

standardized biopsy protocol. Although inadequate biopsy depth might be a potential explanation (only 85% of biopsies contained lamina propria or deeper structures), buried glandular mucosa has been detected after ablation with other thermal techniques (PDT, argon plasma coagulation, multipolar coagulation), so there is evidence to suggest that biopsies after thermal therapy do penetrate deeply enough to detect this abnormality.

In summary, the study by Fleischer et al shows that complete eradication of IM by using circumferential and focal ablation techniques with radiofrequency energy is technically feasible and well-tolerated by patients with nondysplastic Barrett's esophagus and has long-term efficacy. However, it is premature to advocate ablation for every patient with nondysplastic IM outside a clinical trial or patient registry protocol. As suggested by the authors, an ideal management paradigm for a nondysplastic population in the future might be to risk stratify patients by assaying for genotypes associated with propensity for neoplastic progression, and then to eradicate the nondysplastic Barrett's esophagus in those patients at highest risk, with surveillance or no action in those patients at lower or null risk.

G. FERNÁNDEZ-ESPARRACH
Endoscopy Unit

J. PANÉS
Gastroenterology Department
Hospital Clínic Barcelona
CIBEREHD
Barcelona, Spain

Reply. We thank Drs Fernandez-Esparrach and Panes for their review of our study. They point out that there is a growing body of evidence showing that endoscopic treatment of Barrett's esophagus (BE) is safe and effective. For those who do not undergo treatment, endoscopic surveillance is the standard of practice. As physicians and patients try to determine whether or not surveillance or endoscopic therapy is appropriate, they are informed by guidelines from gastroenterological societies. The 2008 guidelines from the American College of Gastroenterology (ACG; *Am J Gastroenterol* 2008;103:788–797) have been the most commonly referenced document for the last 3 years. In March 2011, the American Gastroenterological Association (AGA; *Gastroenterology* 2011;140:1084–1091) released the AGA Medical Position Statement on the Management of Barrett's Esophagus, which goes beyond the ACG guideline with regard to low-grade dysplasia (LGD) and nondysplastic BE. Although there were no recommendations for endoscopic treatment for patients with nondysplastic BE or with LGD in the ACG paper, the Medical Position Statement states that “although endoscopic eradication therapy is not suggested for the general population of patients with BE in the absence of dysplasia, we suggest that RFA with or without endoscopic mucosal resection (EMR) should be a therapeutic option for select individuals with non-dysplastic BE who are judged to be at increased risk for progression to HGD or cancer.” It also states that “endoscopic eradication therapy with

RFA should also be a therapeutic option for treatment of patients with confirmed LGD.” The AGA position paper points out that the recommendation that is made takes into consideration endpoints other than reduction in cancer deaths. For example, an intermediate endpoint such as sustained elimination of Barrett's mucosa at 5 years may be an acceptable clinical outcome. As the authors state, “there is no consensus and there remains an area of controversy influenced by various and legitimate but different points of views.”

I believe that this document represents a “tipping point.” In Malcolm Gladwell's best seller, *The Tipping Point*, he writes that, “with social changes that mark every-day life, there is a critical mass of opinion at which a group moves to change.” I believe there are at least 5 reasons that we are “tipping” with regard to endoscopic therapy of BE. First, there is new scientific information about the safety, efficacy, and durability of RFA in patients with BE (*N Engl J Med* 2009;360:2277–2288). Second, cost-effectiveness models and quality-of-life studies support endoscopic therapy (*Gastroenterology* 2009;136:2101–2114; *Endoscopy* 2009;41:1–9). Third, there is increasing satisfaction among clinicians and patients with the procedure. Fourth, there is a continued awareness of the limitations of surveillance. Falk pointed out that “at least half of the patients who develop high-grade dysplasia (HGD) and/or cancer had 2 consecutive initial endoscopies without dysplasia” (*Clinical Gastroenterol Hepatol* 2006;4:556–572). Fifth, respected leaders in the field explain that endoscopic treatment is supported by the same rationale that supports colonoscopic polypectomy (*Gastroenterology* 2011;140:386–388).

More scientific studies, particularly with biomarkers, will provide better data. But even now, there is enough information for a clinician to meet with his/her patient to help guide them to a thoughtful decision.

DAVID E. FLEISCHER
Division of Gastroenterology
Mayo Clinic
Scottsdale, Arizona

IS IRRITABLE BOWEL SYNDROME A RHINITIS OF THE GUT?

Klooker TK, Braak B, Koopman KE, et al. (Department of Gastroenterology, Academic Medical Center, Amsterdam, The Netherlands). The mast cell stabilizer ketotifen decreases visceral hypersensitivity and improves intestinal symptoms in patients with irritable bowel syndrome. *Gut* 2010;59:1213–1221.

The view on the pathogenesis of irritable bowel syndrome (IBS) has changed fundamentally over the last 10 years, with increasing substantial evidence that IBS comprises most likely several distinct entities with different underlying disorders, co-founders, and triggers. Mast cells were suggested to play a key role in the generation of hypersensitivity and other pathophysiologic changes and thus in the generation

o symptoms of IBS (*Gastroenterology* 2004;126:693–702). Moreover, in animal studies the mast cell stabilizer doxantrazole decreased visceral perception, suggesting that blocking mast cell degranulation may be a promising therapeutic approach in patients with IBS (*Neurogastroenterol Motil* 1997;9:271–279). Numerous studies in animals suggest that the inhibition of release of mediators from mast cells by mast cell stabilizers may be 1 underlying mechanism.

Based on these reports, it was important to perform a prospective, randomized, placebo-controlled trial on the effect of a mast cell stabilizer like ketotifen in patients with IBS. Of 108 patients with IBS in an academic tertiary referral center, 60 were included in a prospective, placebo-controlled trial. All patients fulfilled the ROME II criteria for IBS and organic causes were excluded by a detailed history, a normal physical examination, a normal sigmoidoscopy, and normal routine laboratory tests, including anti-tissue transglutaminase antibodies and negative stool examinations. Psychiatric and other significant disorders (diabetes, endocrine, and cardiovascular disorders) were excluded. All medications likely to interfere were discontinued 7 days before inclusion in the study.

In 29 patients, biopsies were taken before the inclusion. These biopsies were taken from the colon descendens and compared with biopsies from the descending colon from 15 healthy volunteers. In detail, immunohistochemical studies on mast cells density and in vitro release studies investigating mast cells mediator release (histamine, tryptase) from the freshly obtained biopsy specimens were performed.

All 60 IBS patients and 22 volunteers underwent 2 barostat studies for the assessment of rectal sensitivity to a air-pressurized balloon. The first examination was performed before ketotifen or placebo treatment and the second after 8 weeks of ketotifen or placebo treatment. The IBS patients were included in a placebo-controlled, double-blind, randomized trial consisting of 2 weeks of screening, 8 weeks of treatment, and another 2 weeks of follow-up after treatment. The randomization was done irrespective of the barostat testing results and for all patients a symptom assessment was performed using a validated gastrointestinal symptom rating scale (Subjective Global Assessment, IBS—quality of life [QOL]).

Chart review revealed that, of the patients included, 22% most likely had postinfectious IBS and 10% reported symptom onset with stress. In the remaining two thirds of the patients, no association with stress, infections, or other suggested co-founders of IBS were reported. The differences in these subgroups were equally distributed between the treatment groups.

There were no differences in the side effects reported by those taking ketotifen (77%) or placebo (67%), respectively. Self-reported weight gain was significantly greater among the ketotifen group ($n = 7$) compared with the placebo group ($n = 1$).

Ketotifen had no effect on the minimal balloon distention pressure, the threshold for the first sensation of the rectal balloon, or rectal compliance to balloon distention, but did significantly increase the threshold for discomfort

in patients with a preexisting hypersensitivity as diagnosed with the basal barostat examination. In patients without preexisting hypersensitivity, ketotifen had no significant influence on visceral sensitivity compared with placebo.

Interestingly, IBS patients (both normosensitive and hypersensitive) had lower tryptase positive mast cell counts compared with healthy controls; there was no difference in the count of CD117-positive cells between IBS patients and healthy controls. In the mediator release studies, a number of observations were striking. For example, the tryptase release was significantly lower in IBS patients compared with healthy controls. Furthermore, there was a significantly higher release of histamine in hypersensitive and normosensitive patients with IBS. Under the tested in vitro conditions, tryptase release could not be blocked or reduced using the mast cells stabilizers ketotifen or doxantrazole.

In the clinical trial, 20% of the patients reported substantial or considerable relief when being treated with ketotifen compared with only 10% in the group treated with placebo. Using individual gastrointestinal symptom scores, there was a significant reduction of abdominal pain, bloating, flatulence, diarrhea, and incomplete evacuation in response to ketotifen. However, because of the small number of patients included, these effects did not attain significance when the paradigm for multiple testing was applied. Ketotifen resulted in a significant improvement of quality of life (all scales of the IBS-QOL Score) in IBS patients, irrespective whether these patients were normo- or hypersensitive on the basal barostat examination. Interestingly, after withdrawal of ketotifen in the verum group, the abdominal complaints returned to baseline levels within 1–2 weeks, again stressing the notion that ketotifen may be beneficial in the symptomatic treatment of patients with IBS.

Comparing the clinical response with the functional testing results and with the in vitro findings, there was no correlation of perception thresholds, mast cell counts, histamine or tryptase release, clinical symptoms, or response of clinical symptoms to ketotifen.

Comment. IBS is a clinical syndrome that is characterized by defined abdominal symptoms, such as abdominal discomfort or pain, bloating, and altered bowel habits with either a predominance or a mixture of constipation or diarrhea. The exact definition and diagnosis of IBS is nowadays based on the ROME III criteria. The cause or causes of IBS are unclear and most likely involve different sites (central nervous system, peripheral and enteric nervous systems), different mechanisms (eg, visceral hypersensitivity, prior infection, low-grade inflammation, impaired barrier function) and different triggers.

Individual responses to inflammation, luminal antigens, psychological stress, or other factors, in combination with genetic and environmental factors may, among others, result in changes of neuronal enteric regulation, gastrointestinal motility, visceral sensitivity (at central and peripheral sites), and epithelial function, resulting in the clinical syndrome of irritable bowel. In fact, some of these individual

responses may be predetermined by certain genetic predispositions and susceptibilities (Clin Gastroenterol Hepatol 2008;6:194–205; Gastroenterology 2010;138:1502–1513; Am J Physiol 2008;295:G219–G225; Hum Mol Gen 2008;17:2967–2977). As a new possible key player, mast cells have been recently suggested being involved in the IBS pathophysiology; both basic and clinical evidence for this notion are strong (Gastroenterology 2004;126:693–702). In patients with IBS, an increased number of mast cells are reported in the small intestine (jejunum; Gut 2007;56:203–209), the terminal ileum (Dig Dis Sci 1993;38:1590–1595; Gut 2004;53:1096–1101; J Gastroenterol Hepatol 2006;21:71–78), the large intestine (Neurogastroenterol Motil 2000;12:449–457; Gastroenterology 2002;122:1778–1783; Gastroenterology 2004;126:693–702; Gut 2004;53:1096–1101; Gut 2008;57:468–473), and the rectum (J Gastroenterol Hepatol 2006;21:71–78; J Gastroenterol 2008;23:1689–1694). In a number of studies, the proximity of the mast cells to the mucosal nerve endings was positively correlated with abdominal pain sensation in patients with IBS symptoms (Gastroenterology 2004;126:693–702; Gut 2004;53:1096–1101; J Korean Med Sci 2003;18:2004–2010).

Biopsies taken from IBS patients were shown to release mast cell mediators such as histamine, tryptase, and serotonin (Gastroenterology 2009;137:1425–1434) and the mediators released from IBS patients were able to excite human enteric nerves in vitro. Excitingly, the mediators released from biopsies from healthy controls did not cause such an activation of human enteric nerves (Gastroenterology 2009;137:1425–1434). Other studies demonstrated that mediators released from biopsies from patients with IBS can increase spike discharge from afferent nerves in animal models (Gastroenterology 2007;132:26–37; J Clin Invest 2007;117:636–647), proving a positive association of mast cell mediator release in IBS patients and neuronal excitation involved in pain processing. Interestingly, in none of these studies was there a difference in the response of neuronal tissues to tissue supernatants from patients with diarrhea and constipation-predominant IBS, suggesting that the motility consequences observed in patients with IBS may not be a helpful grouping when studying the pathophysiology of IBS. The pharmacology associated with the eliciting these excitatory responses to mediators released from biopsies of patients with IBS showed an involvement of both serotonin and histamine receptors, as well as an involvement of protease-mediated mechanisms (Gastroenterology 2009;137:1425–1434). The release of mast cell mediators from colonic biopsies in patients with IBS was increased in most of studies (Gastroenterology 2004;126:693–702; J Clin Invest 2007;117:636–647), whereas in some studies no such increased mediator release was shown. It yet has to be determined whether these difference in mediator release are due to technical differences between the different studies, or whether these differences resemble disparities in patient selection, or even environmental or genetic differences in the patient cohorts.

In rats, the mediators released from colonic biopsies from IBS patients induced an increased firing of mesenteric nerves and an increased stimulation of neurons in the dorsal root ganglia, providing strong evidence that the released mediators activate the neuronal pathways involved in visceral sensation. According to current knowledge, this may result in increased sensation and thus visceral hypersensitivity. In about two thirds of the neurons studied, this activation was capsaicin sensitive further stressing the notion that nociceptive pathway are activated (Gastroenterology 2007;132:26–37). In this context, it is of special interest that a recent paper found an increase increased presence of TRPV1-receptor-positive neurons together with an increased presence of mast cells in the lamina propria of patients with IBS. Furthermore, this publication again demonstrated a positive correlation of abdominal pain scores of patients with IBS and the number of mast cells found (Gut 2008;2008:923–929).

It has been speculated that the proteases may interact with the proteinase activated receptor (PAR subtype 2) and with other receptors, such as the histamine and the serotonin receptors, and thus may play a key role in the regulation of the integrated neural response (J Clin Invest 2007;117:636–647; Biochem Pharmacol 2003;66:519–525; Gastroenterology 2002;122:1035–1047; J Physiol 2003;552:589–601). Differences in the expression of the protease-activated receptors 1 and 2 (PAR 1 and PAR 2) were shown especially in patients with diarrhea-predominant IBS. Thus, in contrast with mast cell degranulation alone, PAR 1 and PAR 2 expression may be involved in the pathogenesis of individual symptoms like diarrhea and constipation (J Gastroenterol 2009;44:666–674).

In addition to mast cells, there is strong evidence for additional cellular mechanisms involved in the pathophysiology of IBS. An increased T-cell recruitment into the intestine, with an increased presence of activated T lymphocytes of both CD4⁺ and CD8⁺ subtypes, an increased expression of $\beta 7$ integrin in the blood-activated T cells and the MAdCAM-1 molecule in the colon were suggested, just to name some of the additional possible cellular pathophysiology. The majority of these colonic mucosal T cells have a “memory” phenotype, whereas the distribution of naive colonic T cells appears normal (for review: Rev Esp Enterol Dig 2010;102:637–647).

Numerous present studies direct toward a cellular concept of IBS pathophysiology and suggest a concept of an altered immunologic response, which concomitantly affects the signaling from the mucosa to the enteric nervous system and the afferent nerve endings. These concepts have led to the idea to treat patients with IBS using immunosuppressants, anti-inflammatory drugs, or mast-cell-stabilizing therapy. However, not all these approaches were successful. For example, among patients with postinfectious IBS, treatment with prednisolone (30 mg/d) given in a randomized, placebo-controlled trial did not affect the number of enterochromaffin cells in biopsies or cause an

improvement in symptoms of the patients with postinfectious IBS (*Aliment Pharmacol Ther* 2003;18:77–84).

In a small, pilot, placebo-controlled, double-blind study, the aminosalicylate mesalazine caused a marked decrease of the mast cells in colon biopsies and significantly increased the general well-being in patients with IBS. However, in this relative small study mesalazine showed no significant beneficial effect on abdominal pain scores or bowel habits (*Aliment Pharmacol Ther* 2009;30:245–252). However, the lack of a significant effect of mesalazine may be due to the small number of patients included and because the results of mesalazine treatment are in line with the concept of immune mechanisms being a potential therapeutic target in IBS, larger studies are needed to explore whether mesalazine may be a potential drug in the treatment of patients with IBS or in specific IBS subgroups.

In animal experiments the mast cell stabilizer doxantrozole prevented the induction of visceral hypersensitivity induced by stress and acetic acid, 2 standard models of testing mechanisms of visceral sensitivity in animals (*Neurogastroenterol Motil* 1997;9:271–279). No other mast cell stabilizers have been tested in animals yet.

The recent study published by Klooker et al was the logical next step to the overarching supporting hypothesis developed in animal research that blocking mast cell degranulation may be beneficial to patients with IBS. The results of the study substantially support these concepts developed by basic scientists, but there are also some drawbacks that need to be discussed.

In contrast with previous reports by the same group of investigators, the authors this time failed to show an increased number of mast cells in colonic biopsies taken from patients with IBS. Thus, their overarching hypothesis of mast cells being increased among patients with IBS was not supported. In line with previous data, there was an increased basal release of histamine in the patients with IBS, whereas the tryptase release was actually decreased. What is more intriguing is that the spontaneous “basal” release of neither histamine nor tryptase could be blocked with ketotifen or doxantrozole, another employed mast cell stabilizer. Thus, the basal release may just reflect a damage release from the tissue specimen and in consequence the mast-cell-stabilizing component of ketotifen is not effective in preventing the basal release. These differences in mast cell numbers and release characteristics may well be due to small patient numbers, different patient cohorts used, sampling error, or technical differences in the studies performed, but it also has to be considered that the mast cell involvement was overestimated in previous studies or that the patient cohort where increased numbers of mast cells are of importance yet has to be defined. This, however, questions the overall relevance of previous studies where an increased basal release of mast-cell-derived mediators has been demonstrated. The lack of effect of ketotifen on the *in vitro* mast cell function directs the authors to speculate that the effect of ketotifen is in fact not due to its mast-cell-

stabilizing effect, but rather to an antihistaminic side effect at the histamine 1 receptor. It is difficult, if not confusing, to understand how this speculation is generated. Presently, the differences of the *in vitro* observations versus previous studies are striking, unclear, and inexplicable. However, the clinical response of the placebo-controlled trial is very convincing and suggests mast cell degranulation blockers as a promising future treatment for patients with IBS.

The study by Klooker et al also underlines that the current concept of classifying diarrhea and constipation being the predominant symptoms might be helpful for an initiation of a symptomatic treatment of patients with IBS. In contrast with pathophysiologic studies in patients with IBS, this classification based on individual symptoms may not be a good parameter to subdivide patients with IBS, and may even limit meaningful research. We need to understand that the gut is limited with respect to the symptoms it can generate and that the symptoms may have nothing to do with the initiating pathophysiology. Individual and environmental factors as well as genetic predisposition may be more important to the individual with IBS and the imbalances resulting in a diarrhea- or constipation-predominant phenotype. The clinical classification may be helpful in directing presently symptomatic therapeutic approaches, but may be useless in studying underlying pathophysiologic aspects. Interestingly, this notion also applies to barostat testing as a marker of visceral hypersensitivity, because barostat testing and grouping of patients into a hypersensitive and a nonsensitive subgroup did not add meaningful directions in this study.

Finally, again we need to understand that IBS may not be explained by a single pathophysiology. Multiple concepts such as mucosal dysfunction, mild or subtle inflammation, mucosal immunity, luminal antigens, increased intestinal permeability, composition of the bacterial flora and multiple other factors account for the complexity and the lack of understanding of the pathophysiology of IBS (*Neurogastroenterol Motil* 2008;20:1110–1118; *Clin Gastroenterol Hepatol* 2008;6:194–205). Because some microbes are known to produce high amounts of serine proteases (*Gut* 2008;57:591–599; *J Appl Bacteriol* 1988;64:37–46) and are able to produce histamine (*Anaerobe* 1996;2:285–297), many of the effects that are presently attributed to altered mast cell mediator release may have a different cause. Changes of the luminal barrier owing to stress (*Gut* 2004;53:494–500) or genetic alterations in response to inflammation or antigens may alter the permeability of the gut to luminal factors, which in turn could further contribute to the changes in enteric function (*Clin Gastroenterol Hepatol* 2008;6:194–205).

The role of the mucosal mast cells in the interplay between luminal factors, flora, mucosal permeability, and immunity and enteric neurophysiology in IBS is not clearly defined. Patients with “atopic disease” are known to have an increased incidence of IBS (*Ann Allergy Asthma Immunol* 2008;100:49–53; *Aliment Pharmacol Ther* 2010;31:1112–

1122), supporting the idea of an immunologic component within the pathophysiology of IBS. Increased permeability of the gut owing to stress (*J Physiol Pharmacol* 2009;60: [Suppl 7]:33–46), infections, or drugs (*Am J Gastroenterol* 2006;101:1295–1298) may cause an increased activation or recruitment of T cells and/or mast cells. Unfortunately, these mechanisms were not studied or could not be demonstrated in the study by Klooker et al.

Finally, ketotifen and mast cell stabilization may be a new tool in the treatment of IBS. The study by Klooker et al may also foster the development of new drugs targeting IBS. This study additionally suggests that the clinical classification of patients with IBS as suggested by the Rome criteria might be helpful in the clinical setting and for choosing the best clinical treatment based on patients symptoms, but could be distracting from the studying the underlying pathophysiological problems. Eventually a different approach to classification of patients with IBS, based on onset (eg, postinfectious), pathophysiologic parameters (eg, hypersensitivity, permeability) or even genetic markers could be desirable.

HANS-DIETER ALLESCHER

Zentrum Innere Medizin

Klinikum Garmisch-Partenkirchen

Academic Teaching Hospital of the Ludwig-Maximilians

University Munich

Munich, Germany

MARTIN STORR

Division of Gastroenterology

Department of Medicine

University of Calgary

Calgary, Alberta, Canada

Reply. We greatly appreciate the comments by Allescher and Storr on our manuscript, in which we have evaluated the effect of the mast cell stabilizer ketotifen on visceral perception, abdominal symptoms, and the release of mast cell mediators. The authors point out that there is an important discrepancy regarding the number of mast cells detected in rectal and colonic biopsies compared with previous reports from our group. We would like to stress that we have never reported increased numbers of mast cells in biopsies of patients with irritable bowel syndrome (IBS). The authors of the commentary are, however, correct that using 2 different markers, namely, tryptase and CD117, we were unable to demonstrate an increase in mast cell numbers, a finding repeatedly reported by other groups. Potential explanations could indeed be patient selection or demographic differences, although we disagree that small number of biopsies, at least in our study, could be a factor. Rectal biopsies were taken from all 60 patients included in the study (ie, when they presented to undergo the rectal barostat study). The 29 patients referred to in the commentary by Allescher and Storr are patients who had additional colonic biopsies before the study during routine endoscopy. In addition, we would like to point out that several other

studies also failed to demonstrate an increased number of mast cells (*Gastroenterology* 2002;122:1778–1783; *J Clin Invest* 2007;117:636–647; *Gut* 2000;47:804–811), confirming our finding and indicating that better identification of patients and perhaps even standardization of biopsy collection, preservation, preparation, staining, and analysis are warranted.

In our view, abnormal or increased activation of mast cells rather than the number of mast cell is more relevant to the pathophysiology of IBS. One way to demonstrate this is by measuring mediators released by biopsies over a given period of time. We demonstrated increased release of histamine, but not of tryptase in IBS. However, assuming that ketotifen exerted its effects by stabilization of mast cells, one would anticipate that the release of mast cell mediators should be reduced after 8 weeks of treatment. In contrast, however, tryptase and histamine release were not reduced by ketotifen. As discussed in detail in our manuscript, the mediator release from biopsies may not reflect the physiologic activation of mast cells; therefore, one may question its value as biomarker. Another interpretation, however, could be that the improvement in symptoms by ketotifen may result from a mechanism unrelated to mast cell stabilization. As ketotifen interacts with H1 receptors, which are known to be involved in visceral perception, we speculate that H1 antagonistic properties of ketotifen may mediate the clinical improvement of ketotifen. Allescher and Storr find it difficult, if not confusing, to understand how this speculation is generated. In the mean time, we have tested an H1 receptor antagonist (ebastine) in our rat IBS model of maternal separation on visceral hypersensitivity. Treatment with this compound indeed normalizes visceral perception of hypersensitive separated rats, confirming our hypothesis. Although more research is definitely required, we hope we have clarified our reasoning and again thank these authors for their positive comments.

MIRA M. WOUTERS

Department of Gastroenterology

Translational Research Center for Gastrointestinal Disorders

Catholic University of Leuven

Leuven, Belgium

TAMIRA K. KLOOKER

RENE M. VAN DEN WIJNGAARD

Department of Gastroenterology and Hepatology

Academic Medical Center

Amsterdam, The Netherlands

GUY E. BOECKXSTAENS

Department of Gastroenterology

Translational Research Center for Gastrointestinal Disorders

Catholic University of Leuven

Leuven, Belgium

and

Division of Gastroenterology and Hepatology

Academic Medical Center

Amsterdam, The Netherlands