Microscopic analysis of endoscopically obtained tissue samples is important for the diagnosis of several gastrointestinal disorders such as gastritis and chronic inflammatory bowel disease (IBD). Histologically disease activity is based on the presence of neutrophilic polymorphonuclear leukocytes in conjunction with epithelial damage. Effective eradication treatment for Helicobacter pylori related gastritis reduces active inflammation rapidly whereas chronic inflammation decreases only slowly. Similar findings have been obtained for IBD. A literature review of clinical drug trials in IBD and the effect of various drugs on the microscopic features of Crohn’s disease and immunohistochemistry for different markers was performed. Diagnostic microscopic features and the features characteristic for disease activity vary with time and treatment. The more recently developed drugs used for Crohn’s disease can induce mucosal healing.

Endoscopy with biopsy is an established procedure for the diagnosis and differential diagnosis of gastritis and chronic idiopathic inflammatory bowel diseases (IBD).12 In recent years biopsies have also become important for the assessment of disease activity and for determination of the efficacy of medical treatment. Since the rediscovery of Helicobacter pylori, the classification of gastritis has been updated and the treatment modified. H pylori related gastritis can now be treated adequately and follow up biopsies have clearly shown the effect of adequate treatment. This has not yet been achieved for IBD. For these conditions, morphological studies have mainly been concentrated on features which are reliable for the diagnosis of IBD.7–9 Severity and activity of the disease are usually measured with clinical and biological parameters occasionally supplemented with endoscopic indices.20–24 Whether microscopic disease activity is important for the clinical course of the disease has not yet been established adequately. However, clinical trials have shown that treatment can modify microscopic disease activity in both ulcerative colitis (UC) and Crohn’s disease (CD).25–26 This review will mainly concentrate on the changes of the morphological features which are characteristic for IBD and their variability under the influence of treatment.

Abbreviations: 5-ASA, 5-acetylsalicylic acid; CD, Crohn’s disease; CDAI, Crohn’s disease activity index; H&E, haematoxylin and eosin; IBD, inflammatory bowel disease; ICAM, intercellular adhesion molecule; LFA, lymphocyte function associated antigen; MHC, major histocompatibility complex; TNFα, tumour necrosis factor α; UC, ulcerative colitis
for less than two weeks. The absence of mucosal architectural abnormalities can thus present diagnostic problems in patients with acute onset of colitis and during follow up.4 Most of the data are based on the analysis of rectal biopsy specimens. Multiple colonic biopsies combined with ileal biopsies can help to solve diagnostic problems in patients with long standing disease, although even in long standing UC histological disease may revert to normal mucosa.16

Inflammatory diagnostic features are equally variable in time. In long standing disease, increase in total lamina propria cellularity provides a good but only partial discrimination between normal and IBD with, overall, 86% of known cases being correctly classified.7 An increase in cells in the basal third of the lamina propria is a more powerful single discriminant for IBD.8 Another helpful feature is the presence of plasma cells. A pronounced difference in plasma cell counts between normal and chronically inflamed rectal mucosa has indeed been noted.15 This was confirmed in a prospective blind evaluation of multiple colon mucosal biopsy specimens from patients with CD and UC. Basal plasmacytosis was present in more than half of the IBD patients.7 Basal plasmacytosis is not, however, consistently present. In a prospective study, focal basal plasmacytosis was found in 38% of patients with symptoms for less than two weeks. One year after the onset of colitis, it had disappeared in half the IBD patients who had no relapse.13 The absence in the early phase and the disappearance during evolution can be confusing when the need for maintenance treatment is questioned and the diagnosis uncertain.

Chronic inflammation, both endoscopic and histological, in a contiguous and symmetrical distribution is believed to be important in distinguishing UC from CD.9 Discontinuous type of infiltration in stepwise biopsies from the colon has been considered a good criterion of CD.12 Several studies have shown, however, that discontinuous inflammation is also common in resolving and long standing UC and that this feature has only a low separating effect.12 16 The evolution in time of granulomas, one of the major features which allows distinction between UC and CD, has not been studied extensively. It is, however, well known that granulomas are not consistently present. They tend to be more common in children and in the early phase of the disease.

MICROSCOPIC FEATURES AND MEDICAL TREATMENT

Complete normalisation of the mucosa, including architectural abnormalities, has been observed in UC with topical 5-acylsalicylic acid (5-ASA) and non-systemic steroid treatment.25 26 Mucosal architectural abnormalities may however persist and appear as “pseudodysplasia” following treatment with cyclosporine.10 Basal plasmacytosis and basal lymphoid aggregates can persist in rectal biopsies from patients with UC treated with sulphasalazine,7 but the intensity can decrease significantly or the infiltrate may even disappear.21 Treatment can induce patchiness or discontinuity of mucosal inflammation in UC, making a differential diagnosis between UC and CD more difficult and confirming the low discriminatory value of this feature.35

In adult CD patients, a high degree of normalisation in histological pattern was found in rectal disease following a two year treatment with a combination of prednisolone and sulphasalazine. Prednisolone monotherapy was less effective, while the effect of sulphasalazine as monotherapy was poor.10 In general the effect of glucocorticosteroid therapy on colon mucosal healing is poor in CD.7 48 In adult steroid refractory CD patients, treatment with antibodies directed against tumour necrosis factor α (TNFα) induced an important reduction of inflammatory features in the small intestine and colon in four weeks, while architectural abnormalities persisted.49 Using endoscopy and histology, significant mucosal healing was also observed in severe postoperative recurrent ileitis and in active CD with long term azathioprine.18 19 In children with small bowel CD, normalisation of the small intestinal mucosa has been obtained with polymeric nutrition.46 A reduction of epithelioid granulomas has been described following long term treatment with prednisolone, sulphasalazine, and 6-mercaptopurine, whereas chronic inflammation may persist.41 Granulomas may, however, persist despite endoscopic healing and near normalisation of the histology, with reduction of chronic inflammation, following azathioprine treatment.42 Not surprisingly, the duration of treatment has a significant impact on evolution of the lesions. Mucosal healing can occur rapidly, but usually takes several months to years. In UC, near normalisation has been observed within two weeks following the start of topical treatment with 5-ASA.13 In adult rectal CD, univariate significant differences in the variables cryptal distance, cryptal diameter, cell content of the lamina propria, and plasma cells were found only after two years treatment.17 Normalisation of small intestinal and colon histology was observed in CD with azathioprine in approximately 60% of patients only after 13–53 months of treatment.14 Other variables that are important for the evolution of microscopic features are the severity of lesions, the intensity of the inflammatory reaction, and the pharmacological properties of the drug or the combination of drugs. In steroid refractory CD, antibodies directed against TNFα (infliximab) can induce a significant reduction of chronic inflammation within four weeks following a single infusion.44

In conclusion, it seems that medical treatment can have a profound effect on mucosal histology but the effect is highly variable. It depends on time, type of treatment, whether topical or systemic, the pharmacological properties of the drug, severity of the lesions, intensity of the inflammatory reaction, and probably several other at present unknown variables. There are important individual differences among patients and the effect of medical treatment is not easy to predict.

MICROSCOPIC DISEASE ACTIVITY IN IBD

Disease activity in IBD is usually assessed with the help of clinical and biochemical parameters often combined in indices such as the Crohn’s disease activity index (CDAI) for CD or the Truelove and Witts score for UC.17 35 For CD it is generally recommended that the CDAI be used as the primary outcome measure of clinical disease activity in patients whose symptoms are or have been predominantly inflammatory in nature. Histology is not generally considered to be very useful.45 When strict rules are followed, however, histology allows a precise identification of inflammation and tissue injury, and these indicate active disease at least in the tissue.4 “Active inflammation” is defined as an injury characterised by unequivocal damage of the epithelium, typically in conjunction with neutrophils.4 The injury can be part of an acute or chronic disorder.4

The presence of neutrophils between epithelial cells is a major feature of disease activity. Several arguments support this view. Neutrophils can reliably and reproducibly be detected in routinely haematoxylin and eosin (H&E) stained sections.12 The choice of neutrophils as indicator for disease activity is in agreement with studies using leucocyte scanning, showing that active inflammation in UC is dominated by neutrophils infiltrating the tissue.46 47 The survival of neutrophils in the tissue, outside blood vessels, is limited in time because of a short half life. Their presence in the tissue therefore indicates recent recruitment and hence persistent aggression. Neutrophils can induce tissue damage through their metabolites and enzymes such as gelatinase B, while the role of immune complex mediated cell damage in IBD is limited.48 Neutrophil polymorph infiltration of crypt epithelium (cryptitis), crypt lumina (crypt abscesses), and surface epithelium is common endoscopy in CD. Crypt abscesses is observed in 64–86% of cases with UC and 48–75% of cases with Crohn’s colitis, which is significantly more common than in infective colitis (39%).
Neutrophils are well established indicators of activity in other diseases such as *H pylori* related gastritis.

Unequivocal damage of surface and crypt epithelium can be identified by the presence of attenuated, flattened epithelial cells, indicating “restitution” which is a phenomenon of rapid tissue recovery. Crypt abscesses, crypt destruction, erosions, and ulcerations are other indicators of tissue injury that can be used as markers of disease activity. Neutrophils are, however, not the only cells which can induce tissue damage. Increased numbers of circulating and tissue eosinophils in patients with active ulcerative colitis are well recognised. They are also able to produce toxic products, such as reactive oxygen species. T cell mediated hypersensitivity and plasma cells also play an important role in tissue damage in CD. Activation of lymphocytes can, however, not reliably be identified on H&E stained sections. This can be done by immunohistochemistry, which allows the study of the expression of activation markers such as lymphocyte function associated antigen (LFA) on immune competent cells, of adhesion molecules such as the intercellular adhesion molecule (ICAM-1) on endothelial or other cells, or the expression of markers on other cells, induced by activated lymphocytes. An example of the latter is the expression of major histocompatibility complex (MHC) class II molecules, normally an exclusive property of professional antigen presenting cells. Aberrant or increased expression is regularly observed on mucosal cells of patients with IBD. Immunohistochemistry is, however, not generally used and should not be used routinely for the analysis of biopsy specimens from patients with IBD.

The significance of histological disease activity, especially in CD, is uncertain and the clinical significance of histological remission has not been established. At present, histological remission should not be used as the primary endpoint for therapeutic trials in patients with CD until histological remission has been defined and correlated with clinical remission and natural history.

### SCORING DISEASE ACTIVITY

Histology as a tool for the measurement of disease activity was first introduced for UC. Many scores have subsequently been proposed. All scoring systems rely on analysis of routinely H&E stained sections and most have been designed for UC. For CD, the use of microscopic scores is much more difficult because of the segmentary nature of the disease and because of the predilection for the ileum. More recently, histology scores have been used for CD. Some of these were originally designed for UC, while others have been developed especially for CD. At present there are many histological scores but a lack of uniformity. The scoring systems can be divided into two groups: stepwise systems and numerical (quantitative) systems. In stepwise systems, the disease activity and/or severity is divided into different grades or phases, for which different grades such as 1, 2, and 3 or names such as normal mucosa, quiescent, inactive disease, chronic persistent, and active disease are used. Active disease can further be subdivided into mildly, moderately, or severely active disease. In numerical systems, different variables or lesions are scored and to each of these a subjective numerical value is given. The final score is the result of the sum of the scores of different variables. Some of the scoring systems are elaborate and contain many variables, while others are extremely simple.

### Table 1 Scoring system according to Keren et al

<table>
<thead>
<tr>
<th>Acute inflammation</th>
<th>Crypt changes</th>
<th>Chronic inflammation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal mucosa</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Active IBD</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Inactive IBD</td>
<td>0</td>
<td>+ or 0</td>
</tr>
<tr>
<td>Reactive mucosa</td>
<td>+ or 0</td>
<td>0</td>
</tr>
</tbody>
</table>

Acute inflammation includes cryptitis, crypt abscesses, and neutrophils in the lamina propria.
Crypt changes include distortion and/or atrophy.
Chronic inflammation: mononuclear cells in lamina propria.

### Table 2 Scoring system according to Gomes et al

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal</td>
</tr>
<tr>
<td>1</td>
<td>Mild oedema, inflammation in the lamina propria</td>
</tr>
<tr>
<td>2</td>
<td>Crypt abscess formation, inflammation in lamina propria</td>
</tr>
<tr>
<td>3</td>
<td>More severe inflammation with destructive crypt abscesses plus or minus granulomatosis</td>
</tr>
<tr>
<td>4</td>
<td>More severe inflammation with active ulceration</td>
</tr>
</tbody>
</table>

Six biopsy specimens are assessed; each is graded on the scale of 0–4; the total score is achieved by adding the individual scores of the six biopsy specimens [maximum = 24].

### Table 3 Scoring system according to Odze et al

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal</td>
</tr>
<tr>
<td>1</td>
<td>Chronic inactive</td>
</tr>
<tr>
<td>2</td>
<td>Chronic active</td>
</tr>
<tr>
<td>3</td>
<td>Cryptitis, crypt abscesses, or surface erosion</td>
</tr>
</tbody>
</table>

### REPRODUCIBILITY OF SCORES

The reproducibility of activity scores has not been studied extensively, although this is essential for a comparison of results. Some data are available, indicating that interobserver agreement is good. Interobserver variation was minor and infrequent, occurring in less than 10% of biopsy samples in the study by Odze and colleagues. The same grade of severity was allocated to each histological feature in 82% of the biopsy sections, and differed by more than one grade in only 2% of the sections in the study by Riley and colleagues. Neutrophil polymorph infiltration of the lamina propria, the crypt epithelium, the crypt lumina, and the surface epithelium can be assessed reproducibly. Using a complex score with six grades, a kappa value of 0.62 was reached in an interobserver study where three different pathologists examined H&E stained sections of 99 patients with UC. With a simple score where neutrophils between epithelial cells were the main criterion for the discrimination between active and inactive disease, the same pathologists reached a kappa value of 0.9.
CORRELATION WITH ENDOSCOPY AND CLINICAL INDICES

The correlation between endoscopy and histology in IBD is not perfect. When the extent of disease needs to be defined, biopsies may double the yield of pathology when compared to the endoscopically visible amount of inflammation, and may be three times more informative than the barium enema radiographic examination. In UC, persistent microscopic evidence of inflammation is common in patients with sigmoidoscopically quiescent colitis. Overall, a good correlation has been found in several studies. A good correlation has also been reported between microscopic and macroscopic scores for Crohn’s colitis ($R = 0.68, p < 0.05$) and for postoperative recurrent ileal CD ($R = 0.54, p = 0.004$). However, endoscopic assessment of inflammation in CD had a better correlation with transmural inflammation than mucosal biopsy and thus with the severity and extent of inflammation. In general, the differences between endoscopy and histology are smaller for active disease and larger for inactive disease. In UC, endoscopy is used for staging disease extensively, but there are some data available. In a controlled trial of various dietary treatments for UC, serial rectal biopsy specimens were examined over a one year period. A twofold increase in relapse rate was found in patients with appreciable microscopic inflammation. These findings were confirmed in a study of 82 patients with UC in clinical and endoscopic remission, where it was shown that relapse was more frequent in patients with persistent acute inflammation.

TREATMENT AND HISTOLOGICAL SCORES

The effect of a large variety of medical treatments on microscopic disease activity has been reported in many clinical trials for both UC and CD. In most studies the evaluation was performed after a few weeks. In UC, mild to moderate improvement of disease activity is usually obtained with 5-ASA and with systemic or non-systemic steroids following either oral or topical administration. The effect of sulphasalazine is usually poor. In a study of 61 patients with UC, showing mild to moderate relapse, 5-ASA or sulphasalazine were given orally for four weeks. A decrease of the histology score from a mean of $3$ (range $1–4$) to $2$ (range $0–3$) was found for 5-ASA while there was no effect for sulphasalazine (mean at entry $= 3$, range $2–4$; mean at completion $= 3$, range $1.5–4$).

In patients with an acute relapse or first attack, 5-ASA enemas (2 g) induced a decrease of the histological score from $3.62 ± 0.3$ at entry to $1.48 ± 0.35$ at four weeks. A better result was obtained with a combination of beclomethasone dipropionate (3 mg) and 5-ASA, inducing a drop from $4.16 ± 0.41$ to $0.32 ± 0.22$.

In active distal UC, budesonide enemas (2 mg/100 ml) were shown to be superior to prednisolone (31.25 mg/100 ml) after two and four weeks. A significant decrease in histology score occurred in the budesonide treated patients after two weeks (mean at entry $= 4$; mean at 2 weeks $= 2.5$); a further decrease was noted after four weeks (mean $= 2$). For prednisolone the mean score value was 3.5 at entry and 2.9 at completion.

These findings were confirmed in other studies comparing budesonide enemas with placebo. Similar results were obtained in other studies comparing budesonide enemas with placebo.

In an open study a decrease of the score from $3.7$ to $2.7$ was observed at four weeks. Using the same score, there was a decrease from a mean of $3.72$ at entry to $1.48$ at nine weeks with oral prednisolone. Intravenous cyclosporine 4 mg/kg/day can induce endoscopic and histological improvement which

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### Table 4: Scoring system according to Danielsson et al.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Normal mucosa</td>
</tr>
<tr>
<td>2</td>
<td>Slight inflammation: isolated inflammatory cells or cell aggregates of either lymphoplasmocytic cells or eosinophils</td>
</tr>
<tr>
<td>3</td>
<td>Intermediate inflammation: marked increase of inflammatory cells with some changes in secretory cells, mild atrophy</td>
</tr>
<tr>
<td>4</td>
<td>Severe inflammation: crypt abscesses; lymphoid follicles in deeper cell layers; massive increase in inflammatory cells and pus; marked atrophy</td>
</tr>
<tr>
<td>5</td>
<td>Fulminant inflammation: ulcerations with pus, crypt abscesses; atrophy; deep follicles</td>
</tr>
</tbody>
</table>

---

### Table 5: Scoring system for Crohn’s disease

<table>
<thead>
<tr>
<th>Histological variable</th>
<th>Grading</th>
</tr>
</thead>
<tbody>
<tr>
<td>1: epithelial damage</td>
<td>$0 =$ normal; $1 =$ focal; $2 =$ extensive</td>
</tr>
<tr>
<td>2: architectural changes</td>
<td>$0 =$ normal; $1 =$ moderate (≥50%); $2 =$ severe (≥50%)</td>
</tr>
<tr>
<td>3: mononuclear cells in lamina propria</td>
<td>$0 =$ normal; $1 =$ moderate increase; $2 =$ severe increase</td>
</tr>
<tr>
<td>4: polymorphonuclear cells in lamina propria</td>
<td>$0 =$ normal; $1 =$ moderate increase; $2 =$ severe increase</td>
</tr>
<tr>
<td>5: neutrophils in epithelium</td>
<td>$1 =$ surface epithelium; $2 =$ crypts; $3 =$ crypt abscess</td>
</tr>
<tr>
<td>6: erosion or ulceration</td>
<td>$0 =$ no; $1 =$ yes</td>
</tr>
<tr>
<td>7: granuloma &amp; 8: number of biopsies affected (total: n≥6 or more)</td>
<td>$0 =$ none; $1 =$ &gt;33%; $2 =$ 33–66%; $3 =$ &gt;66%</td>
</tr>
</tbody>
</table>

Each variable is scored independently. The total score is the sum of all individual scores (max = 16).
parallels clinical improvement. There was a decrease in the histology score from 10.7 ± 0.6 (maximum 16) at week 0 to 7.0 ± 1.4 at week 4 in 14 patients with a severe attack of UC. For other drugs, such as a leukotriene biosynthesis inhibitor, microscopic improvement is less impressive, correlating well with clinical impression. In general the effect of different treatment modalities on the features of active inflammation (presence of neutrophils; cryptitis and crypt abscesses) is more pronounced than their effect on mucosal architectural abnormalities and chronic inflammation, especially when the data are analysed after a short period of treatment, such as for four weeks. It is well known that clinical and endoscopic improvement after treatment can occur rapidly in UC. In contrast, histological improvement usually takes longer.

A similar evolution is noted in *H pylori* related gastritis, where neutrophils disappear within weeks following successful eradication. At the end of therapy, the mucosa is virtually devoid of polymorphs in most patients. The resolution of chronic inflammation is much slower. Incomplete regression of the lymphoplasmocytic infiltrate was described at five months and one year. Resolution was found in 51% at one year post-eradication. Lymphoid aggregates and follicles were shown to remain present at follow up one year after eradication. A treatment with infliximab as primary therapy induced an important reduction of disease activity in children with small bowel disease. The histology score with a maximum of 3 dropped from a median of 2 (range 1–3) at entry to 0.7 (range 0–1) at completion. Cyclosporine (score at entry 1.5, range 1–2; score at completion 1.0, range 0–2) and prednisolone (score at entry 1.0, range 1–2; score at completion 1.5, range 0–2) had only a limited effect. The data with prednisolone in children confirm the findings obtained in adult patients. In patients with adult CD and using a score with a maximum of 16, there was a decrease of a mean of 13 at entry to 7 at completion using azathioprine after several months, and a drop from 8.8 ± 1.7 (range 2–10) to 2.7 ± 1.7 (range 0–8) at four weeks using infliximab. In the placebo group of the latter study the score was 11.0 ± 2.3 before and 9.0 ± 1.9 after treatment.

Etanercept, an injectable TNF receptor fusion protein, induces clinical improvement. We observed, however, no significant decrease of the inflammatory score in 10 patients studied in a pilot trial. The median score in the colon was 5 (range 4–12; maximum 16) before and 4.8 (range 2–10) after 12 weeks of etanercept.

The evolution of histological scores during treatment provides some information about the treatment efficacy. However, many variables in the scores are described as continuous spectra, for example, chronic inflammation, but are divided into discrete groups (for example, mild, moderate, marked). This means that these features are ordinal categorical variables rather than continuous real numbers. The consequences of this are that these grades cannot be used in analytical processes which require continuous variables, such as linear regression. Therefore analysis using mean grades may not be appropriate. Frequency distribution histograms or possible median grades seem more appropriate.

**MEDICAL TREATMENT AND OTHER MARKERS**

Several studies have shown that increased expression of HLA-DR, MHC class II molecules in UC is reduced or disappears following different types of treatment such as corticosteroids or 5-ASA. Similar results have been noted in CD following treatment with cyclosporine, antibodies directed against CD4 lymphocytes, and antibodies against TNFα. In general, treatment with infliximab induces a profound down regulation of the inflammation in Crohn's ileocolitis, including a reduction of the expression of ICAM-1 on endothelial cells and of ICAM-1 and LFA-1 on immune competent cells.

We have also shown that infliximab decreases mucosal lymphocyte proliferation in CD, whereas epithelial cell proliferation remains largely unchanged.

**CONCLUSIONS AND PERSPECTIVES**

The microscopic features associated with IBD which are useful for diagnosis, assessing disease activity, or both show considerable variation in time and with treatment. The variability in time and severity has been recognised for a long time. The improvement of medical treatment has influenced the evolution of both diseases. Histological scores show that most drugs have a substantial influence on the microscopic picture, especially on the features of disease activity. Medical treatment increases the variability. Changes in the microscopic features are observed with most drugs used for IBD. They mainly affect signs of mucosal injury and the presence of neutrophils. These can disappear or diminish substantially within four weeks. Reduction of lamina propria cellularity usually takes months to years if it occurs, although more recent drugs can profoundly down regulate mucosal inflammation in four weeks. Medical treatment can promote histological healing. It is, however, not yet clear whether this should be a primary endpoint in clinical trials.

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K Geboes and I Dalle

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