphenoxylate and opiates
- Improves diarrhea, urgency, borborygmi<sup>2</sup>
- Decreases frequency of bowel movements and improves stool consistency<sup>3</sup>
- Does not affect abdominal pain or distention<sup>3</sup>

References: 1. Paterson et al. *JAMA*. 1999;161:154. 2. Cann et al. *Dig Dis Sci*. 1984;29:239-247. 3. Jailwala et al. *Ann Intern Med*. 2000;133:136-137.

Loperamide seems particularly effective at treating patients with IBS who complain of loose, frequent stools and urgency of defecation.<sup>1</sup> Several studies of loperamide reported significant improvement in diarrhea, including decreased frequency of bowel movements and improved stool consistency, but no improvement in abdominal pain and distention.<sup>2</sup>

### References:

1. Cann PA, Read NW, Holdsworth CD, Barends D. Role of loperamide and placebo in management of the irritable bowel syndrome. *Dig Dis Sci*. 1984;29:239-247.
2. Jailwala J, Imperiale TF, Kroenke K. Pharmacologic treatment of the irritable bowel syndrome: a systematic review of randomized, controlled trials. *Ann Intern Med*. 2000;133:136-147.

## Tricyclic Antidepressants and SSRIs

### Symptomatic treatment of pain

- Reserved for patients with severe or refractory pain

Reference: Drossman and Thompson. *Ann Intern Med.* 1992;116(pt 1):1009-1016.

For patients with severe or refractory pain, impaired daily function, or associated depressive or panic-like symptoms, tricyclic antidepressants and SSRIs can be helpful.<sup>1,2</sup>

#### References:

1. Drossman DA, Thompson WG. The irritable bowel syndrome: review and a graduated multicomponent treatment approach. *Ann Intern Med.* 1992;116(pt 1):1009-1016.
2. *Drug Facts and Comparisons*®. St. Louis, MO: Facts and Comparisons; 1999:262I-262M.

## Low-Dose Psychotropic Agents

- Seven trials
  - Four parallel
  - Three crossover
- Five recorded global improvement
- Four reported significant improvements in
  - Abdominal pain
  - Diarrhea

Reference: Jailwala et al. *Ann Intern Med* 2000;133:136.

Seven clinical trials evaluating psychotropic agents demonstrated their benefits. Global improvement was reported in 5 trials. Four of the 7 trials reported improvement in abdominal pain and diarrhea. Three drugs were evaluated:

- Amitriptyline
- Nortriptyline
- Desipramine

**Reference:**

Jailwala J, Imperiale TF, Kroenke K. Pharmacologic treatment of the irritable bowel syndrome: a systematic review of randomized, controlled trials. *Ann Intern Med.* 2000;133:136-147.

## **Serotonergic Agent for the Treatment of C-IBS**

### **Tegaserod maleate**

- 5-HT<sub>4</sub> receptor partial agonist
- Indicated for the short-term treatment of women with IBS whose primary bowel symptom is constipation

Reference: Complete Prescribing Information for Zelnorm® (tegaserod maleate) Tablets. Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, 2004.

## Serotonergic Agent for the Treatment of D-IBS

### Alosetron hydrochloride

- 5-HT<sub>3</sub> receptor antagonist
- Indicated only for women with severe diarrhea-predominant IBS who have:
  - Chronic IBS symptoms (generally lasting 6 months or longer),
  - Had anatomic or biochemical abnormalities of the GI tract excluded, and
  - Not responded adequately to conventional therapy
- Diarrhea-predominant IBS is severe if it includes diarrhea and one or more of the following:
  - Frequent and severe abdominal pain/discomfort
  - Frequent bowel urgency or fecal incontinence
  - Disability or restriction of daily activities due to IBS
- Because of infrequent but serious gastrointestinal adverse events associated with LOTRONEX, the indication is restricted to those patients for whom the benefit-to-risk balance is most favorable
- Clinical studies have not been performed to adequately confirm the benefits of LOTRONEX in men or patients under the age of 18

## A Comprehensive Multicomponent Approach

Treatment program is based on dominant symptoms and their severity and on psychosocial factors

- Diet
- Medical management
- Psychological or behavioral options
  - Psychotherapy
  - Stress management

Reference: Drossman. *Aliment Pharmacol Ther.* 1999;13(suppl 2):3-14.

IBS is a complex disease and needs to be managed on several levels. Diet plays a key role in IBS, and patients need to learn what their triggers are and which foods provide relief (ie, high-fiber foods for constipation). Medical management may include treatments that help keep symptoms under control, even though this may mean prescribing lifestyle changes and a regimen of products. Patients with chronic diseases may become discouraged or have a preexisting psychological condition. Psychotherapy and/or stress management may be helpful for some patients.

**Reference:**

Drossman DA. Review article: an integrated approach to the irritable bowel syndrome. *Aliment Pharmacol Ther.* 1999;13(suppl 2):3-14.

## Diagnosis and Current Management of IBS: Summary

- It is important to establish a positive diagnosis of IBS<sup>1,2</sup>
- The optimal medical management approach should treat a complex of symptoms<sup>3</sup>

References: 1. Paterson et al. *Can Med Assoc J.* 1999;161:154-160. 2. American Gastroenterological Association. *Gastroenterology.* 1997;112:2120-2137. 3. Drossman and Thompson. *Ann Intern Med.* 1992;116(pt 1):1009-1016.

Precision in diagnosing IBS has been enhanced and simplified through the use of symptom-based criteria. If a patient presents with chronic ( $\geq 12$  weeks) bowel function disorders including abdominal pain as the dominant symptom with altered bowel function, a diagnosis of IBS is quite likely. To rule out an alternative or coexisting diagnosis, look for red flags such as weight loss, rectal bleeding, or anemia. Next, order laboratory studies and perform a physical exam to confirm the absence of organic disease.<sup>1</sup> Once the diagnosis has been confirmed, initiate a treatment program and follow up in 3 to 6 weeks.<sup>2</sup>

Because IBS generally presents as a complex of symptoms, management options traditionally have included specific agents for specific symptoms.<sup>3</sup> For example, anticholinergics have been useful in cases of severe pain. When constipation is the predominant symptom, fiber or psyllium products can be beneficial. When diarrhea is the predominant symptom, antidiarrheals are used to decrease intestinal transit, enhance water and ion absorption, and strengthen rectal sphincter tone.

### References:

1. Paterson WG, Thompson WG, Vanner SJ, et al. Recommendations for the management of irritable bowel syndrome in family practice. *Can Med Assoc J.* 1999;161:154-160.
2. American Gastroenterological Association. Irritable bowel syndrome: a technical review for practice guideline development. *Gastroenterology.* 1997;112:2120-2137.
3. Drossman DA. Review article: an integrated approach to the irritable bowel syndrome. *Aliment Pharmacol Ther.* 1999;13(suppl 2):3-14.