Peripheral Mechanisms in Irritable Bowel Syndrome

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T HE IRRITABLE BOWEL SYNDROME (IBS) AFFECTS 10 TO 20% OF THE POPULATION in developed countries. Specific peripheral mechanisms result in symptoms of IBS, including abnormal colonic transit and rectal evacuation; intraluminal intestinal irritants, such as maldigested carbohydrates (producing short-chain fatty acids) or fats, an excess of bile acids, and gluten intolerance; alterations in the microbiome; entero-endocrine-cell products; and genetic susceptibility to inflammation or altered bile acid synthesis. These luminal and mucosal irritants alter mucosal permeability and cause immune activation or inflammation, which in turn activates local reflexes that alter intestinal motility or secretion. The irritants also stimulate sensory mechanisms, leading to visceral hypersensitivity and pain. A greater understanding of these mechanisms may foster individualized, specific treatments for patients with IBS.
relieving constipation and associated IBS symptoms such as pain and bloating.\textsuperscript{11}

Disorders of rectal evacuation (spasm of the puborectalis muscle, anisms, and the descending perineum syndrome) cause symptoms of constipation-predominant IBS\textsuperscript{12} — that is, constipation, straining, a sense of incomplete rectal evacuation, bloating, and left-sided abdominal pain, which are relieved with bowel movement. Treatment of the evacuation disorder relieves the symptoms of constipation-predominant IBS.\textsuperscript{13} An evacuation disorder should be suspected when patients with constipation do not have a response to first-line therapies such as fiber\textsuperscript{14} and simple (e.g., osmotic) laxatives.

Diarrhea-predominant IBS is associated with acceleration of colonic transit in 15 to 45% of patients.\textsuperscript{5,10} Several disorders mimic diarrhea-predominant IBS or cause accelerated transit and should be ruled out, such as food allergy or intolerance, disaccharidase deficiencies, celiac disease, gluten intolerance without celiac disease, microscopic colitis, and idiopathic bile acid malabsorption.\textsuperscript{15}

MECHANISMS INVOLVED IN BOWEL IRRITATION

Luminal and mucosal factors activate immune, motor, and sensory mechanisms in the small intestine or colon. Such “irritation” leads to the symptoms and pathophysiological features of IBS (Fig. 1 and Table 1).

LUMINAL FACTORS

Responses to Food Ingestion

Pain is temporally related to eating in patients with IBS,\textsuperscript{16} especially in those with diarrhea-predominant IBS who have repeated, high-amplitude, propagated colonic contractions\textsuperscript{17} (i.e., contractions that traverse \textgreek{1}0 cm of colon and propel colonic content). Patients with diarrhea-predominant IBS, as compared with healthy controls, also have increased ileocolonic transit,\textsuperscript{18} typically induced by meals containing fat and providing at least 500 kcal.\textsuperscript{19} In addition, one study involving patients with IBS showed that scores for urge, discomfort, and pain in response to rectal distention were significantly increased after a 368-kcal meal relative to fasting, though the magnitude of these differences in sensation was small.\textsuperscript{19} The fat content of the meal, rather than the carbohydrate content, appears to have a key role in sensations of discomfort and pain.\textsuperscript{20}

Malabsorbed or Maldigested Nutrients

Malabsorption of sugars, such as lactose, fructose, and sorbitol, may mimic the features of IBS, but its prevalence across ethnic groups and races is unclear.\textsuperscript{21,22} A Norwegian case–control study suggested that IBS and lactose malabsorption were separate entities.\textsuperscript{21} Fructose and sorbitol malabsorption were observed in patients with IBS from Denmark,\textsuperscript{22} but not in patients from the Netherlands.\textsuperscript{23}

Maldigestion of complex carbohydrates may be more prevalent than malabsorption in patients with IBS. Fecal short-chain fatty acids, which contain fewer than 6 carbon atoms, are increased in stool from patients with diarrhea-predominant IBS.\textsuperscript{24} Short-chain fatty acids or medium-chain fatty acids (which contain 6 to 12 carbon atoms) reach the right colon in patients with borderline absorptive capacity or rapid transit in the small bowel. In a study involving healthy volunteers, 2 to 20% of dietary starch escaped absorption in the small bowel,\textsuperscript{25} providing substrate for the generation of short-chain fatty acids by colonic bacteria. The short-chain fatty acid receptor 2 (called free fatty acid receptor 2 [FFA\textsubscript{2}] or G-protein–coupled receptor 43) is expressed by enteroendocrine cells and mucosal mast cells in rat intestine.\textsuperscript{26} Short-chain fatty acids stimulate colonic transit and motility through intraluminal release of 5-hydroxytryptamine (5-HT)\textsuperscript{27} from enteroendocrine cells\textsuperscript{28} in rats. Short-chain fatty acids also initiate high-amplitude propagated contractions in the colon, propelling colonic content rapidly in dogs.\textsuperscript{29} An in vitro study in guinea-pig colon showed that the short-chain fatty acid propionate induced transepithelial ion and fluid transport in mucosal preparations from the distal colon and increased the expression of FFA\textsubscript{2}, which colocalizes with chromogranin A–enteroendocrine cells.\textsuperscript{30}

Fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAPs) are poorly absorbed in the small intestine and may induce symptoms of IBS\textsuperscript{31} through the production of short-chain fatty acids and their effects on colonic motility and secretion. Conversely, dietary manipulation of FODMAP content may reduce IBS symptoms.\textsuperscript{32} The role of the colonic microbiota in these nutrient-induced symptoms requires further elucidation.
Gluten Intolerance

The prevalence of celiac disease among patients with IBS is similar to that among controls. Celiac disease–free patients with IBS who carry HLA-DQ2 or HLA-DQ8 genotypes (which confer a predisposition to celiac disease) were five times as likely to have a response to gluten withdrawal as were patients without these genotypes. A randomized, placebo-controlled trial involving patients who previously reported intolerance to gluten and a response to its withdrawal confirmed that gluten was associated with symptoms of IBS. In mice sensitized to wheat glycoprotein, gliadin treatment increased responses to contractile and secretory stimuli (carbachol and electrical-field stimulation). In a recent randomized, controlled trial of a gluten-containing diet versus a gluten-free diet in patients with diarrhea-predominant IBS, those receiving gluten had increased stool frequency and bowel permeability and reduced messenger RNA expression of tight-junction proteins in bowel mucosa.

Increased Levels of Intracolonic Bile Acids

Although the ileum is excessively sensitive to the secretory effects of perfused bile acids in patients with IBS, the effects of bile acids are mainly manifested as cholerheic enteropathy with diarrhea. A systematic review of the literature suggested that bile acid malabsorption accounts for approximately 30% of cases of diarrhea-predominant IBS. In other studies, about 25% of patients with diarrhea-predominant IBS had an elevated rate of either bile acid synthesis (as measured by the fasting concentration of serum 7α-hydroxy-4-cholesten-3-one [C4, a bile acid precursor]) or 48-hour total fecal bile acid excretion.

Excess intracolonic bile acid in diarrhea-predominant IBS results from alterations in the enterohepatic circulation of bile acids. Synthesis of bile acid is regulated homeostatically by feedback inhibition of hepatocytes provided by fibroblast growth factor 19 (FGF19), which is produced by ileal enterocytes. FGF19 is secreted into the portal circulation and binds to fibroblast growth factor receptor 4 (FGFR4) and the klotho-β (KLB) receptor on the hepatocyte cell membrane, triggering intracellular signals that suppress bile acid synthesis. Given that a defect in bile acid absorption has been demonstrated in diarrhea-predominant IBS, it appears that excessive synthesis of bile acids overcomes ileal absorption capacity, leading to bile acid diarrhea.

Various mechanisms have been suggested to cause the elevated levels of intracolonic bile acid reported in diarrhea-predominant IBS or functional diarrhea. One potential mechanism is a deficiency in ileal secretion of FGF19. Walters et
### Table 1. Peripheral Factors in the Biology of Irritable Bowel Syndrome (IBS). *

<table>
<thead>
<tr>
<th>Peripheral Mechanism</th>
<th>Pathophysiological Effect</th>
<th>Examples of Factors Involved</th>
<th>Comments and Clinical Correlates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colonic motility</td>
<td>Accelerated or delayed colonic transit due to altered motility may be a consequence of altered secretion</td>
<td>Neuroumuscular dysfunction, enteroendocrine-cell products (e.g., 5-HT, granins), organic acids (bile acids, SCFAs), genetic predisposition to impaired bile acid synthesis (KLB SNP) or enterocyte secretion (GUCY2C mutation)</td>
<td>Affects up to 45% of patients with diarrhea-predominant IBS, 25% of patients with constipation-predominant IBS</td>
</tr>
<tr>
<td>Colonic motor and sensory response to food ingestion</td>
<td>Neurally (e.g., vagally) mediated induction of colonic HAPCs, increased ileocolonic transit, increased rectal sensitivity</td>
<td>Fat content of meal, high caloric content</td>
<td>Contributes to postprandial pain, urgency, diarrhea</td>
</tr>
<tr>
<td>Sensing and responses in the small bowel and colon</td>
<td>Activation of local secretory or motor reflexes and sensory mechanisms</td>
<td>Food stimulation of enteroendocrine-cell products, organic acids (bile acids, SCFAs)</td>
<td>Typically associated with diarrhea, bloating, pain</td>
</tr>
<tr>
<td>Rectal evacuation</td>
<td>Failure of rectal emptying with reflex inhibition of colonic motor function</td>
<td>Anismus, pelvic-floor dysynergia, descending perineum syndrome</td>
<td>Typical symptoms of constipation-predominant IBS plus incomplete evacuation and straining reversed with pelvic-floor retraining</td>
</tr>
<tr>
<td>Small-bowel mucosal permeability</td>
<td>Increased permeability, altered expression (mRNA, protein) of tight-junction proteins</td>
<td>Previous gastroenteritis, atopy, food intolerance (e.g., gluten, FODMAPs), stress</td>
<td>Typically associated with diarrhea-predominant IBS; may increase fluid secretion or activate sensory mechanism</td>
</tr>
<tr>
<td>Colonic mucosal permeability</td>
<td>Increased permeability, altered expression (mRNA, protein) of tight-junction proteins</td>
<td>Malabsorption of carbohydrates or fats, which increases levels of SCFAs; bile acid malabsorption (in 25% of patients with diarrhea-predominant IBS); immune activation; genetic predisposition to inflammation or immune activation (e.g., TLR9, TNFSF15) and altered feedback regulation of bile acid synthesis (KLB SNP)</td>
<td>Typically associated with diarrhea-predominant IBS; may increase fluid secretion or activate sensory mechanism</td>
</tr>
<tr>
<td>Mucosal immune activation</td>
<td>Increased permeability, activation of submucosal secretory reflexes and sensory mechanisms</td>
<td>Previous gastroenteritis, mast cells, T lymphocytes, circulating cytokines</td>
<td>Typically associated with diarrhea-predominant IBS and abdominal pain</td>
</tr>
<tr>
<td>Colonic microbiome</td>
<td>Production of SCFAs, with effects on motor, secretory, and sensory functions</td>
<td>Increased level of firmicutes or ratio of firmicutes to bacteroidetes, modified by antibiotics or probiotics; microbial species influenced by bile acids</td>
<td>Associated with abdominal bloating, pain, diarrhea</td>
</tr>
</tbody>
</table>

* FODMAPs denotes fermentable oligosaccharides, disaccharides, monosaccharides, and polyols; GUCY2C the gene encoding the guanylate cyclase C receptor; HAPCs high-amplitude propagated contractions; 5-HT 5-hydroxytryptamine; KLB the gene encoding klotho-β; mRNA messenger RNA; SCFAs short-chain fatty acids; SNP single-nucleotide polymorphism; TLR9 the gene encoding toll-like receptor 9; and TNFSF15 the gene encoding tumor necrosis factor (ligand) superfamily, member 15.
al. found that ileal production of FGF19 (reflected in plasma levels of this hormone) was reduced in patients with chronic diarrhea associated with bile acid malabsorption. There was an inverse relationship between fasting serum FGF19 levels and serum C₄ levels (a finding that is consistent with increased bile acid synthesis); this inverse correlation was confirmed in patients with diarrhea-predominant IBS. Another potential mechanism is mutation of the ileal bile acid transporter (also termed apical sodium-dependent bile acid transporter or solute carrier family 10, member 2), resulting in malabsorption of bile acid. This condition is extremely rare, even among familial cases of bile acid malabsorption. A third potential mechanism is genetic variation in bile acid synthesis or G-protein–coupled bile acid receptor 1 (GPBAR1), also known as TGR5 (discussed below).

Microbiota and Organic Acids

The precise role of the fecal or mucosal microbiome in IBS is unclear. An abundance of firmicutes bacteria in the fecal microbiome has been observed in patients with IBS, either as the sole finding or in combination with a decrease in bacteroidetes bacteria. An increase in the ratio of firmicutes to bacteroidetes has been reported to be associated with longer colonic transit time and increased levels of mental depression in IBS. Studies of mucosa-associated microbiota in patients with diarrhea-predominant IBS have shown increases in bacteroides and clostridia and a reduction in bifidobacteria.

A role of the microbiome in the causation of IBS symptoms is supported by randomized, controlled trials of the minimally absorbed antibiotic rifaximin and a meta-analysis showing the efficacy of probiotics, particularly for abdominal pain and bloating. In addition, a probiotic mixture has been shown to retard colonic transit in patients with diarrhea-predominant IBS.

The fecal microbiome causes changes in colonic functions that induce IBS symptoms through microbial interactions with intraluminal factors. IBS is characterized by alterations in the profiles of organic acids (e.g., short-chain fatty acids) and the proportion of secondary bile acids (deoxycholic and lithocholic acids) as compared with primary bile acids (cholic and chenodeoxycholic acids). For example, the proportion of primary bile acid in stool is higher in patients with diarrhea-predominant IBS than in healthy controls, possibly reflecting the reduced time for bacterial dehydroxylation in the colon due to rapid transit. Colon bacteria deconjugate and dehydroxylate bile acids to different extents, yet the primary or secondary bile acids with at least two α-hydroxyl groups (chenodeoxycholic, cholic, and deoxycholic acids) all induce secretion in mammalian intestine or colonic epithelial-cell monolayers. Moreover, chenodeoxycholic acid induces high-amplitude propagated contractions in healthy persons and acceleration of colonic transit in patients with constipation-predominant IBS, and deoxycholic acid induces colonic inflammation and hypersensitivity in rats. The bacterial dehydroxylation of chenodeoxycholic acid to lithocholic acid would theoretically reduce colonic secretion, but lithocholic acid constitutes only about 20% of total fecal bile acid. Therefore, the total proportion of secretory bile acids is only modestly altered by bacterial hydroxylation in the colon.

Overall, microbial differences appear to be unlikely to alter colonic function through changes in bile acid metabolism. Conversely, bile acids may modify the microbial content of the colon. For example, in rats, administration of cholic acid results in cecal microbiota that reflect the ratio of firmicutes to bacteroidetes observed in patients with IBS.

Enteroendocrine Signals Arising In the Mucosa

The release of several peptides and amines, such as serotonin, from enteroendocrine cells is triggered by luminal factors, such as exogenous dietary amines or tastants or their metabolites (e.g., short-chain fatty acids), and by endogenous chemicals involved in the digestive process, such as bile acids. The potential role of serotonin in IBS is supported by the increased circulating levels of 5-HT in patients with diarrhea-predominant IBS and decreased 5-HT levels in patients with constipation-predominant IBS; the generally stimulatory effects of 5-HT on motor, secretory, and sensory functions, and the effect of selective serotonin agonists and antagonists in the treatment of different IBS phenotypes. Enteroendocrine cells also release granins. Chromogranins and secretogranins are present in secretory vesicles of nervous, endocrine, and immune cells. Activation of nicotinic cholinergic receptors (e.g., by acetylcholine released from submucosal nerves) induces granin release from these
cells. Chromogranin A can induce the formation of mobile secretory granules and promote the sorting and release of other peptide hormones from enteroendocrine cells. Chromogranin-derived peptides secreted by such cells have antimicrobial properties against bacteria, fungi, and yeasts. As compared with healthy controls, patients with IBS, particularly those with rapid colonic transit, have higher levels of fecal chromogranin A, secretogranin II, and secretogranin III but lower levels of chromogranin B. These findings are nonspecific, since increased fecal granins or chromogranin cell density in colonic mucosa is observed in other diarrheal diseases, such as lymphocytic colitis and celiac disease. Chromogranin A cells also express FFA2 receptors that respond to short-chain fatty acids. Overall, the data are mostly consistent with the hypothesis that granins (through their role in the sorting and packaging of neuropeptides) are indirect biomarkers, rather than direct stimulators, of colonic secretion or motility.

**CONSEQUENCES OF IRRITATION OF THE COLON**

**IMMUNE ACTIVATION WITH MINIMAL INFLAMMATION**

Öhman and Simrén have summarized the evidence of inflammation or immune activation in the blood in at least some subsets of patients with IBS. The evidence of mast-cell and other immune (e.g., cytokine) activation in intestinal or colonic mucosa is less consistent. Inflammation, manifested as increased levels of T lymphocytes in the rectal mucosa in patients with IBS, has been associated with increased intestinal permeability. These data, in addition to the epidemiologic and clinical observations of postinfectious IBS and colonic mucosal gene-expression profiles showing functional alterations of several components of the host mucosal immune response to microbial pathogens, support a role of immune activation and altered bowel barrier function in a subgroup of patients with IBS. Genetic susceptibility may confer a predisposition to immune activation in a subset of patients with IBS (discussed below).

**INCREASED MUCOSAL PERMEABILITY**

Several studies in adults have documented increased small-bowel or colonic mucosal permeability in vivo, in mucosal biopsy specimens in vitro, or in Caco-2 monolayers in response to fecal supernatants from patients with IBS (summarized by Rao et al.). Children with IBS also have evidence of increased proximal-gut and colonic permeability and low-grade inflammation. Factors associated with increased mucosal permeability and IBS include cow’s milk allergy, previous nonspecific infection, atopic disease (e.g., rhinoconjunctivitis, rhinitis, and eczema), stress, and dietary fat.

Two lines of investigation support the role of stress in increased bowel permeability in humans. First, when the stress hormone corticotropin-releasing hormone was applied to the serosal side of colonic mucosal biopsy specimens from healthy persons, there was increased transcellular uptake of horseradish peroxidase, an effect that was mediated by mast cells. Second, stress induced by having study participants place their hands in cold water increased jejunal permeability in healthy women but not in healthy men.

A high-fat diet results in gut-derived endotoxemia and may contribute to the immune activation observed in some patients with IBS. Studies in animals have shown that emulsified fats increase intestinal permeability, causing endotoxemia and inflammation.

The link between increased mucosal permeability and IBS is supported by the observation that increased permeability enhances mucosal inflammation and activates local reflex mechanisms, stimulating secretion and sensory pathways that lead to increased visceral sensation.

**GENETIC FACTORS**

The published literature on potential genetic factors conferring a predisposition to IBS is summarized elsewhere. The reported genetic factors of greatest interest confer a predisposition to inflammation, bile acid synthesis, expression of bioactive neuropeptides, and intestinal secretion through a mutation in the guanylate cyclase C secretory pathway.

**SUSCEPTIBILITY TO INFLAMMATION AND IBS SYMPTOMS**

Among 30 susceptibility loci for Crohn’s disease that are associated with epithelial transport, barrier function, bacterial recognition, autophagy, prostaglandin production, and differentiation of interleukin-17–producing helper T cells, Zucchelli et al. identified a significant association between
the gene encoding tumor necrosis factor (ligand) superfamily, member 15 (TNFSF15) and IBS phenotype in separate populations of Swedish and U.S. patients;90 the strongest association was with constipation-predominant IBS (odds ratio for development of the disease, 1.79; 95% confidence interval, 1.41 to 2.26; P<0.001). In a cohort from the United Kingdom, genetic variations in TNFSF15 were protective against diarrhea-predominant IBS.91 Villani et al. reported that four genes were associated with postinfectious IBS in patients in Walkerton, Ontario, Canada, and these susceptibility loci included toll-like receptor 9 (TLR9).92 In a univariate analysis, colonic transit in patients with IBS was found to be associated with four inflammation-susceptibility genes that included TLR9 and the genes encoding cadherin 1 (CDH1) and interleukin 6 (IL6).93

**GENETIC VARIATION IN BILE ACID SYNTHESIS**

Genetic variation in KLB, to which FGF19 binds, is associated with diarrhea-predominant IBS and accelerated colonic transit.94 A functional genetic variation in KLB (Arg728Gln), resulting in impaired KLB synthesis, prevents FGF19 from binding to the combined KLB–FGFR4 receptor on the hepatocyte. This reduces the FGF19 feedback inhibition of hepatocyte synthesis of bile acids, resulting in more bile acid reaching the bowel and, potentially, causing accelerated transit and diarrhea.

A second potential mechanism is genetic variation in GPBAR1. The receptor is located on myenteric, cholinergic, and nitrergic neurons in the colon and proximal small intestine. Genetic variation in GPBAR1 may be associated with small-bowel and colonic transit in healthy persons and in patients with IBS.95

**GENETIC VARIATION IN EXPRESSION OF NEUROTRANSMITTERS AND CYTOKINES**

Neuropeptide S (NPS) receptor 1 (NPSR1) is expressed by gastrointestinal enteroendocrine cells and induces the production of several neuropeptides. The NPS–NPSR1 ligand–receptor complex is involved in inflammation, anxiety, and nociception. Three single-nucleotide polymorphisms (SNPs) of NPSR1 are significantly associated with colonic transit in IBS.96

The endocannabinoid anandamide is inactivated by fatty acid amide hydrolase (FAAH). A SNP in human FAAH (G385A or rs324420) reduces FAAH expression. FAAH heterozygosity or homozygosity for the minor allele A at this SNP, as compared with the CC genotype (homozygosity for the major allele C), increases the odds of diarrhea-predominant IBS or IBS with alternating bowel function and is significantly associated with accelerated colonic transit in diarrhea-predominant IBS.97

The gene controlling the serotonin transporter (SLC6A4) protein, 5-HTTLPR, is associated with IBS phenotype in some ethnic groups, but the findings are inconsistent. The short allele is associated with reduced SLC6A4 function. As compared with the long allele, the short allele is associated with higher ratings of rectal pain98 and increased activation of regional cerebral blood flow during painful colorectal distensions.99

**GENETIC MUTATION IN THE GUANYLATE CYCLE C SECRETORY PATHWAY**

Fiskerstrand et al.100 described a Norwegian family with a rare form of familial diarrhea, characterized by the onset of symptoms in infancy and chronic, relatively mild diarrhea diagnosed as diarrhea-predominant IBS. This dominantly inherited, fully penetrant disease is due to a mutation in the gene encoding the guanylate cyclase C (GUCY2C), which induces enterocyte secretion. The mutation was a heterozygous base substitution, c.2519G–T, in exon 22 of chromosome 12.

**CLINICAL AND THERAPEUTIC IMPLICATIONS**

IBS is no longer regarded as an idiopathic bowel dysfunction that originates exclusively from psychological stress or brain dysfunction. Fecal tests (e.g., measurements of fecal calprotectin and lactoferrin levels) or colonic imaging (e.g., colonoscopy) may be indicated clinically to rule out inflammatory bowel disease and neoplastic diseases. Patients who do not have a response to lifestyle and dietary modifications and symptomatic remedies should undergo tests to identify causative factors. These include tests of colonic transit and rectal evacuation in patients with constipation-predominant IBS and tests for carbohydrate or fat mal-digestion (leading to the formation of short-chain fatty acids), increased bile acid synthesis or increased fecal bile acid excretion, and, possibly, dietary intolerance (e.g., gluten) in patients with diarrhea-predominant IBS.
It is anticipated that the relationship of diet, microbiome, endogenous irritants, barrier function, immune activation, and genetic factors to the motor, sensory, secretory, and psychological dysfunctions in IBS will be further elucidated. Future research will address the overall hypothesis that, like inflammatory bowel disease, IBS results from interactions between the host and genetic factors. These advances will lead to the development of more specific, individualized treatment that is based on the underlying peripheral pathophysiological mechanisms, including dietary recommendations (e.g., gluten or FODMAP exclusion), biofeedback-based treatment of defecation disorders, bile acid sequestrants and 5-HT3 antagonists for diarrhea and urgency, prokinetics or secretagogues for patients with constipation-predominant IBS, and possibly probiotics, nonabsorbable antibiotics, anti-inflammatory agents, or tight-junction modulators (e.g., larsazotide) for patients with evidence of immune activation or increased mucosal permeability.

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Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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