

REVIEW

# Indeterminate colitis: definition, diagnosis, implications and a plea for nosological sanity

G T Martland & N A Shepherd

*Departments of Histopathology, Gloucestershire Royal Hospital, Gloucester and Cheltenham General Hospital, Cheltenham, UK*

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Martland G T & Shepherd N A

(2007) *Histopathology* 50, 83–96

## Indeterminate colitis: definition, diagnosis, implications and a plea for nosological sanity

In 1978, Price introduced the concept of indeterminate colitis to describe cases in which colonic resections had been undertaken for chronic inflammatory bowel disease (CIBD), but a definitive diagnosis of either of the classical types of CIBD, ulcerative colitis and Crohn's disease, was not possible. This was especially apposite in cases of acute fulminant disease of the colorectum. More recently, the term indeterminate colitis has been applied to biopsy material, when it has not been possible to differentiate between ulcerative colitis and Crohn's disease. In our opinion, and in those of other workers in this field, the term should be restricted to that originally suggested by Price. This then provides a relatively well-defined group of patients in whom the implications and management of the disease are becoming much clearer. Cases where there are only biopsies with CIBD, but equivocal features for ulcerative colitis and Crohn's disease,

should be termed 'CIBD, unclassified', 'equivocal/non-specific CIBD' or IBD unclassified (IBDU), in line with recent recommendations. When the diagnosis is correctly restricted to colectomy specimens, there is now good evidence that the majority of cases will behave like ulcerative colitis. Furthermore, the diagnosis should not be a contraindication to subsequent pouch surgery. When the latter is undertaken, surgeons and patients can expect an increased complication rate, compared with classical ulcerative colitis, especially of pelvic sepsis, but most patients fare well. Only very occasional patients, around 10%, will eventually be shown to have Crohn's disease. This review describes the pathology of cases appropriately classified as indeterminate colitis and the implications of that diagnosis. It also highlights recent advances in its pathological features, clinical management and its immunological and genetic associations.

**Keywords:** backwash ileitis, caecal patch lesion, chronic inflammatory bowel disease, Crohn's disease, ileal pouch, indeterminate colitis, pathology, ulcerative colitis

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## Introduction

In the 1970s, it was first appreciated that there was a cohort of patients undergoing colectomy or proctocolectomy for chronic inflammatory bowel disease (CIBD) in whom a diagnosis of classical Crohn's disease (CD) or ulcerative colitis (UC) (or even certain infectious diseases) was not possible.<sup>1–3</sup> The macroscopic and

microscopic features, equivocal for CD and UC, confounded a definitive diagnosis. Price coined the term 'colitis indeterminate' to describe these patients' pathology. The disease is now more commonly known as indeterminate colitis (IC).

The appellation indeterminate colitis (IC), originally applied to resection specimens, has in recent years, and in our opinion wrongly, been applied to biopsy specimens.<sup>4–12</sup> The incorrect use of IC is now common vocabulary for surgeons and clinicians as well as for some pathologists. For instance, and somewhat embarrassingly, one of us is an author of the British Society of

Address for correspondence: Professor N A Shepherd, Department of Histopathology, Gloucestershire Royal Hospital, Great Western Road, Gloucester GL1 3NN, UK. e-mail: neil.shepherd@glos.nhs.uk

Gastroenterology guidelines on the biopsy reporting of CIBD which upholds the misdemeanour concerning the usage of IC for biopsy material.<sup>13</sup> Furthermore, one popular UK endoscopy reporting system uses the term 'indeterminate colitis' to describe initial colonoscopic features in patients with putative CIBD in whom no pathological investigation has been undertaken at all. This seems totally inappropriate. Some workers have set out criteria for the diagnosis of IC in biopsy specimens, which is clearly missing the point of Price's original definition.<sup>14,15</sup>

We agree with the recently published World Congress of Gastroenterology Montreal recommendations, which state that (i) the diagnosis of IC should be made only after colectomy and (ii) the term inflammatory bowel disease, unclassified (IBDU) should be used in all other cases where definitive features of CD and UC are absent.<sup>16,17</sup> Even so, subsequent publications, published this year, continue to use the term IC for cases of equivocal CIBD in biopsy material.<sup>18</sup>

A more appropriate term, for use in equivocal biopsy cases, is 'CIBD unclassified' or 'equivocal/non-specific CIBD'.<sup>12</sup> Inflammatory bowel disease unclassified (IBDU) has been suggested by the Montreal Working Party.<sup>16,17</sup> Whilst we agree that there is a danger that these terms may end up as a 'diagnostic dustbin',<sup>19</sup> we would emphasize that, if the term indeterminate colitis is restricted to CIBD colectomy specimens, this then defines a patient group with much more specific and defined pathology, in whom management and prognostic implications are relatively clear.

There are two main reasons why the terms IC and IBDU should not be confused. Labelling a patient as IC can have potential major consequences for subsequent management, especially in pouch surgery (see below). How a patient fares following a colectomy with IC is vastly different from how a patient classified with IBDU fares. Confusing IC and IBDU also ensures that these two entities cannot be appraised separately with a view to future management and research into their implication and prognosis. Reviews of the literature indicate that there is wholesale confusion, largely engendered by the inappropriate use of terminology.

## History and epidemiology

Lockhart-Mummery and Morson described the distinguishing features of colorectal CD and UC in the 1960s from St Mark's Hospital in London, UK, and these definitions were further refined in the 1970s.<sup>20-23</sup> In 1970, Kent first described colectomy specimens in which it was difficult to distinguish between UC and

CD, which he termed indeterminate/indeterminant cases.<sup>1</sup>

Working originally with Morson, Price highlighted the particular difficulty of differentiating between UC and CD when the colectomy was performed as an emergency procedure for so-called 'fulminant colitis' and he introduced the concept of IC.<sup>2,3</sup> In the 1980s the Research Committee of the World Organization of Gastroenterology proposed a scoring system for the correct diagnosis of inflammatory bowel disease (IBD) with a diagnostic accuracy rate of 96%.<sup>24</sup> However, in a fulminating colitis, it was acknowledged that the macroscopic and microscopic features for both CD and UC remained blurred, with few distinguishing features.

It is now fully recognized that pathological assessment difficulties in these cases were mainly due to the severity of the inflammation.<sup>25,26</sup> This is especially so in exceptionally severe or fulminant IBD with associated systemic toxicity and, in some cases, toxic megacolon. It was many of these cases, following thorough clinical, macroscopic and microscopic evaluation, that Price called indeterminate colitis (IC). Such cases, today, make up the bulk of the cases appropriately designated IC.

From the literature, IC cases show an equal sex distribution and the mean age at onset is 36–39 years.<sup>25,27,28</sup> IC is diagnosed in between 9% and 20% of colectomy specimens.<sup>3,25,29-31</sup> In our experience, the diagnosis is made in only about 5% of colectomy specimens for IBD, but this may reflect our particular practice of IBD. This may, on the other hand, represent changing practice, with pathologists more likely to make a definitive diagnosis of UC, now that it is recognized that pouch surgery is not contraindicated in such acute fulminant cases and that discontinuous disease is no longer considered an absolute contraindication to the diagnosis of UC.

## Pathological features of 'indeterminate colitis'

At the outset, it is important to emphasize that, despite Price's original excellent descriptions of the disease and subsequent exemplary contributions to the literature on this subject,<sup>2,3,10,16,17,32</sup> CIBD represents a spectrum of disease, both macroscopically and microscopically, with classical UC and classical CD at either end but numerous cases liberally distributed in the spectrum between. Some of these cases, especially those in the middle ground, represent 'indeterminate colitis'.

## MACROSCOPIC FEATURES

As gastrointestinal pathologists recognize, a comprehensive assessment of the macroscopic features of colorectal resection specimens is just as important as the microscopic features for attaining the correct diagnosis. The cardinal features of UC are a continuous mucosocentric pathology, with the rectum bearing the brunt of the disease and a variable extension of disease proximally. On the other hand, CD shows two chief patterns. One is a fibro-stricturing pathology and the other primarily inflammatory and associated with deep fissures and fistulation.<sup>33</sup> There may be overlap between these two patterns of CD and highly characteristic macroscopic features of the disease are discontinuous pathology, bowel wall thickening, transmural disease and connective tissue changes. For example, it has been mooted that fat-wrapping, one of the more prevalent and important connective tissue changes of CD, is highly specific to CD and is not seen in either UC or IC.<sup>34</sup>

It is no surprise that IC cases show overlap of these two disease processes (Table 1). The affected colectum in IC demonstrates an extensive colitis, which itself can take two main patterns. The first pattern is that of severe continuous disease throughout the colon, often with relative rectal sparing (Figure 1).<sup>3,10,35</sup> The second is that of extensive intermittent ulceration that can give the false impression of skip lesions (Figures 2 and 3). The mucosa between these ulcers may appear normal.<sup>3,29</sup> Typically, more than 50% of the mucosal surface of the colon is involved and the disease process tends to affect the right and transverse colon more severely than the left (Figure 1).<sup>32</sup> Fissures may also be seen macroscopically.<sup>10</sup> Some of the cases may be diagnosed radiologically as 'toxic megacolon' and show dilation accordingly (Figure 2) (Table 1).<sup>3</sup>

## MICROSCOPIC FEATURES

Microscopically, the picture is dominated by severe and extensive ulceration (Figure 4) (Table 2). This is

**Table 1.** Morphological macroscopic features seen in indeterminate colitis

Extensive ulceration
Involvement of transverse and right colon (more severely than distal colon)
Involvement of >50% of the mucosal surface
Usually diffuse disease, but may show rectal sparing
Toxic dilation may be present

usually most prominently seen in areas of the colon that are maximally dilated, notably the transverse colon, although very severe cases will show very extensive ulceration almost throughout the colon and rectum. Because of the fulminant disease, IC also shows myocytolysis, telangiectasia and some fissuring (Table 2).<sup>3,35,36</sup> However, the quality of the fissuring ulcers is different from that seen in CD. The fissures may take the form of either squat V-shaped clefts or knife-like breaks, both of which may extend into the submucosa and may extend into the superficial muscularis propria (Figures 4 and 5).

The V-shaped clefts of IC tend to be sparsely lined by inflammatory cells, are often multiple and are usually in areas of extensive ulceration: the adjacent bowel shows myocytolysis and capillary engorgement.<sup>3,10,29,35</sup> The second type of fissure seen in IC, described variably as 'knife-like', 'slit-like' or even 'rake-like', is vertically oriented defects lined by granulation tissue (Figure 6).<sup>29,36,37</sup> These ulcers occur mostly singly (one to three per colectomy specimen).<sup>36</sup> They are associated with marked chronic inflammation in the adjacent mucosa. They may be relatively deep and extend into the superficial muscularis propria.<sup>36</sup>

Both of these types of fissures, seen in IC, contrast with those in CD. The fissures in CD are characteristically serpiginous in character and covered by ebullient granulation tissue.<sup>35</sup> However, even then there is some overlap between the two diseases in terms of fissuring pathology and none of these types of fissures can be deemed, *per se*, specific to IC or CD. Indeed, some fissuring ulceration is well described in otherwise classical UC.<sup>35</sup>

Many cases of IC, despite apparently discontinuous disease macroscopically, will show some evidence of a diffuse mucosal pathology away from areas of ulceration. The amount of such chronic UC-like chronic inflammation, crypt architectural changes and Paneth cell metaplasia is largely dependent on the length of the history. If there is a short history, then these changes may be almost absent and, in those patients, there may be almost normal mucosa bordering the deep ulceration. On the other hand, patients with a longer history are more likely to show these features, despite the presence of superimposed acute fulminant pathology.<sup>35</sup>

Because of the extensive ulceration, there may be some 'non-specific transmural inflammation', but this does not have the character of the 'Crohn's rosary', the presence of lines of lymphoid aggregates along the outer border of the muscularis propria, a feature which, like fat-wrapping, is effectively pathognomonic of CD (Figure 7).<sup>35</sup> The transmural chronic inflammatory

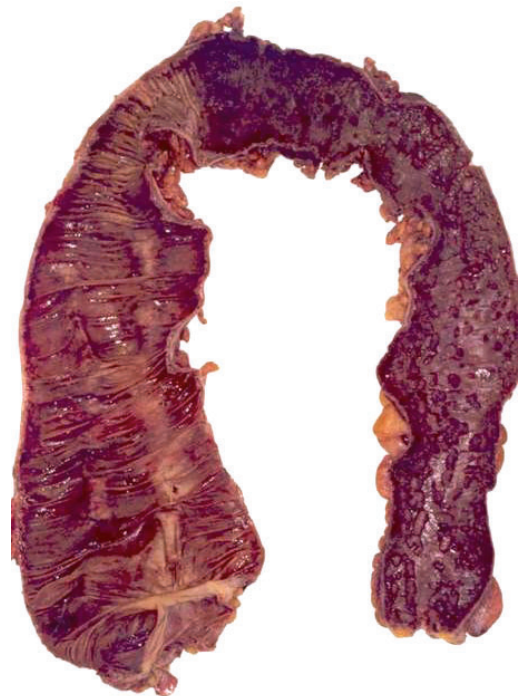


**Figure 1.** A total colectomy specimen showing indeterminate colitis. There is continuous disease more proximally with relative rectal sparing. The transverse colon is dilated with early 'toxic megacolon'. The involved areas show widespread ulceration.

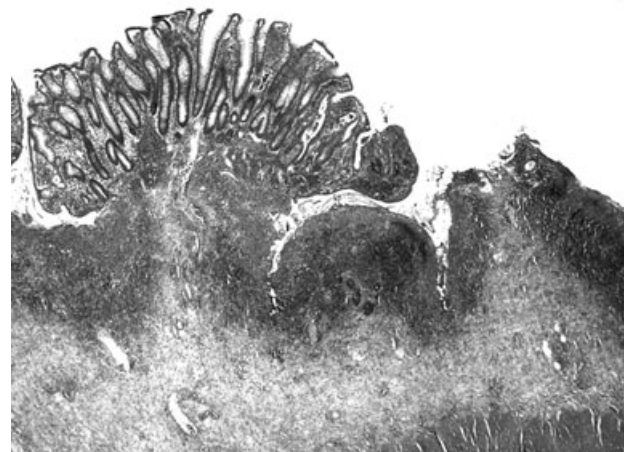


**Figure 2.** A total colectomy specimen showing indeterminate colitis. The transverse colon is notably dilated and there is extensive ulceration with the appearance of 'skip lesions'. The depth of the ulceration is evidenced by the fact that muscularis propria is discernible in the bed of the more extensive areas of ulceration, especially in the transverse colon.

infiltrate may be multifocal and may thus be misinterpreted as 'skip lesions'.<sup>38</sup> The intervening mucosa tends to be minimally congested and there may be a sharp



**Figure 3.** A total colectomy specimen showing indeterminate colitis (IC). Perhaps the features here might seem to favour ulcerative colitis (UC), as there is continuous distal disease, but there is focal inflammation and ulceration in the proximal colon, producing skip lesions. There are few stigmata of chronic UC microscopically and this serves to sustain the designation of IC.



**Figure 4.** The microscopy of indeterminate colitis. There is extensive ulceration with typical superficial V-shaped fissures, parallel to each other. The surviving mucosal islands show modest stigmata of chronic inflammatory bowel disease.

transition to normal adjacent mucosa; this is often paradoxically healthy mucosa with no evidence of inflammation, crypt distortion or atrophy.<sup>12,29,39</sup>

**Table 2.** Morphological microscopic features seen in indeterminate colitis

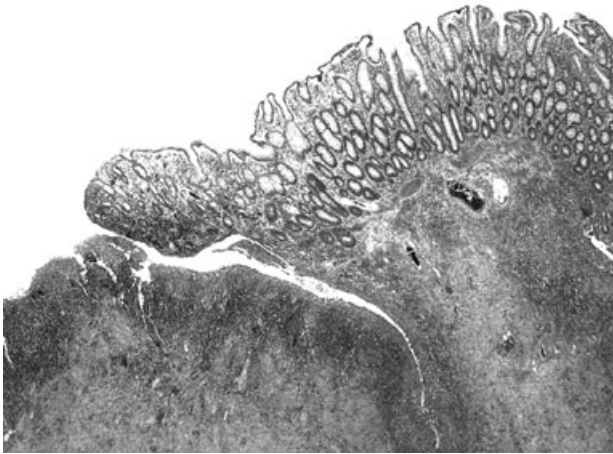
Extensive ulceration with a sharp transition to normal adjacent mucosa

Transmural lymphoid inflammation, with an absence of lymphoid aggregates

Absence of well-defined, epithelioid granulomas distant from crypts

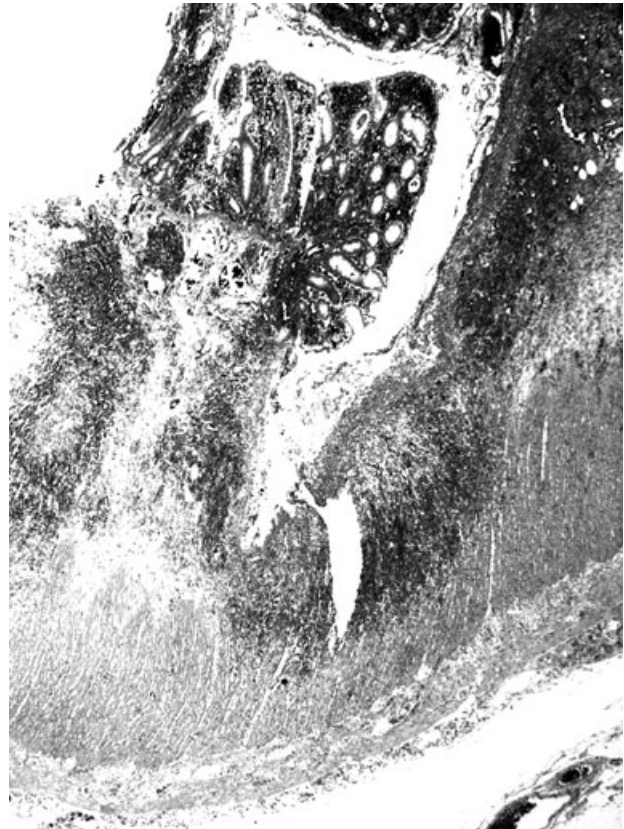
Multiple squat V-shaped ulcers, lacking surrounding inflammation<sup>3</sup>

Scanty deep penetrating slit-like fissures, described more recently by some authors as 'knife-like', spreading into the superficial half of the muscularis propria<sup>29,36,53</sup>



**Figure 5.** This case of indeterminate colitis shows undermining ulceration with fissuring beneath intact mucosa. The latter shows chronic inflammation but little crypt architectural change.

We have already affirmed that fissuring ulceration may be seen in IC and we have noted that a form of transmural inflammation, although not in the form of lymphoid aggregates, may also be seen in IC.<sup>3,35</sup> The third of the triumvirate of pathological features of CD, aside from fissuring ulceration and transmural inflammation in the form of lymphoid aggregates, is granuloma formation and, in fulminant cases of CD, the two most important factors in favour of that diagnosis are stated to be granulomas and lymphoid aggregates.<sup>40</sup> The usefulness of the presence of microgranulomas is more debatable.<sup>41,42</sup> Although, in Price's original dissertation, it was stated that granulomas do not occur in IC,<sup>3</sup> it has now become clear that the presence of granulomas does not exclude IC. Whilst the presence of transmural granulomas, well circumscribed and sarcoid-like, would suggest that the pathology is much

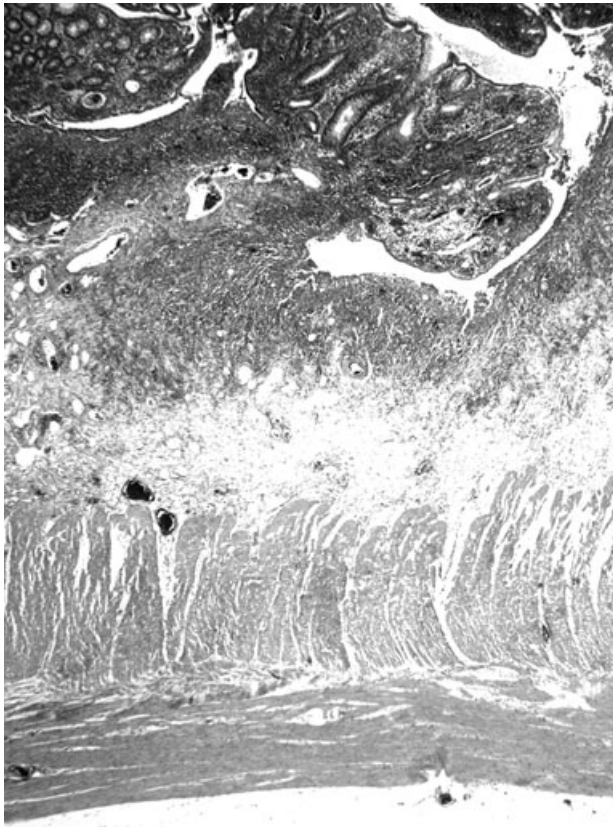


**Figure 6.** This indeterminate colitis case shows the second type of fissure with deep knife-like fissuring extending into the muscularis propria. There is evidence of an inflammatory reaction at the peritoneal surface because of impending perforation elsewhere.

more like that of CD, we would caution that the presence of mucosal granulomas, especially those adjacent to inflamed and disrupted crypts, is certainly not specific to CD, despite some suggesting that it may be,<sup>42</sup> and are well seen in both IC and, indeed, in classical UC.<sup>43,44</sup>

#### CATEGORIZATION OF IC

Some authors have advocated a subclassification of cases with IC-like features into three categories: (i) IC favouring UC, (ii) IC favouring CD and (iii) IC (unclassified, 'true' IC).<sup>25,31,45</sup> The parameters allowing categorization into each group have been variable and no pathological feature has been deemed entirely specific to one of these groups.<sup>25,31,45</sup> We believe that this categorization exaggerates the already subjective nature of the pathological analysis and, in the absence of standardization of criteria, we find the usefulness of this subclassification questionable. We thus cannot recommend such categorization for routine usage and have



**Figure 7.** A full-thickness image of the colon in a case of indeterminate colitis. There is extensive ulceration but there is no 'trans-mural inflammation in the form of lymphoid aggregates' that would be characteristic of Crohn's disease.

never used it in our practice. As well as further confusing an already difficult area, it may also have untoward clinical consequences for the patient, in that a surgeon may be reluctant to perform an ileal pouch-anal anastomosis (IPAA) if there are putative Crohn's-like features, when all the evidence so far suggests that most patients with IC have favourable outcomes (see below).

### The differential diagnosis of IC

We have already indicated that IC is an inevitably heterogeneous patient group that includes those who may eventually be found to have either UC or CD, although most will be shown to be UC-like (see below). It is worth emphasizing the importance of a full diagnostic biopsy history. This, in itself, may provide useful evidence in favour of either UC or CD, as the disease may be less severe in those biopsies than in the resection specimen showing IC features and thus a definitive diagnosis of either type of CIBD may be more ascertainable in such biopsy material. All attempts

should be made therefore to review previous pathological material before making a definitive diagnosis of IC. This may provide difficulties if the patient has been referred from one hospital to another or has moved from a different area. The significant interobserver variation in histopathological diagnosis also makes diagnosis and subsequent management difficult.<sup>46</sup> Some centres have suggested a pathology-review approach, where a diagnosis is made after consideration by two pathologists, one a gastrointestinal specialist.<sup>47</sup>

### ULCERATIVE COLITIS

Whilst UC is classically considered to involve the rectum and distal colon in a diffuse and continuous fashion, there are certain situations where UC may appear patchy or segmental. This can give the false impression of a 'skip lesion' and might suggest a diagnosis of either CD or IC, the latter especially in cases where most of the features point to a diagnosis of UC but the skip lesions are confounding. In fulminant UC, the predominant impact of the disease is in the more proximal colon, in particular the transverse colon. This may give an impression of rectal sparing, a recognized feature of colonic CD. Fulminant UC is often associated with a variable intensity of inflammation throughout the colorectum, which can be confused with the characteristic skip lesions of CD.<sup>29,35,40</sup>

Treatment by enemas can accentuate apparent sparing of the rectum and lower left colon. Both oral steroids and sulphasalazine may also cause patchiness of disease. Topical and/or systemic treatment can lead to complete histological reversal of the morphological features of UC activity and even chronicity on biopsy.<sup>35,48-53</sup> So, floridly active UC treated with anti-inflammatory enemas can lead to notable amelioration of the disease in the rectum and sigmoid colon and thus apparent (relative) sparing of the distal colorectum. This may encourage the pathologist to label such a case erroneously as IC. Pathologists should be aware of any recent treatment when assessing IBD resection specimens. In paediatric practice, some discontinuous disease is a well-recognized feature of UC patients and relative rectal sparing is also a commoner feature in children with UC than in adult patients.<sup>53-56</sup>

The appendix may show involvement by UC and this may be discontinuous. This was previously considered a rare phenomenon, but now is thought to be relatively common, reported to occur in up to 86% of colonic resections.<sup>35,53,57-64</sup> Originally described as a 'skip lesion' of UC, such acute mucosal appendicitis in UC may occur with the proximal colon entirely normal: it is not, *per se*, a rationale for a diagnosis of IC.



**Figure 8.** A total colectomy specimen. This is ulcerative colitis (UC), in a 'substantial colitis' distribution with sparing of the ascending colon. However, the caecum also shows involvement. This is characteristic of the 'caecal patch' lesion of UC and does not merit the alternative designation of indeterminate colitis.

Similarly, a small cohort of UC patients, with left-sided disease, may demonstrate involvement of the caecum and/or proximal ascending colon, whilst the distal ascending colon and transverse colon are spared. The term 'caecal patch' is used for this occurrence, encompassing the inflammation seen in both the caecum and the proximal ascending colon (Figure 8).<sup>35,65,66</sup> Like acute mucosal appendicitis, it is entirely acceptable to see such discontinuous pathology in UC and it, too, does not necessitate the alternative diagnosis of IC. Finally, backwash ileitis in UC must not be mistaken for terminal ileal involvement by CD or lead to the alternative diagnosis of IC because there are features 'atypical' for UC. Backwash ileitis occurs when severe colonic disease causes incompetence of the ileocaecal valve, leading to retrograde flow of colonic contents into the terminal ileum, with resulting inflammation. It occurs in up to 15% of UC colectomy specimens.<sup>35,53,59</sup>

#### CROHN'S DISEASE

In our experience, CD is over-diagnosed in the acute fulminant colitis setting. The usual microscopic indi-

cators of CD may be of little discriminatory value: linear ulcers and deep fissures are common in acute fulminant colitis, regardless of the cause.<sup>53</sup> Fissuring ulceration is well documented as occurring in IC and UC as well as in CD, although the nature of these fissures often differs (see above).

We have already emphasized that mucosal granulomas may be seen in IC and even UC, especially in reaction to inflamed and disrupted crypts. Transmural epithelioid cell granulomata speak in favour of a diagnosis of CD, as does classical transmural inflammation in the form of lymphoid aggregates.<sup>35</sup>

In the acute fulminant CIBD setting, we believe it is inappropriate to make a definitive diagnosis of CD in the absence of collateral evidence to support such a diagnosis. Too often the diagnosis is made on relatively scant evidence and this has very considerable implications for the patient, in terms of further management, in many centres disallowing subsequent pouch surgery, and future prospects, with considerable implications for future employment and insurance. Without definite features of CD, the appropriate diagnosis in cases of acute fulminant colitis is indeterminate colitis. Patients with CD will often present with more classical features, such as perianal disease or small intestinal stricturing pathology, allowing the diagnosis to be made then. However, most patients in this situation will have a relatively good prognosis, especially after pouch surgery.

#### INFECTIVE COLITIS

There is considerable overlap between infective colitis and CIBD, especially fulminant CIBD, and thus infection is an important consideration in cases adjudged to represent IC. Not only can infective colitis itself cause acute fulminant colitis, mimicking CIBD, but such infections can also trigger an initial attack of CIBD, which may itself be fulminating, and may also exacerbate established disease or induce relapses. Implicated infections, in this regard, are, logically, those that invade the mucosal surface, including *Clostridium difficile*, in the context of antibiotic-associated colitis/pseudomembranous colitis, *Shigella*, *Salmonella*, *Campylobacter*, enteropathogenic *Escherichia coli* and *Yersinia enterocolitica*. Amoebiasis, schistosomiasis, herpes simplex virus and cytomegalovirus can also cause a fulminant colitis or, in the case of the latter, can exacerbate established CIBD, causing an IC-like picture.<sup>6,35</sup>

Whilst histopathological analysis may be helpful in establishing infection as a cause of the pathology, in

many cases of acute fulminant 'colitis' excluding infection may be difficult. In up to 50% of patients it may not be possible to isolate a pathogen.<sup>10</sup> In the absence of evidence of infection, other causative agents, such as drugs (notably antineoplastic agents) should be considered as potential causes of acute fulminant colitis.<sup>6</sup>

#### DIVERSION PROCTOCOLITIS IN ACUTE FULMINANT CIBD

IC is inevitably a diagnosis made after total colectomy (or at least it should only be made at that time) and this operation is often completed by rectal diversion. When following up IC patients, one should consider the changes induced by diversion in the rectal stump, to avoid a postoperative misclassification of CD, which could deny the patient the advantage of a pelvic ileal reservoir (see below).<sup>53,67,68</sup> Diversion proctocolitis results in considerable additional inflammation in UC and IC patients with characteristic lymphoid follicular hyperplasia.<sup>69</sup> When the rectum is then excised, there may be intense mimicry of CD with transmural inflammation and even granulomas all well described.<sup>68,69</sup> If the changes seen in the colectomy specimen are equivocal and thus labelled IC, the pathologist may be tempted by the changes seen in the rectum to make a definitive, but ultimately erroneous, diagnosis of CD. Once again, an open mind on the appropriate diagnosis is appropriate in this situation, not least to save surgeon and patient considerable angst in this postoperative period.

Curiously, diversion of the rectum may also yield clues as to the final diagnosis. Severe inflammation, with the mimicry of CD-like changes, characterizes the diverted rectum in UC patients and may also be seen in IC, whereas inflammation in CD has a tendency to regress or even resolve with diversion of the faecal stream.<sup>12,35,70</sup>

### Clinicopathological correlations and implications

IC remains a useful and indeed valuable concept in terms of management of CIBD, when strictly applied to colectomy specimens only. Despite an initial diagnosis of IC, the nature of the underlying colitis often becomes evident as time progresses. Clues to the correct diagnosis may be found in previous or subsequent biopsy specimens. Careful follow-up of the diverted rectum is often helpful, with CD often recovering from diversion, but UC often exacerbated.<sup>26</sup>

**Table 3.** A comparison of pouch complications in indeterminate colitis (IC) and ulcerative colitis (UC) patients in large series of pouch surgery (in chronological order)

	Patient numbers IC/UC	Pelvic	
		abscess and/or sepsis (%) IC/UC	Pouch failure (%) IC/UC
Pezim <i>et al.</i> 1989† <sup>94</sup>	25/489	8/4	8/4
Koltun <i>et al.</i> 1991* <sup>37</sup>	18/235	–	28/0.04
Atkinson <i>et al.</i> 1994 <sup>47</sup>	16/158	25/1	19/5
Foley <i>et al.</i> 1995* <sup>86</sup>	31/366	–	6.5/1.4
McIntyre <i>et al.</i> 1995† <sup>71</sup>	71/1232	7/5	19/8
Yu <i>et al.</i> 2000† <sup>72</sup>	82/1437	17/7	27/11
Delaney <i>et al.</i> 2002‡ <sup>95</sup>	115/1399	9.7/2.2	3.4/3.5
Rudolph <i>et al.</i> 2002 <sup>30</sup>	35/71	–	0/6
Dayton <i>et al.</i> 2002 <sup>28</sup>	79/565	0/1.1	2.5/1.2
Gramlich <i>et al.</i> 2003‡ <sup>45</sup>	115/231	8.7/2.2	1.7/2.1
Pishori <i>et al.</i> 2004 <sup>11</sup>	13/285	15.3/6.3	0/2.1
Brown <i>et al.</i> 2005 <sup>96</sup>	21/1135	19/2	10/6

\*†‡These represent series from the same centres. There may be some overlap of cases.

#### NATURAL HISTORY OF IC

Of cases of IC diagnosed at colectomy, as many as two-thirds to 80% of patients will eventually be reclassified as either UC or CD.<sup>25,27,38</sup> Of these, >80% will behave like UC, if there are no features prior to operation to suggest CD.<sup>71,72</sup> In the major series, between 1% and 15% of IC patients are ultimately diagnosed as CD (Table 3).<sup>28,71–75</sup> An eventual diagnosis of CD may be more likely if patients present with fever at onset of their symptoms, have segmental endoscopic lesions or extraintestinal complications or are current smokers.<sup>30</sup> Conversely, UC as a subsequent outcome is decreased in those with appendectomy before diagnosis.<sup>76</sup>

#### IC AND POUCH SURGERY

Pouch surgery involves the removal of all (or nearly all) the diseased colorectum, preserves normal defaecation and provides acceptable continence, obviating the need for a permanent ileostomy. It is most commonly

performed for patients with UC and there is now good evidence for its indications and long-term prospects for patients diagnosed with IC. First described by Parks and Nicholls in 1978,<sup>77</sup> the operation involves total colectomy and proctectomy with the pouch fashioned out of ileum, which is then anastomosed to the anus, creating the IPAA, the term by which the operation is most commonly known today. In the earlier operations, a rectal mucosectomy was performed, removing all the at-risk mucosa. However, better functional results occur with a double-stapled anastomosis to the top of the anal canal, although this involves a risk of leaving potentially diseased lower rectal mucosa.<sup>69</sup>

It is important to understand, in any dissertation concerning IC, that pouch surgery is carried out in up to three stages. IPAA may be performed immediately after proctocolectomy. IC may be diagnosed by the pathologist on examination of the resection specimen but, then, the pouch has already been constructed. Attaining the correct diagnosis is of more importance in the two- and three-stage procedures when the initial operation involves total colectomy with the diverted rectum left in place and the ileal pouch not yet constructed. This leaves time for the pathologist to analyse the colectomy specimen. A diagnosis of CD at this time may well be a contraindication to pouch surgery, whilst diagnoses of UC and IC should allow such surgery. The only difference between the two- and three-stage procedures is whether a covering ileostomy is used after ileal pouch construction and pouch-anal anastomosis to protect the anastomosis lines.

The histological diagnosis of the colectomy specimen is crucial for subsequent management. If UC is present, then IPAA is performed, whilst in CD this is usually (but not always, depending on the centre concerned) contraindicated due to the increased risk of complications. It has been shown that more than one-half of CD patients will experience recurrence of CD in their pouch and there is an unacceptably high pouch failure rate.<sup>28,73,74,78,79</sup> These failures are due to disease recurrence, fistulas, abscesses, strictures and, ultimately, a higher incidence of pouch failure which reaches 45%.<sup>74,78–86</sup>

Some studies suggest that outcome depends upon the distribution of the disease prior to operative procedures. Comparable results have been seen in UC and CD patients, when the CD patients were chosen with the criteria of having neither perianal or small bowel disease.<sup>73</sup> One study found comparable results in patients who underwent restorative proctocolectomy with a preoperative diagnosis of colonic-only CD.<sup>87</sup> Thus, in conclusion, pouch surgery can be recommended in some cases of CD, although the

patient must be counselled about the high rates of potential complications.<sup>73,88–90</sup> Many cases of CD will have ano-perineal disease and, in them, IPAA remains contraindicated.

The diagnosis of IC, especially with the uncertainties surrounding its very name, may inhibit surgeons from undertaking pouch surgery, presumably because they are worried about the increased risk of complications if the disease process turns out to be CD.<sup>91</sup> However, there is now substantial evidence from large series in the literature (Table 3) that, on the whole, IC patients do much better with ileal pouches than those with CD and have a long-term success with such surgery much more equivalent to that in UC patients.<sup>76</sup>

Earlier studies comparing IC and UC patients with IPAA showed a low rate of complications in UC, compared with a higher complication and pouch failure rates in IC.<sup>37,47,67,72,92</sup> The causes of the pouch failure were fistulation, pelvic sepsis or both.<sup>93</sup> However, six more recent studies of IC have shown similar long-term functional results to UC patients with pouch failure rates of between 3% and 10%, almost identical to that of UC patients (Table 3).<sup>11,28,30,45,94–96</sup> The change may reflect gradual changes in pathological diagnosis, with pathologists now more likely to make a diagnosis of acute fulminant UC, especially with the recognition of such phenomena as 'skip lesions' and discontinuous inflammation as being *bona fide* accompaniments of classical UC.

However, whilst the IPAA procedure is generally considered successful in IC patients, there is an undoubted increase in incidence of pelvic sepsis and/or fistulae.<sup>30,31,67,72,95,96</sup> More recently, it has been suggested that certain types of IC, those with superficial fissuring-type ulcers, may also be associated with an increased risk of pouchitis.<sup>36</sup>

Overall, current opinion is that IC patients are appropriate candidates for IPAA, although they should be counselled as to the increased complication rates compared with classical UC (Table 3).<sup>85,93</sup> The differing natural histories of the three major types of CIBD diagnosed at the time of colectomy, UC, IC and CD, underpin the importance of accurate pathological assessment of those specimens, whilst ensuring that all other information, from previous clinical, endoscopic, histopathological, microbiological and imaging investigations, is also available to the pathologist to maximize the diagnostic accuracy.

## IC, ancillary tests and the future

In an ideal world, we would foresee the term IC being abolished, as new diagnostic techniques enable a

definitive diagnosis to be made at the initiation of the disease process. Some promising techniques are emerging which will perhaps lead the way towards the unravelling of this diagnostic conundrum.

#### SEROLOGICAL MARKERS

Current theories suggest that IBD is the result of an aberrant immune response to gut bacteria in a susceptible individual, with that susceptibility governed by some known, and some unknown, genetic predispositions. Increased levels of various antibodies directed against bacterial components and cross-reactive antigens reflect this. Potential serological markers for IBD are thus rapidly increasing, opening avenues, as one gastroenterologist quipped, to determine the indeterminate.<sup>97</sup>

The oligomannan anti-*Saccharomyces cerevisiae* antibodies (ASCA) and perinuclear antineutrophil cytoplasmic antibodies (pANCA) have been most studied. In one study, a ASCA+/pANCA- phenotype predicted CD in 80% of patients with IC and a ASCA-/pANCA+ phenotype predicted UC in 63.6% of patients with IC.<sup>98</sup> A fact which may itself reflect a distinct clinicoserological entity is that 48.5% of patients do not show antibodies against either ASCA or pANCA.<sup>98</sup> Whilst some subsequent studies have cast doubts over the usefulness of these markers, many have concurred with the original findings.<sup>99-103</sup>

Molecular studies amplifying *Yersinia* DNA from CD resection specimens have shown up to 31% positivity. However, further studies are needed to determine whether the presence of *Yersinia* DNA is an epiphenomenon or a feature of CD pathogenesis.<sup>104,105</sup> New groups of bacterial antigens such as I2 (from *Pseudomonas fluorescens*), OmpC (outer membrane porin C of *E. coli*) and flagellin have also been described in CD.<sup>101,106</sup> Pancreatic antibodies are also present in the serum of more CD than UC patients.<sup>101</sup>

A panel of markers (ASCA, pANCA, OmpC and I2) may be a useful prerequisite to surgery, especially where pouch formation is considered. For example, a significantly higher incidence of continuous pouch inflammation has been described in those IC patients with a particular antibody reactivity profile.<sup>107</sup> The main difficulties with serological markers are the lack of specificity and standardization.<sup>101</sup> The discovery of these markers, associated not only with disease type but also with susceptibility and in some cases with prognosis, has led to the proposal for an integrated approach of CIBD classification.<sup>16,17</sup>

#### GENETIC TECHNIQUES

There has been extraordinary progress in our knowledge and understanding of the genetics of CIBD in the last decade. In 2001, CD was shown to be associated with variants of the gene *CARD15/NOD2* on chromosome 16, the gene product of which is involved in controlling the gut inflammatory response to bacteria.<sup>108,109</sup> Mutations in this gene are almost always associated with small-bowel CD and thus its usefulness, with regards to IC, is questionable, despite some UC patients also having *CARD15/NOD2* variants.<sup>110</sup> The contribution of the HLA region, which has been widely studied, shows low sensitivity and specificity for CD and UC. Other genes still being evaluated include the *IBD5* region, multidrug resistance 1 (*MDR1*), drosophila discs large homologue (*DLG5*) and toll-like receptor 4 (*TLR4*).<sup>16,17</sup> Although it is very early days, such genetic analyses have considerable potential so that, in the future, we may have much more rigorous technology than we do currently for the subclassification of CIBD.<sup>16,17</sup>

#### UPPER GI ENDOSCOPY AND HISTOPATHOLOGY

Upper gastrointestinal endoscopy, with evaluation of gastric biopsies for focally enhanced (or focal active) gastritis (FEG), has been advocated in the diagnostic work-up of a patient with suspected or equivocal CIBD, as the demonstration of FEG is said to make a diagnosis of CD more likely.<sup>111</sup> However, some have found that such changes have a low sensitivity and specificity for CD<sup>112</sup> and it should also be noted that gastro-duodenal involvement may occur in UC, especially in children pre-colectomy.<sup>113-118</sup> Increasing use of capsule endoscopy for the assessment of the entire small intestine may be valuable in equivocal cases.<sup>17</sup>

#### Recommendations

- Restrict the term 'indeterminate colitis' to CIBD pathological features present at colectomy (macroscopically and microscopically).
- Remember that 'indeterminate colitis' is a temporary term, to be used until a diagnosis of either UC or CD is established.
- Never label biopsy cases as 'indeterminate colitis'. These should be classified as 'equivocal CIBD', 'non-specific CIBD', 'unclassified CIBD' or 'inflammatory bowel disease, type unclassified' (IBDU).
- Refrain from subclassifying IC, as this further complicates matters and can mislead clinicians.

- Do not deny IC patients reconstructive surgery such as pouch surgery, as the overall failure rate is similar to that of UC, but careful preoperative assessment to exclude CD is essential.
- Await further research, particularly genetic and molecular analysis, to enable better differentiation of CD from UC and ultimately (hopefully) abrogate the need for the term 'indeterminate colitis'.

## Conclusion

Ultimately we recognize that clinically, endoscopically and pathologically, colorectal CIBD represents a spectrum of disease with classical UC and CD at either ends of that spectrum. What we recognize as IC in colectomy specimens and IBDU (or equivocal/non-specific CIBD) in colorectal biopsies both lie in the middle ground but are certainly not the same disease. Whilst advances in serological assays and in molecular and genetic biology show some promise and may assist in the clarification of the type of CIBD in individual cases, it may be that these technologies reinforce the concept of this spectrum and that we shall continue to encounter CIBD cases with equivocal features.

It seems that pathologists are reluctant to make a diagnosis of IC, perhaps because they perceive that such a diagnosis may be interpreted as an indicator of their own diagnostic uncertainty. In the second opinion practice of one of the authors (N.A.S.), IC is often the diagnosis ultimately made, as even 'expert' gastrointestinal pathologists cannot necessarily differentiate between UC and CD in fulminant colitis cases. It must be emphasized, therefore, that IC may be an entirely appropriate diagnosis and should not be perceived as a reflection of the quality of the pathological assessment. Pathologists must accept that diagnostic equivocation may well be appropriate and there is now sufficient evidence, from the literature, to guide pathologist, surgeon and patient to the relevant management in the majority of cases of acute fulminant CIBD.

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