Microscopic Colitis – Creating Awareness for an Underestimated Disease

Dealing with Our “In-vironment”: New Aspects in IBD Pathogenesis and Therapy
Phosphatidylcholine inhibits TNF-α-induced NFκB translocation in Caco-2 cells incubated with TNF-α together with different phospholipids.


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Published by FALK FOUNDATION e.V.

Falk Workshop

Microscopic Colitis – Creating Awareness for an Underestimated Disease

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Falk Symposium 183

Dealing with Our “In-vvironment”: New Aspects in IBD Pathogenesis and Therapy

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Leinenweberstr. 5
79108 Freiburg
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www.falkfoundation.org

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Text

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1st edition 2012

Portraits, photographs p. 6, 28, 34 and 35
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Title image, p. 2 and fig. 24

Phosphatidylcholine inhibits TNF-α-induced NFκB translocation in Caco-2 cells incubated with TNF-α together with different phospholipids.


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Falk Symposium 183

Dealing with Our “In-vironment”: New Aspects in IBD Pathogenesis and Therapy

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Inflammatory bowel disease” has always meant one of two things: Crohn’s disease or ulcerative colitis. Until now, that is. A paradigm shift has occurred: Microscopic colitis has become the third disease entity to join this group. Like the two “established” inflammatory bowel diseases, microscopic colitis is characterized by chronic bowel inflammation and severe diarrhea that represents a significant burden for patients and profoundly limits their quality of life.

As frequently occurs with new kids on the block, this disorder has remained underestimated – and, as a result, diagnosis often comes relatively late. To review our current knowledge of its epidemiology and pathogenesis, and the available diagnostic and therapeutic options was the objective of the Falk Workshop “Microscopic Colitis – Creating Awareness for an Underestimated Disease”.

Beyond “welcoming” a new disease entity, however, there was also much that is new to report in the area of inflammatory bowel diseases. The pathogenesis of these disorders is increasingly well understood. The countless factors relating to the genetic predisposition as well as the internal environment of the bowel and the outside world – hence, the “invironment” and “environment” – that are involved in the development of these diseases are slowly coalescing into a continuous image. Together, they form a network whose regulation is becoming more and more apparent.

Finding and following these many threads, however, has led to just a few main strands of cellular regulation – or dysregulation. These new findings were the subject of lively discussion at the Falk Symposium 183 “Dealing with Our ‘Invironment’: New Aspects in IBD Pathogenesis and Therapy”. They also nourished the hope that new therapy concepts will result in a more effective management of inflammatory bowel diseases.
Watery diarrhea persisting longer than four weeks, day and night, an imperative urge to defecate. Coupled with symptoms such as abdominal pain and unintended weight loss, these are signs that should always prompt the clinician to think about microscopic colitis.

This is a disease entity characterized by chronic intestinal inflammation whose importance remains quite underestimated. It predominantly affects women, usually in the fifth and sixth decades of life. The reason for this distribution remains unclear.

Two disease forms

Two different disease forms have been described. The first, lymphocytic colitis, is characterized by a lymphoplasma cellular inflammation of the lamina propria. In the second form, collagenous colitis, a thickened subepithelial band of collagen is the typical morphological feature. As the name suggests, these changes cannot be detected by direct visual examination of the bowel and the findings of endoscopy are typically unremarkable. Instead, the diagnosis is confirmed histologically, which requires careful stepped biopsy of the colonic mucosa (figures 1 and 2).
Comorbidity with autoimmune disorders is found in 40–50% of patients with microscopic colitis. The background of this phenomenon remains unclear. An increased risk of colorectal carcinoma has yet to be described.

**Unknown pathogenesis**

As with the “established” inflammatory bowel diseases (IBD), Crohn’s disease and ulcerative colitis, the pathogenesis of microscopic colitis is not yet clearly understood. Analogous to the classical IBDs, the development of microscopic colitis appears to depend on the interplay of genetic and environmental factors. As discussed at the Falk Workshop “Microscopic Colitis – Creating Awareness for an Underestimated Disease”, these include abnormal immunological reactions to exogenous and luminal factors such as infections, bile acids or drugs in predisposed persons.

**Underestimated incidence and prevalence**

There is no doubt that microscopic colitis is a disease entity that has been – and remains – quite underestimated. It is by no means a rare disorder. In fact, recent studies in Europe and North America show that its incidence and prevalence are significantly higher than had long been assumed and are comparable to frequencies reported for both Crohn’s disease and ulcerative colitis. The clinical overlap with irritable bowel syndrome (IBS) suggests that a significant number of cases go undiagnosed (figure 3).
A quite treatable disorder

Patients with microscopic colitis live under the pressure of an enormous burden of symptoms including daily watery diarrhea, an imperative urge to defecate and, in many cases, significant gastrointestinal comorbidity.

An exact diagnostic work-up, however, is important, not least because microscopic colitis is a quite treatable disorder.

Drug of choice is the corticosteroid budesonide, whose effects, because of a high first-pass effect in the liver, are restricted almost exclusively to the bowel. Given at a dose of 9 mg daily for six to eight weeks, budesonide successfully induces remission in more than 80% of patients (figures 4 and 5).

Should the disease recur following discontinuation of medication, budesonide can be restarted at a lower dose of 3–6 mg daily. Antidiarrheals may suffice in patients with milder symptoms or can be employed additively if needed.

“European Microscopic Colitis Group”

Increasing clinicians’ awareness of microscopic colitis as a disease entity whose importance must no longer be underestimated is the goal of the European Microscopic Colitis Group (EMCG). Founded in September 2010, the EMCG is a group of experts with long-term clinical and research experience in the field of inflammatory bowel diseases in general and with microscopic colitis in particular.

“We are of the opinion that microscopic colitis has long been denied its rightful attention both in clinical practice and even in the scientific world. There is still an enormous information deficit regarding this disorder”, explained A. Münch, Linköping (Sweden), in Basel.

“In not a few cases, this may not only delay the final diagnosis but even result in misdiagnoses and inadequate treatment, causing unnecessary suffering among these patients.”

The EMCG therefore has as its goal both to facilitate research on microscopic colitis and educate clinicians about this disorder. This will help assure that the importance of this disorder is no longer underestimated and that patients with microscopic colitis will benefit from more reliable diagnosis and treatment.

The EMCG Members

Fig. 4
Clinical remission and response to budesonide 9 mg per day in lymphocytic colitis given for 6–8 weeks

Budesonide 9 mg/day for 6–8 weeks

Miehlke et al., Gastroenterology 2009
Pardi et al. DDW 2009
The precise value of other therapy concepts, such as the aminosalicylates, bismuth salts and colestyramine, together with immunosuppressants or anti-TNF antibodies, remains unclear (figure 6).

Still, many open questions remain regarding the pathogenesis of microscopic colitis, as well as on how to more readily diagnose and treat it. Until these questions are answered, attention should primarily be paid to elucidating the background of this disorder and to raise clinicians’ awareness that patients’ complaints of diarrhea are more than simply a kind of indisposition.

In fact, microscopic colitis is a serious disorder that must clearly be considered the third entity among the inflammatory bowel diseases.
Microscopic colitis has long been considered a rare disease. Even today it is frequently overlooked as a disease entity, reported C. Tysk, Örebro (Sweden). The prevalence of chronic diarrhea in Western populations stands at 4–5%, increasing as high as 7–14% among the older segments of the population. The prevalence of both lymphocytic and collagenous colitis among persons with chronic diarrhea remains seriously underestimated, C. Tysk concluded.

Collagenous colitis was first described in 1976 by the Swedish pathologist, Clas Lindström, who studied middle-aged women complaining of persistent watery diarrhea. The first report of lymphocytic colitis followed in 1989.

The term “microscopic colitis,” first coined in 1980, subsumes both disease forms, which can only be diagnosed on the basis of histological findings. Since the 1980’s, the scientific world has shown increasing interest in microscopic colitis, which, C. Tysk observed, is reflected in the jump in the number of scientific publications that have addressed various aspects of this disorder.

By no means a rare disease

Microscopic colitis is hardly as rare as was once believed. Reported yearly incidence figures vary widely, noted J. Bohr, Örebro (Sweden), falling in the range of 0.8–16.8/100,000 persons for collagenous colitis and 0.5–12.9/100,000 persons for lymphocytic colitis. “The increased incidence and prevalence that has been registered since the 1980’s may be due to the increased awareness of the disease,” J. Bohr cautioned. In recent years, the average reported incidence of collagenous colitis has been in the range of 4.6–6.2/100,000 persons for collagenous colitis and 4–5.5/100,000 persons for lymphocytic colitis, which, in J. Bohr’s opinion, likely reflect realistic levels. The highest incidences have been reported for northern Europe and North America and there appears to be a distinct north-to-south gradient in the frequency of this disorder.

The Swedish scientist estimated the prevalence of microscopic colitis together with the other inflammatory bowel diseases (IBD) at about 1% of the population. The mean age at first diagnosis of microscopic colitis is about 60 years. Women are disproportionately affected: The female predominance, however, is greater among patients with collagenous colitis than with lymphocytic colitis.

Still unclear is whether conversion between the two disease forms is possible, that is, whether collagenous colitis can switch to lymphocytic colitis and vice-versa. Spontaneous remission is possible in both forms, J. Bohr ob-
served, but is much more frequently seen among patients with lymphocytic colitis than in those with collagenous colitis.

Comorbidity with other disease is not uncommon. About 4% of microscopic colitis patients also suffer from celiac disease. Thyroid disease is found in about 1–2%, Diabetes mellitus affects 0.7–1% of patients, while 1–3% suffer from a rheumatic disorder and 1–8% exhibit a further inflammatory bowel disease, such as ulcerative colitis or Crohn’s disease. In fact, “11.5% of patients with collagenous colitis and up to 17.5% of those with lymphocytic colitis exhibit at least one other chronic disease,” J. Bohr reported.

**Profound impact on patients’ quality of life**

The impact of microscopic colitis on patients’ quality of life can be profound, observed H. Hjortswang, Linköping (Sweden). This statement is confirmed by a cross-sectional study of 116 Swedish patients whose health-related quality of life (HRQoL) was assessed using a standardized questionnaire.

Responses to the survey showed a significantly reduced quality of life in patients with active disease compared both to healthy controls and even to patients in remission. The latter group, in fact, enjoyed a quality of life corresponding to that of the healthy population. By contrast, patients with active disease reported limitations in their daily activities as well as worries about their state of health and a generally reduced feeling of wellbeing. Patients also reported problems related to feeling that they could not control their bowels. This, in turn, caused them in many cases to feel “dirty” and less attractive, as well as to feel insecure.

Once treatment with budesonide began, however, patients reported a significant improvement in their quality of life, reported H. Hjortswang. Patients noted improvement as early as the induction phase of therapy and this was maintained during the phase of remission maintenance.

To date, however, there are no clearly defined criteria for remission in microscopic colitis. For the time being, the treatment aims at a long-term improvement in symptoms and a general improvement in the health-related quality of life. In this context, H. Hjortswang proposed the following criteria for remission: Reduction in stool frequency to less than three times per day with no more than one watery stool per day.

**Differential diagnosis of irritable bowel syndrome vs. microscopic colitis**

<table>
<thead>
<tr>
<th></th>
<th>Irritable bowel syndrome</th>
<th>Microscopic colitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at first onset</td>
<td>Often younger than 50 years</td>
<td>Often older than 50 years</td>
</tr>
<tr>
<td>Stool consistency</td>
<td>Variable from soft to hard</td>
<td>Watery/Soft</td>
</tr>
<tr>
<td>Abdominal pain/abdominal discomfort</td>
<td>Obligatory</td>
<td>Variable</td>
</tr>
<tr>
<td>Nocturnal diarrhea</td>
<td>Very rare</td>
<td>Possible</td>
</tr>
<tr>
<td>Feeling of incomplete rectal emptying</td>
<td>Common</td>
<td>No</td>
</tr>
<tr>
<td>Weight loss</td>
<td>Rare</td>
<td>Frequent</td>
</tr>
<tr>
<td>Fecal incontinence</td>
<td>Rare</td>
<td>Frequent</td>
</tr>
<tr>
<td>Feeling of fullness</td>
<td>Frequent</td>
<td>Rare</td>
</tr>
<tr>
<td>Associated with autoimmune disorders</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Fig. 7
Because about one in four patients with irritable bowel syndrome exhibit a form of the disorder in which diarrhea dominates the clinical picture, microscopic colitis may easily be mistaken for this functional disorder. And, as R.C. Spiller noted, the disorders do share a number of common features. For example, both disorders disproportionately affect females. In addition to diarrhea, there may be pronounced associated symptoms, including a general feeling of abdominal discomfort, tiredness, fatigue and reduced physical capacity. The Rome criteria also do not help much with the differential diagnosis. Instead, the clinical should focus more on the clinical picture: Here, the presence of nocturnal diarrhea and weight loss support a diagnosis of microscopic colitis. Even more decisive in differentiating between these two disorders is the observation that patients with microscopic colitis report a fairly constant symptomatology. This is in stark contrast to irritable bowel syndrome in which patients may report a broad spectrum of symptoms which may be quite variable. “It is not uncommon for patients to report that they experience periods with significant symptoms interspersed with days on which they report being practically complaint-free. This kind of variability in terms of clinical symptoms is not seen in patients with microscopic colitis.”

**Histological diagnostic criteria**

A definitive diagnosis of lymphocytic or collagenous colitis can only be made on the basis of histological findings. According to D.E. Aust, Dresden (Germany), a diagnosis of lymphocytic colitis is likely when histological examination reveals an increased number of intraepithelial lymphocytes (more than 20 IEL/100 epithelial cells). Also characteristic for this form of the disease is a degenerated surface epithelium. By contrast, the histological picture of collagenous colitis is characterized by a thickened subepithelial collagen band (> 10 μm). Other characteristic features include chronic mucosal inflammation with enclosed capillaries, erythrocytes and inflammatory cells. In addition, D.E. Aust explained, there have been cases of pseudomembranous collagenous colitis and collagenous colitis with giant cells.

**Pathogenesis – Many open questions remain**

The etiology of microscopic colitis remains unknown. According to A. Münch, Linköping (Sweden), current thinking postulates a multifactorial process in which genetic factors, infections, drugs, bile acids, as well as mucosal and/or autoimmune factors are considered potential triggers.

As with the other forms of IBD, an abnormal immunological reaction to luminal toxins has been discussed as a disease trigger in genetically predisposed persons. “This reaction may lead to a disturbance of the mucosal barrier function as a basis for the chronic inflammatory reaction,” A. Münch explained. The diarrhea would presumably be caused by osmotic and secretory mechanisms.

**Fig. 8 Collagenous colitis**

In some cases, not all diagnostic criteria for microscopic colitis are met. This can lead to uncertainty as to whether or not microscopic colitis is the correct diagnosis, noted L. Munck, Køge (Denmark), suggesting “incomplete microscopic colitis” as a third form along side collagenous and microscopic colitis.
Another factor involved in the pathogenesis is the mucosal immune system, observed E. Hultgren-Hörnquist, Örebro (Sweden). As evidence for this, the Swedish researcher noted that increased numbers of CD8+ cells are found in both the epithelium and lamina propria of patients with microscopic colitis. Also indicative of an immunological process are fecal markers such as the frequently elevated calprotectin.

"These biomarkers serve as a surrogate parameter for assessing inflammation and can provide valuable information of patients’ disease activity," reported S. Wildt, Hvidovre (Denmark).

Risk factors for microscopic colitis

A better understanding of the risk factors for microscopic colitis may provide valuable clues to the pathogenesis of this disorder. For example, tobacco smoking is clearly associated with an elevated disease risk. "This holds equally for both lymphocytic and collagenous colitis," noted L.U. Vigren, Malmö (Sweden).

The connection between smoking and microscopic colitis has been confirmed in three studies. For example, a multicenter study in Sweden found that smokers with collagenous colitis develop the disease significantly earlier on average than do non-smokers. "First onset of the disease occurs, on average, 14 years earlier, L.U. Vigren observed.

Genetic predisposition?

Does genetic predisposition trigger the development of microscopic colitis? This remains unclear but, as A. Madisch, Hannover (Germany), noted, "to date there are practically no data regarding a genetic background for this disorder."

There are, however, case reports that show an increased incidence in some families. In addition, some findings suggest a genetic polymorphism for this disorder.

Also supporting a genetic background is the association with autoimmune diseases and especially the presence of certain HLA haplotypes.

For example, the frequency of the HLA-DQ2 haplotype is disproportionately high in patients with microscopic colitis, while lymphocytic colitis is associated with the HLA-A1 haplotype.

Fig. 9 Lymphocytic colitis
Pay special attention to patients’ medication history

Quite a few drugs can cause diarrhea. Hence, a careful medication history is an essential part of the work-up of any patient presenting with unexplained diarrhea. A correlation with the administration of certain drugs is also observed in microscopic colitis, noted F. Fernández-Bañares, Barcelona (Spain). For example, associations with drugs such as the proton pump inhibitors (PPIs), non-steroidal anti-inflammatory drugs (NSAIDs) and selective serotonin reuptake inhibitors (SSRIs) have been reported. If there is evidence of medications as a possible cause of diarrhea in individual cases, every effort should be made to switch to alternative agents for treatment of patients’ underlying disorder.

Budesonide – the only effective therapy option

In the absence of other discernible causes, treatment may follow an algorithm, said S. Miehlke, Hamburg (Germany), noting that antidiarrheals, such as loperamide, will suffice only for patients with mild symptoms. Favorable therapeutic effects have been reported for mesalazine, colestyramine and bismuth salts but the precise role of these agents has yet to be definitively established. To date, only budesonide has been shown to have a clear therapeutic benefit in patients with active microscopic colitis. In fact, five randomized, controlled studies have established that the administration of 9 mg of budesonide daily for six to eight weeks produces a significant reduction in symptoms.

“Thus, budesonide remains the only medication with clear evidence of efficacy in the treatment of active microscopic colitis and should be considered the agent of choice,” S. Miehlke concluded. The response rate in these studies is high: Standing at more than 80%, this represents a very good result, the gastroenterologist added. Remission is also rapid: 61% of patients reach this point within as little as two weeks, with 79% in remission within four weeks.

Clear improvement in the quality of life

As patients’ symptoms improve, so, too, does their quality of life, returning to a practically normal level. Relapse, however, is likely, occurring in 62% of patients within two weeks after discontinuing medication. Within three months, fully 88% again suffer from chronic diarrhea. In these patients, S. Miehlke went on, a long-term treatment with budesonide is indicated.

A lower daily dose is often adequate: A randomized, double blind study showed that a majority of patients suffering relapse after discontinuing the initial budesonide therapy experience long-term remission with a daily maintenance dose of only 6 mg of budesonide.

The therapeutic alternatives are limited

For the small number of patients who do not respond to budesonide, the thera-
Mucosal alternatives are limited. In fact, as A. Münch, Linköping (Sweden), observed, there are practically no alternative therapies for which data from controlled studies are available. He opined that about 5–10% of patients may be candidates for an immunomodulatory agent, such as azathioprine or 6-mercaptopurine (6-MP), if they do not respond to, or tolerate, budesonide. Methotrexate has been shown to be ineffective and a trial of an anti-TNF agent would only then be justified if there is no other way to avoid a colectomy with ileostomy, A. Münch stated.

D.S. Pardi, Rochester (USA), also spoke in favor of treatment with budesonide, noting that there have not been any data from larger controlled studies in the USA supporting the efficacy of potential therapeutic alternatives. One study has investigated the value of bismuth salts but the number of patients was very small (n = 14) and no statistical analysis of the data has been published. There have also been trials of mesalazine with or without colestyramine, but the published data do not currently permit a definitive assessment of this option. The situation with budesonide is quite different: Its clinical efficacy has been adequately documented in studies and, from an American perspective, it is considered the agent of choice for treating microscopic colitis. If treatment with budesonide proves unsuccessful, D.S. Pardi continued, a trial of azathioprine is the option most clearly supported by the available experience.

On the look-out for further therapeutic alternatives

The current treatment of microscopic colitis is based on experience with the therapy of the inflammatory bowel diseases. However, as O.K. Bonderup, Silkenborg (Sweden), observed, only budesonide has been shown to be a really effective therapy option. The locally acting steroid has been shown to be effective for treating both collagenous and lymphocytic colitis, and results in a significant improvement in both the diarrhea and patients' quality of life. Future research, however, must continue to focus on identifying further therapy alternatives.
Microscopic colitis is an important disease entity that seriously impacts patients’ lives. A deeper insight was provided by Prof. Dr. Stephan Miehlke, Hamburg (Germany) in an interview.

Editors:
Professor Miehlke, why is Gastroenterology currently so focused on microscopic colitis?

Professor Miehlke:
Microscopic colitis is a disease entity that has long been underestimated – both among the general public and even in the medical world. This is due, in part, to the fact that no macroscopic changes are apparent during endoscopic examinations. And, until just a few years ago, we assumed that microscopic colitis was a rare disease. An assumption that was proven to be quite false. In fact, this disorder is much more common than we had assumed and its incidence and prevalence hardly lag behind those of the other inflammatory bowel diseases. Still, we know very little about its pathogenetic background. For this and other reasons, collagenous and lymphocytic colitis have attracted the attention of gastroenterologists.

Editors:
Is it really justifiable to think of microscopic colitis as a third inflammatory bowel disease beside Crohn’s disease and ulcerative colitis?

Professor Miehlke:
Yes, certainly. The disorder is characterized by chronic inflammatory processes in the bowel. As with the other two disorders, these processes, if untreated, lead to chronic diarrhea and significant symptoms beyond the bowel. As with Crohn’s disease and ulcerative colitis, the pathogenesis of microscopic colitis appears to be based on the interplay between genetic and environmental factors.

Still more importantly, this disorder, if left untreated, results in significant suffering for patients and profoundly impacts the quality and conduct of their lives. We are witnessing a fundamental shift in our perception of microscopic colitis.

Editors:
Have these new findings been recognized in the medical world and has this new knowledge been translated into more targeted diagnostics and therapies?

Professor Miehlke:
The digestion and implementation of these new findings represent a process which is still ongoing. Many physicians certainly remain less than fully informed about microscopic colitis, and about its diagnosis and treatment. We have seen at the symposium...
in Basel that the interest on the part of gastroenterologists is enormous. There was quite active participation and we enjoyed not only interesting presentations about exciting advances in the field but also very intense discussion on what these advances really mean. This shows that we are becoming increasingly conscious about the disorder as a serious disease entity deserving of its proper attention. I am quite certain that, in future symposia, we will be treating Crohn’s disease, ulcerative colitis and microscopic colitis as three quite equally significant diseases.

Editors: How have patients with microscopic colitis been treated?

Professor Miehlke:
As a rule, these patients have been seen repeatedly in the gastroenterologist’s practice complaining of diarrhea and other gastrointestinal symptoms. Because diarrhea is nearly always the chief complaint, treatment has been symptomatic – patients have been prescribed antidiarrheals. Yet, this is essentially like giving loperamide to a patient with Crohn’s disease: One might provide him with some relief for a short period but antidiarrheals do not touch the cause of the disease. Beyond antidiarrheals, patients have been offered everything else that has been tried for the treatment of irritable bowel syndrome.

Editors: How does microscopic colitis differ in terms of its clinical symptomatology from irritable bowel syndrome?

Professor Miehlke:
Patients with irritable bowel syndrome experience recurring phases of diarrhea. For patients with microscopic colitis, however, watery diarrhea is a daily burden. In many cases, they may find themselves in the bathroom as many as seven or eight times during the day. Nor is the diarrhea the only burden: Many patients are awakened during the night by the diarrhea with the result that their sleep is terribly disturbed. Daytime tiredness and fatigue is the result. Yet another aspect is the imperative urge to defecate which many patients with microscopic colitis experience. The urge to pass stool may be so overwhelming and sudden that patients, who have frequently experienced it, may no longer wish to leave home unless they are absolutely certain of having a restroom nearby. Shopping trips are planned to accommodate this and activities such as the theater or cinema may only be possible if an antidiarrheal is taken beforehand. Imperative urge to defecate – it’s so easy to say. I am familiar with the case of a teacher who could not even make it from home to school each morning without stopping twice along the way to use the restroom. When this happens nearly every day, it has a profound impact on anyone’s wellbeing and activities of daily life. By contrast, even in cases of IBS in which diarrhea predominates, patients experience diarrhea on about 10 days each month. Patients with microscopic colitis experience watery diarrhea practically every day.

Editors: Are there extraintestinal complications, such as the development of stenoses or fistulae, as occur, for example, with Crohn’s disease?

Professor Miehlke:
No – at least, this has not been reported to date. According to our current state of understanding, microscopic colitis does not appear to induce any organic or structural changes. In addition, as far as we currently know, the disorder, despite the chronic inflammatory activity, is not associated with an increased risk of colorectal carcinoma. Nevertheless, the symptomatic burden is enormous and the situation is comparable to Crohn’s disease. We must not forget that patients suffer greatly due to the diarrhea. This is analogous to the situation with the gastroesophageal reflux disorder in which patients complains of heartburn although endoscopic findings are usually unremarkable. The comparison with GERD is quite appropriate for another reason as well. For decades, heartburn was treated as a minor ailment. It has only been in quite recent years that heartburn has been considered to be a disease-defining symptom that deserves appropriate treatment.

Editors: How do you go about treating microscopic colitis?

Professor Miehlke:
There is practically only one option: Treatment with budesonide. As a locally acting steroid, budesonide is very effective clinically and is also well tolerated. During treatment, more than 80% of patients experience complete remission. Usually, we interrupt therapy after about six to eight weeks. Many patients continue in remission past this time. If, however, they do relapse, they are restarted on budesonide. For this, we select the lowest effective dose. Because patients often do require a long-term therapy, we also give calcium and vitamin D to head off the risk of osteoporosis.

Editors: Are there still any open questions?

Professor Miehlke:
Unfortunately, there is still a series of open questions. First, regarding the pathogenesis, which we are nowhere near understanding. Second, regarding the age and sex distribution, and why microscopic colitis predominantly affects older women. There are also open questions about treatment. Although we have in budesonide a highly effective therapy option, not all patients respond and individual patients may not tolerate the medication. Just how to treat these patients remains unclear. Currently, there are no evidence-based therapeutic alternatives to budesonide.

Professor Miehlke, thank you very much for the interview.
Inflammatory bowel diseases (IBD) are disorders with a highly complex pathogenetic background.

It has long been clear that no single factor acts as a disease trigger in either Crohn’s disease or ulcerative colitis.

The pathogenesis of inflammatory bowel diseases (IBD) has been an area of intense research in recent years. Gradually, more and more genetic and environmental factors have been implicated as potentially being involved in the development of these diseases. There is now quite a grab bag of factors that may be involved, either individually or in association with other factors, as triggers in the complex pathogenesis of these disorders.

Their interactions lead to immunological changes that ultimately cause a chronic inflammatory reaction in the bowel. This was the subject of the Falk Symposium 183 “Dealing with Our ‘In-vironment’: New Aspects in IBD Pathogenesis and Therapy” that convened in Basel.
Today, that tangle of factors has begun to unravel. It is becoming increasingly clear that there are special “story lines” along which the “drama of pathogenesis” of the inflammatory bowel diseases progresses. The process features the interplay of four separate realms: Genetics, environment, the microbiome (the entirety of all intestinal microorganisms) and immunological factors. If current thinking is accurate, a conjunction of pathogenetic factors from all four realms practically guarantees manifestation of one or another IBD (figure 13). Less clear is whether changes in only two or three of these pathogenetic areas suffice to trigger a disease outbreak.

A story about PAMPs and DAMPs

Genetic and environmental factors have long been known to affect disease development in IBD. The role of the microbiome, however, which determines the internal environment, or “in-vironment”, has long been underestimated. The internal milieu of the gut has far-reaching consequences. Here, the enormous variety of bacteria that constitute the intestinal flora plays a decisive role as is reflected in the pronounced pathogen-associated molecular patterns (PAMPs).

PAMPs affect the cells of the intestinal mucosa, change the expression of receptors and may even induce modulation of gene expression.

Normally, the involved cells react via their surface receptors and are well regulated in terms of their cellular functions. Apoptosis is the ordinary cellular response to any disturbances that might occur.

Things are quite different under the influence of pathological factors. These may cause an inadequate expression of surface receptors. Processes that, under normal physiological conditions, are well regulated may become unbalanced. Cell necrosis may follow – this, in turn, releases further unphysiological factors. Immunological changes and, in particular, inflammatory reactions against such “damage-associated molecular patterns” (DAMPs) are the consequence (figure 14).
Hope for therapeutic advances

Advances in disease understanding nourish hopes for advances in the therapeutic management of IBD. To date, center stage has been held by agents such as mesalazine, and by the steroids, both conventional systemic agents and, more recently, locally acting steroids such as budesonide. If these agents proved ineffective in inducing sustained remission, patients are offered immunosuppressants such as azathioprine. Non-responders to immunosuppressants are increasingly undergoing anti-TNF-α strategies and current studies suggest that there may be therapeutic advantages to a combination of azathioprine with a TNF-α blocker.

The foreseeable future appears to be ripe for further therapy alternatives, such as treatment of helminth ova and with the phospholipid, phosphatidylcholine (figures 17 and 18).

Therapy objective: Deep remission

The objective of therapy no longer lies simply in making the patient complaint-free. The bar for optimum treatment is now much higher and consists in a complete, endoscopically verifiable mucosal healing (figure 19).

A low-level inflammatory reaction may persist “under the radar” even in essentially asymptomatic patients. Not only does this likely set the stage for disease recurrence but may in the long term promote disease progression and facilitate the occurrence of complications, such as stenoses, strictures and fistulae.

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Should a definitive mucosal healing prove impossible, therapy should at the very least have as its goal the establishment of “deep remission,” a novel treatment concept presented in Basel. This represents a disease state characterized by complete control of symptoms, minimal signs of inflammation, low disease activity and no signs of disease progression.
Risk factor: Genetics

Do the genes affect the intestinal flora?

To date, genome-wide association studies (GWAS) have identified 71 gene regions associated with Crohn’s disease and another 47 that correlate with ulcerative colitis. In most cases, explained A. Franke, Kiel (Germany), these represent gene regions associated with other chronic immunologically mediated disorders, such as multiple sclerosis, rheumatoid arthritis, vitiligo and bronchial asthma. Thus, there is a significant overlap between IBD and other diseases with respect to the genetic risk factors. There are also more specific overlaps on the genetic level between Crohn’s disease and ulcerative colitis: Currently, 28 genes have been identified that may be involved in the pathogenesis of both disorders.

The genetic background of IBD is not mono- but polygenetic in nature. This, said S. Schreiber, Kiel (Germany), is beyond doubt. Certain gene constellations, however, appear to mediate an especial susceptibility for the disease. The disease becomes manifest when non-genetic risk factors interact with the genetically-determined susceptibility to these diseases.

Long underestimated in this regard, S. Schreiber explained, is the effect of the bacterial microflora of the bowel, which is significantly altered in IBD patients. This may have profound effects on the integrity of the barrier function of the intestinal mucosa and the resulting antigen contact may provoke immunological reactions. Beyond this, however, there is increasing evidence that certain gene constellations may actually affect the composition of the bacterial flora of the gut.

There are also epigenetic factors

The story does not stop with genetics. Epigenetics, too, may complicate the disease process. For example, factors such as the acetylation of histones and the methylation of DNA directly impact gene expression and, by extension, the functioning of the genome, explained S. Gay, Zurich (Switzerland). Special importance attaches to DNA methylation, which is already reflected in the term “methyloma”.

Another regulatory factor cited by the Swiss researcher are microRNAs (miRs).
These are short RNA sequences, comprising only 19–25 nucleotides. By binding with complementary mRNA regions, they also unfold a regulatory effect on cellular processes. More than 800 such miRs have already been identified. They play a significant role in embryonic development, cell differentiation, the induction and progression of malignant tumors and in viral infections.

**The pathogenetic factors are tightly interwoven**

The many pathogenetic factors involved in the development of IBD are densely interwoven and mutually affect one another. Their interactions, however, are still by no means adequately understood, explained C. Fiocchi, Cleveland (USA). “We really need further studies,” the American researcher argued. This need affects all the central areas involved in the pathogenesis of IBD. In addition to genetics, the environment, the microbiome and immunology represent the crucial factors involved in the development of these diseases.

Progress on this front will require a precise analysis of how the individual factors mutually modulate one another. For example, it remains unclear how genetic constellations mutually affect each other: In other words, how gene-gene interactions operate in the overall context. The situation is similar in our understanding of the interaction between genetic factors and the environment: We know that they interact but the details of this interaction remain unclear. Because of the innumerable factors involved, elucidating this process will be an enormous scientific challenge, C. Fiocchi concluded.

**Does the “in-vironment” spin out of control?**

One of the important causes underlying the development of IBD appears to be that the normal barrier function of the intestinal mucosa is compromised. A deficiency in defensins may be responsible, said J. Wehkamp, Stuttgart (Germany). Defensins are effector molecules that play a central role in maintaining the integrity of the mucosal barrier function, thus preventing bacterial invasion through the intestinal mucosa. In their absence, gaps open in the protective shield they mediate: This allows bacteria to penetrate, triggering corresponding defense reactions on the part of the immune system. This activation of the immune system can also lead to chronic inflammatory processes. “Our understanding of the disease has led to a paradigm shift,” J. Wehkamp emphasized. “We no longer believe that the inflammatory bowel diseases are autoimmune disorders. Instead, a barrier defect seems more likely to be a cause of the disease.”

**Dysfunction or autophagy?**

In addition to disturbances on the intestinal barrier function, according to M. Scharl, Zurich (Switzerland), patients with IBD appear to exhibit a disorder of autophagy – the process of targeted degradation of the cell’s own components. Researchers distinguish three mechanisms by which autophagy is accomplished, namely, microautophagy, which involves degradation of directly soluble proteins; macroautophagy, which involves the action of lysosomes and autophagosomes; and chaperone-mediated autophagy. Of particular importance is the process of macroautophagy, by which the formation of autophagolysosomes is genetically regulated. The process is activated by fasting, hypoxia and by the actions of pathogens and hormones.

Autophagy is a very important mechanism for cells. On the one hand, it generates ATP, while, on the other, it serves the disposal of defective proteins and damaged cell organelles. It plays an important role in apoptosis and also in the xenophagy of invading pathogens. In addition, it can activate the acquired immune system.
A reduction in autophagy has been well documented in patients with Crohn’s disease. This is due to the reduced activity of ATG16L1, a gene that is important for autophagy. This defect results in the increased production of cytokines which, in turn, can induce a chronic intestinal inflammatory reaction.

The intestinal microflora is more than just a collection of bacteria

The complexity of the intestinal microflora is still often underestimated. According to L. Biedermann, Zurich (Switzerland), it is more than just a collection of bacteria that happen to inhabit the bowel. In fact, there are complex interactions between the intestinal microflora and the physiology of the bowel. These have a wide-ranging impact on the metabolism and on immunological functions.

Sheer numbers serve to illustrate just how complex this system really is, L. Biedermann explained. For example, the bowel hosts 300 to 1000 different bacterial species totaling up to 100 trillion microorganisms. The microbial composition does not remain constant but is influenced by a variety of factors, including diet, medications and smoking. Thus, metabolic factors may also affect the intestinal flora. For example, a tight interaction is known to exist in metabolic syndrome.

**Helminths induce immunotolerance**

How the immune system reacts to antigens is to a great extent determined during childhood. For example, there have been observations suggesting that an over-concern with hygiene during childhood promotes the occurrence of exaggerated immunological reactions in later life, a phenomenon that has become known as the “hygiene hypothesis”. This phenomenon appears to play a role in IBD, explained J.V. Weinstock, Boston (USA). Frequently implicated are helminths, certain worms, which, as endoparasites, appear “train” the immune system in its defensive functions. The absence of this stimulus seems to favor the later development of IBD.

This is an observation that could have therapeutic importance. It has been shown, for example, that confrontation with helminths (Trichuris suis) or their products, such as their ova, helps normalize the abnormal immune reaction in patients with IBD. “The worms would appear to mitigate the exaggerated reactivity of the immune system,” J.V. Weinstock explained. Initial clinical studies in patients with Crohn’s disease and ulcerative colitis are currently in progress and there may be further indications for this concept in the treatment of other immunologically mediated diseases, such as multiple sclerosis, psoriatic arthritis, autism and bronchial asthma.

![Autoimmune disorders incidence](image1)

![Helminths infestations incidence](image2)

![Fig. 20 Hygiene and worm infestations](image3)
The intestinal epithelium: Boundary between “inside” and “outside”

Maintaining a selective barrier is one of the functions of the intestinal epithelium. It must permit the absorption of nutrients but prevent permeation by microorganisms and toxins. In order to maintain this function, the intestinal epithelium depends for its regeneration on circulating stem cells. Studies by N.F. Shroyer, Cincinnati (USA), suggest that the genetic signature of the Paneth cells and circulating stem cells is altered in patients with Crohn’s disease.

Defective tight junctions mean increased permeability

Also crucial for the barrier function are the so-called tight junctions, special structures that not only join cells but also serve to seal the intercellular space. According to J.-D. Schulzke, Berlin (Germany), a variety of proteins are involved in the construction of tight junctions, which join two or, in many cases, even three cells.

Disturbances of the tight junctions necessarily result in increased intestinal permeability, allowing for an increased transcytosis of ions, antigens and even macromolecules (figure 21).

As M. Chamaillard, Lille (France), explained, PPAR-γ controls the activity of the defensins and is thus centrally involved in regulating the microbial milieu of the bowel. “PPAR-γ thus even controls intestinal inflammation,” the French researcher emphasized. This new knowledge may open the way for the development of new therapy concepts in the management of Crohn’s disease and ulcerative colitis.

Also involved in the regulation of internal homeostasis is the so-called nuclear receptor peroxisome proliferator activator complex-γ – PPAR-γ for short.

This barrier function is controlled by different cell types, explained S. Danese, Rozzano (Italy), citing endothelial cells, mesenchymal cells and cells of the extracellular matrix. Also involved, however, are immune cells and special dendritic cells, as well as macrophages, neutrophils and NK cells.

Fig. 21
Junctional complex between two epithelial cells, consisting of a tight junction, zonula adhaerens and macula adhaerens © PD Dr. H. Jastrow, Essen
The increasing incidence of Crohn’s disease cannot be explained by genetic factors, said C.N. Bernstein, Winnipeg (Canada), arguing that environmental factors must be causative. Implicating the true culprits, however, will likely be extremely challenging: Life in the Western world has undergone fundamental change in recent years. Changed hygienic conditions may certainly be part of the picture. C.N. Bernstein also cited the role of helminths which may influence the immune system, agreeing that this aspect may be therapeutically important.

By comparison, inflammatory bowel diseases are practically unknown in developing countries. This may, of course, be due to the difference in hygienic conditions, not to mention the much less frequent use of antibiotics and simpler living conditions. Also, the high levels of psychological stress in the Western world may contribute to changes in the intestinal microflora and resulting immunological reactions.

Patients’ dietary habits must also be considered in this regard, emphasized P. Lepage, Jouy-en-Josas (France). It has long been known that certain dietary factors, such as the consumption of refined sugar, had unfavorable effects on patients with inflammatory bowel disease. Also problematic were foods such as cheese, margarine and animal proteins, especially the generous consumption of eggs and milk.

Just how complex the situation actually is was expounded by C. Müller, Bern (Switzerland). Involved in this process are numerous damage-associated molecular patterns, or DAMPs, most of which are endogenous stress proteins, as well as pathogen-associated molecular patterns (PAMPs), which are bacterial factors, that is, generally pathogens that sustain immune reactions. In addition, the so-called pattern recognition receptors, or PRRs, represent a group of receptors that can bind DAMPs and PAMPs and directly exert their influence. Microparticles, which are structures less than 1 μm in diameter, may also impact the intestinal immunity. This effect is well established for titanium dioxide, a white pigment that is primarily contained in toothpaste, chewing gum, tablet coatings and sugar toppings, explained G. Rogler, Zurich (Switzerland).

Titanium dioxide is rapidly ingested by macrophages and may induce inflammatory processes in the respiratory tract and probably also in the bowel. This occurs because titanium dioxide accumulates in the cells and triggers the increased production of reactive oxygen species, which, in turn, can have a pro-inflammatory effect.

Our improved understanding of these relationships opens the way for the development of effective therapeutic regimens for managing inflammatory bowel diseases, explained R.B. Sartor, Chapel Hill (USA). This may, in the future, allow for an individualized treatment that is adapted to patients’ unique genetic, microbial and immunological profile.
The path to an effective therapy

Good biological markers that could help stratify patients according to their likelihood of responding to a given therapy – something quite desirable, opined F. Rieder, Cleveland (USA). This would be especially helpful in deciding for or against therapy strategies such as immunosuppression that are associated with a considerable risk of side effects. Possible candidates include serological antibodies, such as gASCA, AMCA and anti-L, which are known to be associated with an increased risk for developing complications in patients with Crohn’s disease.

Certain clinical factors may also indicate an elevated risk of complications, explained L. Peyrin-Biroulet, Vandoeuvre-les-Nancy (France), citing features such as the localization and extent of lesions, patients’ age at disease onset and smoking status. Also important are factors such as the occurrence of extraintestinal manifestations and how soon after first diagnosis patients required steroids to control their disease.

Biomarkers that would facilitate the diagnosis and differential diagnosis and assist in more reliably assessing the risk of complications would also be useful, emphasized C. Beglinger, Basel (Switzerland). Biomarkers could also assist in therapy control and monitoring. These include clinical parameters, such as the Crohn’s Disease Activity Index (CDAI), as well as their symptomatology in general and weight progression; laboratory parameters such as C-reactive protein (CRP) and stool tests (calprotectin, lactoferrin); and the findings of diagnostic imaging. To date, however, there are still no markers that specifically reflect the extent of the inflammatory reaction in the bowel.

The chronic inflammation that characterizes IBD may lead to vitamin deficiency syndromes, warned S. Vavricka, Zurich (Switzerland). Hence, IBD patients should be closely monitored with respect to their vitamin status, which, conversely, may have consequences for the disease activity. Patients’ levels of vitamins C, B3 (niacin), B6 and B12 should be closely monitored. Particular attention should be paid to vitamins D and A, both of which possess immunomodulatory functions.

Putting the “in-vironment” to therapeutic use

The intestinal microflora plays an important role in the pathogenesis of inflammatory bowel diseases. Measures that impact the microbial environment might, however, also provide therapeutic leverage that could affect management of these disorders (figure 22). Some possible options may relate to the use of antibiotics, explained H. Lochs, Innsbruck (Austria).

One potential agent is rifaximin, an antibiotic which is not absorbed from the bowel. Other options, said W. Kruis, Cologne (Germany), include the use of probiotics and stool transplantation, a measure that is being tested in patients with ulcerative colitis. To date, 22 reports are available, detailing “quite good results” for this method.

Fluorescence in-situ hybridization (FISH) with a specific probe for bacteria (yellow) and a non-specific probe for DNA structures (blue), which also stains leukocytes.

Swidsinski et al., Inflamm. Bowel Dis. 2007;13:51–56

A large number of leukocytes in the mucus layer (red arrows) and bacteria adhering to the mucosal membrane (white arrows).
**Phosphatidylcholine as a new therapy option?**

Patients with ulcerative colitis have a significantly reduced concentration of phosphatidylcholine (PC) in the gut. These observations, said W. Stremmel, Heidelberg (Germany), might provide a basis for new therapy options. In healthy persons, as W. Stremmel explained, PC is packed into lamellar structures of the mucus layer (figure 23). This phospholipid appears to exert a protective function, helping to defend against pathogenic microorganisms and protecting the mucosa against damaging factors. The reduced intestinal concentration of PC in patients with ulcerative colitis may explain the disturbance of the mucosal barrier function seen in this disorder. This hypothesis is supported by findings from preliminary studies investigating the local substitution of this phospholipid. For example, a randomized, double blind, placebo-controlled study of 60 patients with ulcerative colitis treated over three months with recombinant PC found significant improvement in disease activity in more than 90% of patients. “The tolerability of the phospholipid was extraordinarily high,” W. Stremmel added.

**Whenever possible: Local therapy**

Mesalazine and/or glucocorticoids have long been the established pharmaceuticals for treating ulcerative colitis, explained V. Gross, Amberg (Germany). The emphasis is on providing local therapy whenever possible. This is possible in patients with distal disease involvement using preparations of mesalazine formulated for rectal application (figure 25). In particular, those with distal ulcerative colitis exhibit very good rates of response, with more than 80% experiencing significant improvement in symptoms and more than one in two going on to full remission.

Topical treatment can also be achieved with budesonide, V. Gross reminded his audience, explaining that this steroid exhibits high tissue penetration but, due to a high first-pass effect, is almost completely metabolized during its first passage through the liver. This explains the high local efficacy combined with a comparatively low rate of systemic side effects. In patients with left-sided ulcerative colitis, rectally applied budesonide is associated with remission rates of about 60%.

Rectal application, however, is frequently associated with adherence problems. Patients’ adherence depends on many things, not the least of which is the applied volume. Patients more readily accept low-volume preparations than those with a higher volume to be applied with each use. Still, whenever possible, clinicians should promote topical treatment and “should constantly strive to optimize topical therapy before escalating toward options with a higher side effect risk,” V. Gross emphasized.
Advantages of combination therapy

In the long term, transition to an immuno-suppressant therapy is unavoidable in many patients, said B.E. Sands, New York (USA), adding, however, that immunosuppression not infrequently spares patients an operation. Immunosuppressive therapy has conventionally followed a step-up approach but can alternately be administered in a top-down fashion characterized by early aggressive immunosuppression with the objective of rigorously attenuating the inflammatory reaction. According to findings of the SONIC study, remission rates were particularly high in patients treated with a combination of the immuno-suppressant, azathioprine, and a TNF-α blocker. “This combined therapy has shown a clear superiority in terms of efficacy,” B.E. Sands observed.

Mucosal healing: A novel goal or old wine in a new glass?

The primary objective in the management of patients with inflammatory bowel diseases is to achieve and maintain remission, and counteract the development of disease related complications, said M. Allez, Paris (France). This, in turn, reduces the hospitalization rate and the need for surgery. Achieving this goal also automatically improves patients’ quality of life and prevents limitations and disability. Beyond this, there has been increasing propagation of mucosal healing as a further goal of therapy. There is evidence that the achievement of complete healing of mucosal lesions enhances long-term treatment success. Thus, the two-year recurrence rate is significantly lower in patients who have achieved complete mucosal healing, M. Allez explained. In addition, these patients less frequently require surgery and, presumably, there might also be a lower risk of developing colorectal carcinoma.

If complete mucosal healing proves elusive, one should at least aim for deep remission, argued J.-F. Colombel, Lille (France). This represents the absence of clinically recognizable signs of disease, analogous to the situation in the treatment of other disorders, such as hypertension or rheumatoid arthritis. Criteria for deep remission include complete control of symptoms with only minimal residual signs of inflammation, a low disease activity (CDAI) and no signs of disease progression.

At the same time, the French researcher noted that the actual clinical meaning of “deep remission” as a treatment goal must be clarified in prospective studies.

In addition to azathioprine, methotrexate may represent a further therapy option when immunosuppression is indicated. According to H. Herfarth, Chapel Hill (USA), however, the value of this agent remains significantly underestimated.

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**Suppositories**
Effective in proctitis
Usually well tolerated

**Enemas / Foams**
Effective in distal ulcerative colitis
Possible problems: – Retention – Discomfort – Pain – Interference with daily routine

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Fig. 25 Rectal formulations for IBD treatment
Study data show good clinical efficacy for azathioprine, not only as monotherapy but also in combination with infliximab. For example, data from the SONIC study of patients with Crohn’s disease and from the UC-SUCCESS study of patients with ulcerative colitis showed better efficacy for the combination of these two agents than for the respective agents when used in monotherapy, emphasized P. Michetti, Lausanne (Switzerland). However, it remains unclear how to proceed with treatment once remission is achieved in patients undergoing the combination therapy.

Other therapy options that should be considered include cyclosporine and tacrolimus, said E.F. Stange, Stuttgart (Germany). Both agents are immunosuppressants and could be used as therapy alternatives in steroid-refractory patients. The data concerning their efficacy in ulcerative colitis is especially good and are equivalent to steroids and infliximab in the treatment of this disorder.

### Outstanding Posters

Three posters were recognized during the Falk Symposium 183 “Dealing with Our ‘In-vironment’: New Aspects in IBD Pathogenesis and Therapy”:

**First prize** was awarded to C. McDonald, Cleveland (USA), for her work on maltodextrin, a dietary supplement that promotes the occurrence of pathogenic phenotypes in bacteria belonging to the intestinal microflora, thus possibly contributing to the onset of inflammatory bowel diseases.

**M.A. Zahid**, Edinburgh (Great Britain), was awarded the second prize. M.A. Zahid analyzed data from colonoscopic screening for colorectal carcinoma and found that these examinations discovered unrecognized cases of IBD in 1.1%.

The **third poster prize** went to B. Weigmann, Erlangen (Germany), for his work on the role of the transcription factor NFATc2 regarding the clinical efficacy of cyclosporine A in the treatment of ulcerative colitis.
**What does the future hold?**

The introduction of the biologicals has resulted in a certain paradigm shift in the treatment of inflammatory bowel diseases, observed **O.H. Nielsen**, Herlev (Denmark). More and more agents of this substance class are becoming available for the treatment of Crohn's disease and ulcerative colitis. The success of treatment with biologicals has led to reduced rates of hospitalization and fewer operations in patients with IBD.

The therapeutic relevance of biologicals is most evident in cases of Crohn's disease complicated by fistula formation. Despite this new substance class, however, there remains a significant need for further optimization of therapeutic options in IBD. For example, up to 40% of patients with Crohn's disease do not experience adequate therapeutic success even when treated with biologicals. Nor is this situation restricted to Crohn's disease but extends to ulcerative colitis. According to **S. Ghosh**, Calgary (Canada), the option of TNF-α inhibitors should be considered in cases otherwise refractory to therapy. Also, studies have shown that the combination of azathioprine with a TNF-α inhibitor is associated with an especially high degree of efficacy in the treatment of ulcerative colitis. The strategy of biologicals continues to be refined and there are further agents in the development pipeline. These include the anti-TNF-α antibody, golimumab, together with the immunomodulators, vedolizumab and rontolizumab, and the JAK-3 inhibitor, tofacitinib.

Autologous stem cell transplantation represents another potential future therapy option for patients with Crohn's disease, said **C.J. Hawkey**, Nottingham (Great Britain). The method has already been tried in individual cases. Allogenic stem cell transplantation is also possible and has also been attempted. The results, however, remain contradictory and deaths have been reported.

Overall, the therapeutic experience with these methods has remained extremely limited. Leukocytes migrate into inflamed tissue and serve to sustain the chronic inflammatory reaction, explained **B.G. Feagan**, London (Canada). Hence, a future therapy alternative might lie in methods that would inhibit this migration. This could conceivably be possible using agents that prevent molecular adhesion. “Anti-adhesion molecules might represent a promising new therapy concept for treating patients with inflammatory bowel diseases,” B.G. Feagan emphasized.

Thus, concluded **W.J. Sandborn**, La Jolla (USA), a whole series of new concepts remains to be developed to further optimize the therapeutic management of both Crohn's disease and ulcerative colitis. This certainly raises the hope that effective disease modification will, in the future, become a more feasible therapeutic objective. Concepts such as mucosal healing and the achievement of deep remission may also contribute to slowing disease progression and reducing the need for surgical intervention and bowel resection.

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**Fig. 26**

Inflammatory activity and progression of bowel damage in a simulated patient with Crohn's disease

Pariente et al., Inflamm. Bowel Dis. 2011;17:1415
New findings that contribute to our understanding of the pathogenesis, diagnosis and therapy of inflammatory bowel diseases were presented at the scientific Falk Symposium in Basel. Prof. Dr. Dr. Gerhard Rogler, Zurich (Switzerland), discussed their ramifications in an interview.

**Editors:**
Professor Rogler, is there really anything new in our understanding of Crohn’s disease and ulcerative colitis?

**Professor Rogler:**
There have been a number of different factors which we, in the past, had assumed were independent triggers in the pathogenesis of IBD. Others, we knew, were somehow related but we simply did not understand how they were related and how they interacted. The darkness, however, is now lifting noticeably and we have now recognized that the pathogenesis of IBD is really an interplay of genetic factors that interact with factors related to the bacterial microflora of the bowel and with other environmental factors. For a long time, we did not understand how such risk factors trigger the development of these diseases but now increasingly understand the correlations. Thus, for example, it appears that environmental factors affect the bacterial composition of the intestinal microflora. This, in turn, can promote chronic inflammatory processes – especially when there is a corresponding ge-
nastic predisposition. The contents of the bowel – we are speaking here of the “in-environment” – represents the interface across which the many different factors interact.

Editors:  
So, the intestinal flora is making us sick?

Professor Rogler:  
Yes. If the intestinal microflora is pathologically changed such that the protective factors in the bowel are displaced and the protective layer is compromised, this opens the door to bacterial invasion. Thus, the bacteria in the bowel actually can set the stage for chronic diseases.

Editors:  
Do the new findings already have therapeutic consequences?

Professor Rogler:  
We are currently at least trying to better elucidate the microflora of the bowel and to find ways of actually making an impact on its bacterial composition. We are confident that this will ultimately result in therapeutic advances in the management of inflammatory bowel diseases.

Editors:  
What do you mean when you speak of the “in-vironment”?

Professor Rogler:  
Until now, we have always spoken about environmental factors. The story, however, does not simply end there. In fact, it is often environmental factors within the bowel itself that make us sick – internal environmental factors, as it were. In order to clearly distinguish these from the more general factors in our global environment we use the term “in-vironment”. These factors are, according to our current state of knowledge, the real triggers of inflammatory bowel diseases. The genetic risk factors have not changed over the past decades and centuries. Nevertheless, we continue to see an increase in the frequency of inflammatory bowel diseases. This can logically be due only to a change in environmental factors – especially the internal environmental factors, the “in-vironment”. Thus, the “in-vironment” is simply the content of the bowel that is impacted by factors of the general “en-vi-ronment”.

Editors:  
During the symposium, speakers have explained that the various regulatory steps are tightly interwoven. Just how complex is the disease process?

Professor Rogler:  
The situation used to be quite confusing. We had identified over 100 high-risk genes and no one could really understand how these genes more or less independently of one another could trigger disease development. We were all quite astonished when it turned out that genes, which had been shown to be related to other functions, for example with the development of immune cells, were apparently interlinked and that the strands of this network and the functional levels of the genes within cells were actually rather limited. Thus, the many individual genes exert their regulatory activity through only three to four different functions and dysregulation translates into malfunction. The system is thus much more understandable than we long had feared.

Editors:  
What are these central functions?

Professor Rogler:  
The central functions are autophagy, cellular stress and certainly also the signal transmission between the innate and acquired immune systems and bacterial recognition. We are developing an increasingly integrative view of the many factors apparently involved in the pathogenesis of these diseases, which helps us better understand their interactions. This gives us hope of developing new options for the treatment of inflammatory bowel diseases because, the better we understand the correlations, the more clearly targeted our potential therapy options will be.

Editors:  
So, you see new perspectives for the future?

Professor Rogler:  
Yes, certainly. One consequence of our new findings is that we may focus somewhat less intensively on the development of new biologicals. It would not seem to make much sense to selectively turn off one individual pathogenetic factor. The concept has not proven particularly effective and I do not believe that it suffices to, for example, give interleukin-10 or eliminate interleukin-12. It is certainly doing too little to try and influence a single factor. Rather, we have to impact the entire network of mediators and the abnormal metabolic pathways if we are to really take control of these diseases. There are already attempts to realize such a strategy. One example is treatment with helminth ova, which may lead someday to the isolation of a single protein from the ova which affects the dysregulation. The intestinal barrier is also very important and is disturbed in patients with inflammatory bowel diseases. It may be possible to fortify the intestinal barrier with phosphatidylcholine. There are other concepts that tend in the same direction and overall attempt to correct the disordered regulation without being immunosuppressive. The focus thus is shifting away from the immune system and toward correcting the dysregulation – if possible on the basis of the pathogenetic process before the signal goes out that sets the inflammatory process in gear.

Professor Rogler,  
thank you very much for the interview.
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Date of information: 06/2012