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Workshop

Pouchitis

The following presentations were given at the Workshop on Pouchitis which took place at St. Mark's Hospital, London, on 27 January 1989. A brief account of discussions which took place is also included.

Presentations

The pathology of the ileal reservoir
N. A. Shepherd

Pouchitis – Incidence and characteristics in the continent ileostomy
L. Hultén

The role of endoscopy in pouch monitoring and pouchitis
G. N. J. Tytgat

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Bacteriology I
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Introduction

R. J. Nicholls

Pouchitis is a problem which those of us who have done pouch surgery will have come across and had to do our best with, and we really know very little about it. I suspect that we do not yet have a proper definition of it and perhaps this day, which I hope will comprise as much discussion as presentation, will give us some basis, certainly in terms of a definition which will allow us in the future to be able to study it in different units talking the same language and using the same definitions. This really is the purpose of this meeting.

It is my great pleasure to welcome three people from outside the United Kingdom as speakers, Professor Guido Tytgat from Amsterdam, Professor Leif Hultén from Gothenburg and Dr. Ronan O'Connell from Dublin. All three of them are very involved with pouch work and Dr. O'Connell has been at the Mayo Clinic so we can have some of his impressions and information from the work he did over there. In addition, I would like to welcome Professor Brummelkamp.

I would also like to thank the companies who have supported this meeting. Smith Kline & French, Squibb Surgicare and Pharmacia have all generously funded and supported the visitors from abroad and also the refreshments during the day.

The pathology of the ileal reservoir

N. A. Shepherd

Restorative proctocolectomy with ileal reservoir is a surgical procedure of increasing importance [1]. The operation is undertaken in patients with diffuse mucosal disease of the large intestine: most patients have ulcerative colitis whilst a small percentage of operations are performed on patients with familial adenomatous polyposis (FAP). The pathological features discussed in this article are based on a study of 160 patients who have undergone restorative proctocolectomy with ileal reservoir at St. Mark's Hospital, London. All of these patients are under rigorous follow-up and sigmoidoscopic biopsies of the reservoir mucosa are taken at least once a year. Some of the findings described in this paper relate to a smaller cohort of patients, 92 in number, who were extensively investigated in a systematic functional and pathological study [2, 3].

The creation of an ileal reservoir with ileo-anal anastomosis is complicated by chronic inflammatory changes in the mucosa of the reservoir in the majority of patients. The infiltrate in the lamina propria includes all cell types associated with chronic inflammation; lymphocytes, plasma cells, eosinophils and histiocytes. These changes are usually associated with villous atrophy, varying from minor irregularities of villous architecture to subtotal villous atrophy (Fig. 1). The inflammatory infiltrate and villous atrophy may vary in sequential biopsies and even within the same biopsy. However when significant acute inflammation is present, there is usually extensive subtotal villous atrophy. Villous atrophy is always accompanied by crypt hyperplasia. The mucosa may resemble that in coeliac disease: the pouch mucosa, however, lacks the high intra-epithelial lymphocyte count of the small intestinal mucosa in coeliac disease. Pyloric metaplasia is present in a small percentage of reservoirs and usually occurs in pouches with previously documented acute inflammation. It may therefore be a useful marker of previous inflammation, particularly pouchitis. The histological changes of mucosal prolapse are a not unexpected finding in a small proportion of biopsies. In very occasional biopsies, well formed epithelial cell granulomas are seen. Granulomas may be seen as a consequence of histocytic reaction to foreign material after superficial ulceration. It should be emphasised therefore that granulomas in the pouch do not necessarily indicate a diagnosis of Crohn's disease.

At St. Mark's Hospital a system for grading the histological severity of both chronic and acute inflammation in the mucosa of ileal reservoirs has been introduced [2]. Polymorph infiltrate and ulceration are used as parameters of acute inflammatory change: chronic inflammatory cell infiltrate and villous atrophy are those for chronic change. These changes are graded from 0 to 6. In our studies there are no significant differences in the chronic inflammatory scores between reservoirs created for ulcerative colitis and those in FAP patients, and there are no detectable differences in inflammatory scores for the different reservoir designs. A patchy superficial acute inflammatory cell infiltrate in the epithelium is not uncommon in pouches of both ulcerative colitis and FAP patients: scores for acute inflammation correlate with the degree of macroscopic inflammation seen on sigmoidoscopy and with the frequency of defaecation. Extensive acute inflammtory cell infiltration, with crypt abscesses and ulceration, corresponds to the clinical condition of pouchitis (Fig. 2). Reservoirs in ulcerative colitis patients show a highly significant increase in acute inflammatory scores compared with those in FAP patients. Furthermore pouchitis has only been described in patients with a previous diagnosis of ulcerative colitis [4].

In a high proportion of reservoirs, the combination of villous atrophy and inflammation creates a histological appearance that is reminiscent of chronic ulcerative colitis (Fig. 1). Mucin histochemical studies have demonstrated a change from small intestinal type goblet cell mucin to colorectal type mucin in about half of the reservoirs studied [3]. This mucin change has been seen in both ulcerative colitis and FAP patients. Both the morphological and histochemical changes in the reservoir mucosa appear to be the direct result of creation of the reservoir. These features suggest that the pouch is undergoing a form of colonic metaplasia. This 'colonisation' may have major implications: there may be a propensity to dysplasia and carcinoma in ulcerative colitis patients and to adenoma and carcinoma development in FAP.

The aetiology of pouchitis is still uncertain. There is no evidence to implicate specific bacteriological changes or functional abnormalities such as stasis. It has been suggested that pouchitis is the result of chronic mucosal ischaemia in the reservoir although many would dispute this theory. Clinical and pathological studies have shown that acute inflammation is more marked in ulcerative colitis reservoirs and that pouchitis only occurs in this group [4]. A hypothesis for the pathogenesis of pouchitis is that the creation of a neorectum which becomes further modified by a process of colonic metaplasia creates an environment which favours

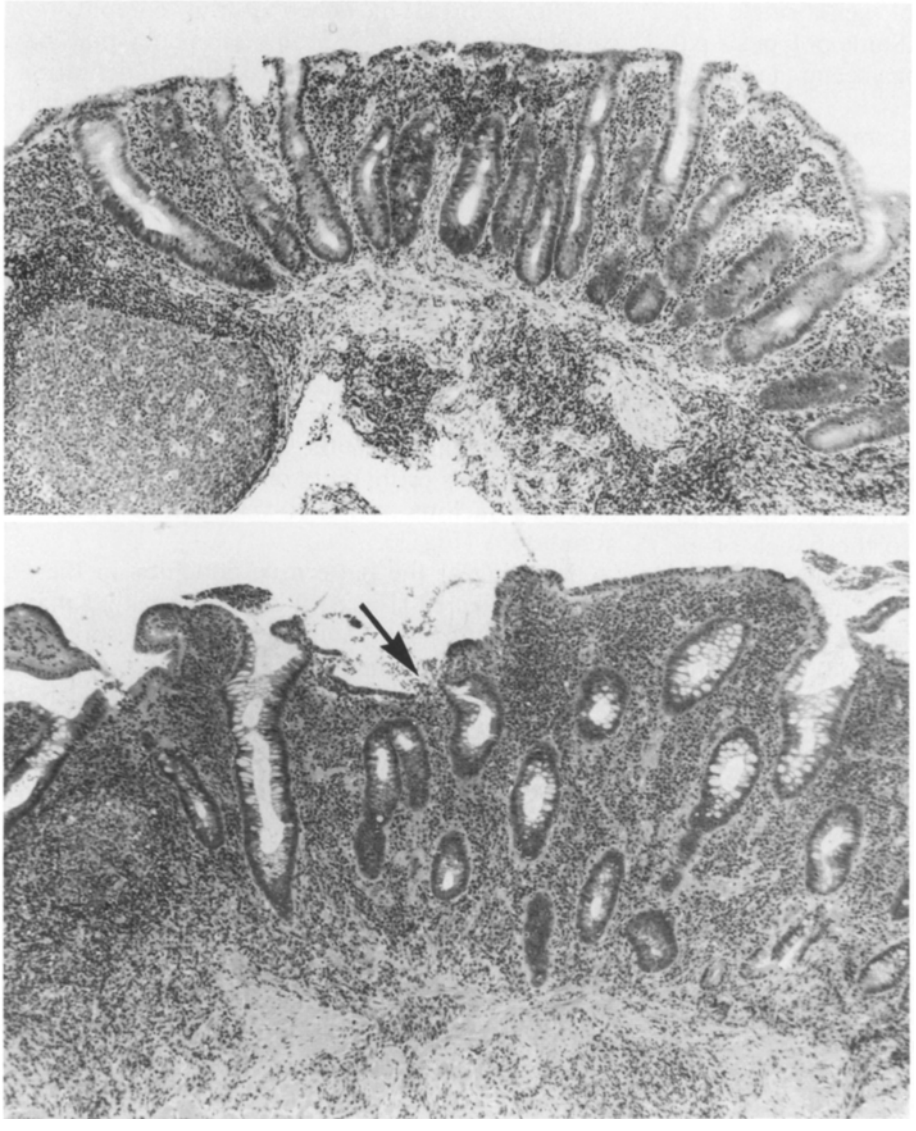

Fig. 1. Pouch mucosa from an ulcerative colitis patient. There is subtotal villous atrophy and a moderate chronic inflammatory infiltrate in the lamina propria. The appearances closely resemble those of inactive chronic ulcerative colitis in colonic mucosa. There is a prominent lymphoid follicle left. H & E ×100

Fig. 2. Pouch mucosa from a patient with pouchitis. There is subtotal villous atrophy, a dense chronic inflammatory infiltrate in the lamina and several incipient crypt abscesses. There is a small area of superficial ulceration (arrow). H & E ×100

the development of an ulcerative colitis-like condition in the ileal reservoir. If this thesis is correct, the reservoir may well prove a useful human model for studies of the aetiology and pathogenesis of ulcerative colitis.

Discussion

Professor Keighley (Q.): What about focal variation in biopsies?
Dr. Shepherd (A.): We haven't specifically studied this but there is no doubt that histological changes can be focal from looking at multiple biopsies taken at the same time.
Professor Keighley (Q.): How do the histological appearances change with time?
Dr. Shepherd (A.): Inflammation seems to come and go as judged by biopsies taken at intervals over a period of time. This appears to be irrespective of treatment.
Dr. Morson (Q.): Is it worthwhile for the pathologist to report whether he thinks the pouchitis is active or inactive?
Dr. Shepherd (A.): Yes, we do this routinely. The grading system gives an idea of activity. This relates significantly with endoscopic appearances.
Dr. Morson (Q.): Does pouchitis not occur in polyposis?
Dr. Shepherd (A.): As far as we can see, no. We need a definition of pouchitis which involves clinical and histopathological features.
Mr. W. H. F. Thomson (Q.): Has dysplasia occurred in the pouch?

Dr. Shepherd (A.): We have not seen a single case of dysplasia in a colitic pouch. Some polyposis patients have adenomas but this has been regarded as part of the disease.
Dr. O'Connell (Q.): Is it truly a pouchitis or could it be a distal ileitis that these patients get? Are changes confined to the pouch or do they go more proximally?
Dr. Shepherd (A.): I do not know.

Pouchitis – incidence and characteristics in the continent ileostomy

L. Hultén

With the introduction of the continent ileostomy in 1969, a new syndrome appeared caused by a mucosal inflammation restricted to the pouch or extending sometimes also into the adjacent intestine. This disorder which has been called mucosal enteritis, pouch ileitis or simply pouchitis is characterized by episodes of crampy pain, diarrhoea with liquid, bloody foul-smelling faeces and general malaise. When severe the pouchitis may be associated with systemic manifestations such as weight loss, fever and arthralgia.

Endoscopically the mucosa is reddened, granular, friable, with contact bleeding with pin point superficial patchy or linear ulcerations. The histological picture is that of an unspecific acute inflammatory reaction varying from mild to moderate or severe. Mucosal histology has been difficult to grade in an appropriate way and in my experience correlates poorly with the clinical picture. In fact, varying degrees of inflammation may be seen in asymptomatic patients undergoing pouch biopsy.

The need for frequent emptying is not due to increased faecal volumes per se. Decrease of pouch capacity or compliance in combination with an exaggerated motility are contributing factors as are also lowered sensory thresholds for pouch filling or urge.

Treatment of the pouchitis has not been systematically evaluated. Favourable responses have been reported with antibacterial agents such as vibramycin, salazopyrine, metronidazole or a combination of these. Local and systemic steroids may also be effective. Recurrent episodes are common however. Local cholestyramine, sucralphate have proved ineffective.

In severe therapy-resistant cases, continuous drainage of the pouch with parenteral nutrition or a defunctioning ileostomy may be needed. In other severe unresponsive cases resection of the pouch may be required.

The reported incidence of this complication varies between 5 and 25%, a discrepancy that may to a great extent be due to variability in definition. Another reason for the great variation in the pouchitis figures is the different numbers of patients investigated and the length of follow-up.

In my group we have defined pouchitis as episodes of increased stool frequency with watery and/or blood stained stools associated with urgency and an inflamed reservoir mucosa on endoscopy and with symptoms severe enough to require treatment. Today I am going to present results based on 84 patients followed for between 3.5 and 10 years. By using actuarial methods which compensate partly for the abovementioned errors the cumulative probability of developing a first attack of pouchitis over a 10-year period would be about 35% (Fig. 3).

Looking at the pattern of pouchitis in the 28 patients affected (Fig. 4) it can be seen that many patients had one single episode responding promptly on treatment, others had frequent episodes and a few continuous and/or severe pouchitis requiring more active long lasting medical therapy or a defunctioning ileostomy or resection.

More than half of the patients developed the first episode within 6 months postoperatively but there were a few patients who did not experience an attack until 2 or 3 years had elapsed (Table 1).

There is little information on laboratory values in pouchitis. In a smaller series of my patients it was possible to compare routine laboratory tests during pouchitis with pre-illness status. While haemoglobin, TIBC and serum-albumin were mostly within normal there were gross abnormalities in sedimentation rate and serum-iron reflecting the severity of inflammation. Low serum-iron does not mean microcytic anaemia in these patients but rather infection. It is an acute phase reactant as reliable and sensitive as is seromucoid or haptoglobin.

The intestinal leakage of plasma proteins, known to occur over an inflamed mucosal surface, was also studied by in vivo labelling by intravenous injection of trace amounts of $^{51}CrCl_3$ measuring its faecal excretion. The median excretion was 3.5%

Table 1. Occurrence of first episode ($n=28$ patients)

	No. of pts	%
Within 6 months	16	57
Within 1 year	18	65
Within 2 years	24	85
Within 4 years	28	100

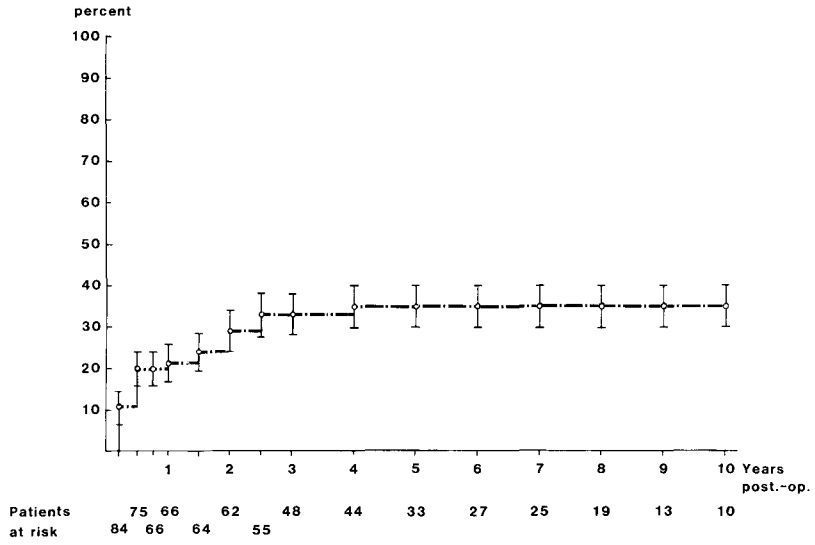

Fig. 3. The cumulative incidence in pouchitis in a group of 84 patients followed for up to 10 years

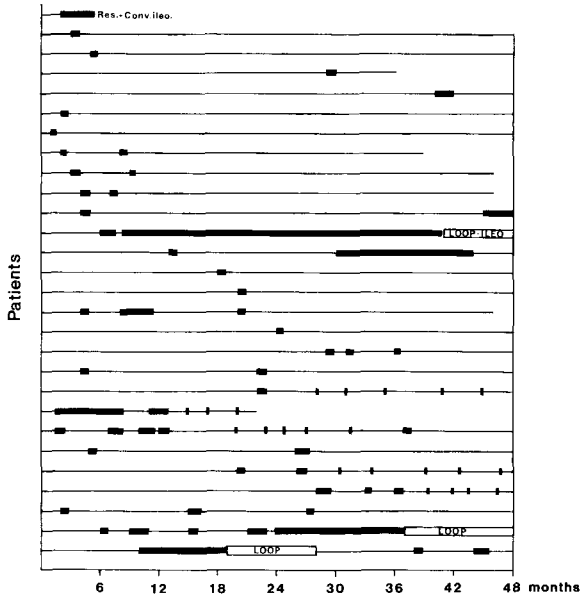

Fig. 4. The frequency and duration of pouchitis in 28 patients followed for 48 months. Loop = loop ileostomy

which is similar to that in conventional ileostomy patients with prestomal recurrence of Crohn's disease.

The aetiology of pouchitis is still unknown. In the search for that it may be important first to look at the consequences that are peculiar to the continent ileostomy.

Long-term consequences

The early changes in mucosal morphology of the Kock pouch involve a 50% reduction in villous height and a 4-fold increase in mitotic activity indicating an increased cellular turnover, findings that initiated speculations that the changes might represent a premalignant potential. Continued follow-up shows evidence, however, that the early changes may be transient only and that there is a tendency towards normal with time. Even in patients followed-up for 16 to 20 years it has not been able to demonstrate dysplasia. Whether the pouch mucosa is more sensitive and apt to develop inflammation is not known.

The bacterial flora in the continent ileostomy is more colon-like than that in a conventional ileostomy. More important is, perhaps, that the flora is constantly in contact with the ileal mucosa. It seems logical to ask whether the change to a colonic flora with increasing numbers of anaerobes bears a relationship to the development of pouchitis. Prompt response to antibiotics may speak in favour of a bacteriological factor, but good response may also be achieved with local steroids. Bacteriology is qualitatively and quantitatively the same in patients with and without pouchitis and bacterial cytotoxins have not been isolated. There is no proven relationship between pouch stasis or poor emptying and subsequent development of pouchitis.

Intestinal absorption in patients with continent ileostomy appears to be largely normal and similar to that in conventional ileostomy patients but there are two important differences in the pouch patients. Apart from defective B_{12} absorption there is an increased excretion of bile acids. Whether the bacterial contamination or the morphological

changes in the reservior contribute more to this malabsorption is not clear. Whether and if so to what extent B_{12} and bile acid malabsorption will be more severe during episode of pouchitis is not clear. Bile salts are known to be cytotoxic but whether they are responsible for the development of pouchitis is unknown.

Aetiology

There are reasons to suspect that neither bacterial overgrowth nor other metabolites are causative factors. At least not alone. Prompt response to broad-spectrum antibiotics, salazopyrine or metronidazole may speak in favour of a bacteriological factor. The mode of action of antibiotic treatment is not clear, however. Salazopyrine is a composite of salicylic acid and a sulphonamide. Is it the antibacterial or the anti-inflammatory component that is the prime beneficial factor? Metronidazole has also been suggested to have effects on the immunological system. An intriguing observation is that pouchitis is seen predominantly in patients where proctocolectomy has been done for ulcerative colitis, whereas patients with polyposis do not exhibit the syndrome, at least not as severely. Could it be that the local as well as systematic manifestations in pouchitis may be the result of immune complex formation? Could it be after all that ulcerative colitis, terminal ileitis, perhaps even backwash ileitis and pouchitis, is a single disease entity? Hypothetically the passage of faecal antigens across a permeable mucosa and their access to subepithelial lymphoid tissue, might reproduce the pathogenic mechanism of inflammatory bowel disease.

Discussion

Mr. Mortensen (Q.): Have you had patients with the Kock pouch who did not originally have UC and who developed a clinical pouchitis syndrome?
Professor Hultén (A.): We do not have very many familial polyposis cases in our clinical series but that among those 12 or 15 cases seen over a 10–15 years period we have not had this problem. A couple of years ago I wrote to units world wide with experience of the Kock ileostomy. None had observed pouchitis in the polyposis patients.
Dr. Shepherd (Q.): Have you seen adenomas in Kock pouches in patients with polyposis?
Professor Hultén (A.): Yes, there have been a few cases but again our experience is very limited as regards familiar polyposis.
Dr. Shepherd (Q.): Do you think that they are increased over what you would expect in normal ileal mucosa?
Professor Hultén (A.): I don't know.
Mr. Nicholls (Q.): Were some of those pouchitis patients ultimately identified as being cases of Crohn's disease?
Professor Hultén (A.): Not very often. We have always taken special care to exclude Crohn's disease. The majority of patients are converted after previous conventional proctocolectomy, so the entire specimen is available for pathological examination. Probably it is a safer way to get an accurate diagnosis. Somebody asked whether pouchitis is confined to the pouch. I have to add then that in colitic patients with pouchitis, inflammation can extend up into the efferent limb. It is very difficult to get up with an endoscope and most examiners will miss these lesions. Fifteen years ago our pathologists were very sure in their diagnosis but today they are often confused and consider many of the changes nonspecific.
Dr. Morson (Q.): One of the things that I find remarkable about the disease we call ulcerative colitis is that, despite a long history of severe chronic inflammation, there is always a minimal fibroblastic response, and that also seems to be true of pouchitis. You don't get strictures, you don't get submucosal fibrosis, you don't get shrinkage of the pouch? Do you get fibrosis?
Professor Hultén (A.): I do not know exactly the frequency but the case is typical, namely the occurrence of a stricture of the efferent limb where it goes into the pouch. This seems to be a very isolated short stricture, and often associated with inflammatory reaction in the mucosa, proximally.

The role of endoscopy in pouch monitoring and pouchitis

G. N. J. Tytgat

Role of endoscopy in pouch monitoring

Endoscopy has a dual role in pouch monitoring. First of all, it is important in monitoring the healing process before closure of the protective ileostomy. Initially, the area of the anastomosis is severely inflamed and friable and some ulceration and swelling is seen along the suture lines. Later on, after two to three months, both the anastomotic

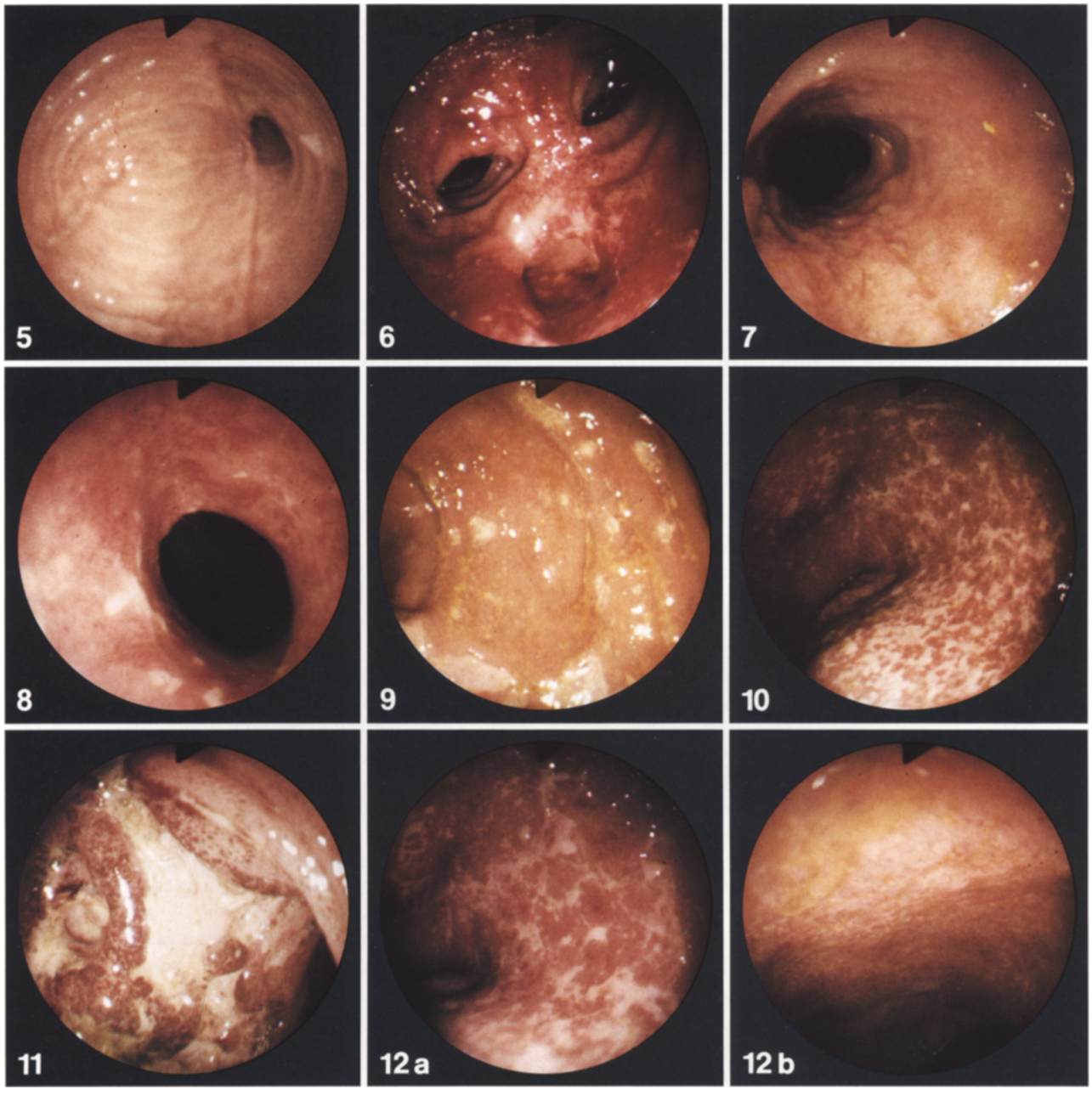

Fig. 5. Appearance of the pouch before ileostomy closure

Fig. 6. The differential diagnosis between severe pouchitis and ischaemia may be difficult; this markedly congestive haemorrhagic appearance is more compatible with ischaemia

Fig. 7. Appearance of the pouch soon after ilestomy closure

Fig. 8. Mild pouchitis with mainly swelling and erythema

Fig. 9. Pouchitis with erythema, swelling and spread-out superficial mucosal destruction

Fig. 10. More severe pouchitis with extensive superficial mucosal destruction and copious amounts of mucopurulent exudate

Fig. 11. Severe pouchitis with extensive deep mucosal ulceration

Fig. 12. **a** Pouchitis before medical therapy. **b** Apperance after therapy with metronidazole. Note the marked improvements of the endoscopic appearance

line and the suture lines have completely healed (Fig. 5). It has been our policy to close the ileostomy only after full endoscopic healing of the pouch. The normal small bowel mucosa has a clearly visible vascular pattern upon distension.

The mucosa is smooth and shiny and non-friable. Occasionally, tiny areas of highlighting may be visible, presumably corresponding to lymphoid follicles. In addition some rather opalescent milky-looking areas may be seen, again, presumably corresponding to lymphoid aggregates.

In some patients abnormalities may be detected which may delay re-anastomosis. One may see small fistulous openings along suture lines. A few weeks later, such fistulous openings usually have completely healed. More common is a partial dehiscence of the anastomosis. An extensive dehiscence of the anastomotic line leading to quite deep defects is rare. A very haemorrhagic aspect of the mucosa is presumably due to ischaemic changes in the pouch (Fig. 6). Ileostomy closure has to be delayed till full mucosal healing has occurred. We wonder whether prolonged rather severe inflammatory changes close to the anastomosis with rather slow healing of the suture lines may not be the expression of impaired micro-circulation.

The aspect of the pouch always changes as soon as the ileostomy is closed and faecal material enters the pouch (Figs. 5, 7). There are always some mild inflammatory changes both at the level of the anastomosis and in the pouch itself. The pouch mucosa becomes slightly swollen and somewhat redder in appearance. The Kerckring fold pattern becomes poorly visible or disappears entirely.

If one examines pouches in patients who are clinically completely well, there always are some minor abnormalities detectable, especially in patients who have had pouchitis in the past.

Endoscopy is very important in the diagnosis of pouchitis. Pouchitis remains a very significant source of postoperative morbidity. It may be seen in 10–20%, even up to 25% of patients, especially in those operated upon for chronic colitis and in those exhibiting extra-intestinal manifestations of their disease. These have led to speculation that pouchitis may actually be a further manifestation of inflammatory bowel disease. The pathogenesis of pouchitis, despite all recent hypotheses, is still poorly understood.

The criteria upon which the endoscopic diagnosis of pouchitis is based are the well known indicators of inflammation: swelling, erythema or redness, friability and petechial punctate haemorrhagic spots, excessive mucopurulent exudative areas and superficial erosive defects or larger ulcerative destruction of the mucosa. Mild pouchitis is characterized by discrete swelling of the mucosa around the anastomosis and in the pouch and some mild friability (Fig. 8). In others, there is obvious erythema, mucopurulent punctate exudate, some small defects and friability (Fig. 9). Occasionally, in slightly more severe forms spread-out small ulcerations, perhaps with some predilection for the mucosal folds may be visible. This appearance of the mucosa may readily mimic the abnormalities seen in Crohn's disease. We have the distinct feeling that far too often the diagnosis of Crohn's disease is reconsidered if surgical problems occur or if pouchitis develops. To some extent this is supported by the pathologists who are indeed rather uncertain and confused at the present time what to call ulcerative colitis and what to call Crohn's disease. Less common is striking erythema, petechial haemorrhages, diffuse inflammation, friability and superficial defects.

The spectrum of the severe forms of pouchitis is rather impressive and consists of striking diffuse erythema, formation of copious exudate and extensive superficial necrosis (Fig. 10). In other patients there is extensive deep ulceration surrounded by severe inflammatory changes of the mucosa (Fig. 11). Such severe changes occasionally occur only a few weeks after closure of the ileostomy. Such abnormalities may also mimic to some extent Crohn's disease. In some patients it may be difficult to distinguish pouchitis from ischaemic damage (Fig. 6). Initially there is severe congestion of mucosa. Later, serpiginous coalescent ulceration develops as one may see in ischaemic damage of the colon.

Endoscopy is also useful in monitoring the effects of therapy. Medical therapy includes metronidazole, drainage, if necessary irrigation and occasionally even steroids, systemically or in enema form, together with 5-aminosalicylic acid (Fig. 12a, b). Some patients with very severe pouchitis do not improve with metronidazole therapy only. Only after switching to corticosteroids and 5-aminosalicylic acid does gradual improvement in the endoscopic appearance occur.

In summary, pouchitis is a new disease, an intriguing medical problem for which endoscopy plays an essential role in the proper diagnosis and in monitoring the response to therapy.

Discussion

Professor Keighley (Q.): Well, we are absolutely thrilled with the pictures and I would like to ask how Professor Tytgat manages to get them. What about bowel preparation on these patients?
Professor Tytgat (A.): Just a saline enema 30 minutes before the examination.

Professor Hultén (Q.): The slides you showed with the nice vascular pattern, were all of them taken before you had closed the ileostomy?
Professor Tytgat (A.): Yes. Once the ileostomy is closed you never see the vascular pattern any more.
Mr. Marks (Q.): Have you had to ever give a patient with a pouch an ileostomy again and what happens to the pouch mucosa then? Do you have to give them back an ileostomy? Does it get better?
Professor Tytgat (A.): We have never performed an ileostomy for pouchitis only.
Mr. Mortensen (Q.): Someone was asking a bit earlier about the proximal ileum upstream of the pouch.
Professor Tytgat (A.): Usually it is normal but we have seen patients with severe pouchitis where there definitely was extension quite a long distance in the pre-pouch ileum.
Mr. Mortensen (Q.): Have you seen these sorts of dramatic changes in polyposis patients?
Professor Tytgat (A.): Never.
Dr. O'Connell (Q.): I think your data show that we can scotch the idea that a chronic ischaemia is responsible for much of the pouchitis as a hypothesis. It must be due to stasis with something that is causing an effect on the mucosa because of that stasis. When it is defunctioned it is normal, we have seen that, and you don't get the same changes. They are similar but they are not the same with chronic ischaemia. Would you agree with that?
Professor Tytgat (A.): Not entirely. I am not entirely convinced that we know after hooking up the ileostomy, whether the vascularisation of the pouch is optimal in these patients. I think there may be patients who are on the borderline and then, depending upon distension and other factors, mucosal perfusion may decrease critically.
Mr. Nicholls (Q.): Do you think you see a pouchitis before the ileostomy closure?
Professor Tytgat (A.): No.
Mr. Nicholls (Q.): So the changes that we might say were pouchitis before closure of the ileostomy you would consider as likely to be due to ischaemia.
Professor Tytgat (A.): The changes that we have seen so far before closure of the ileostomy we have interpreted as compatible with ischaemia.
Dr. Morson (Q.): Has there been a biopsy done on these patients?
Professor Tytgat(A.): I do not know. I concentrated on endoscopy and did not look at all the histology material.
Dr. Morson (Q.): If you think it is ischaemia a biopsy would be likely to show changes different from what have been illustrated as pouchitis.
Professor Tytgat (A.): It all depends at which time you take the biopsies, in the very early days or after the phase of sloughing.
Mr. Mortensen (Q.): How many of those completely resolved?
Professor Tytgat (A.): They all did.
Mr. Mortensen (Q.): There is always a nice, pink, healthy pouch in Amsterdam before closure of the ileostomy.
Professor Tytgat (A.): We aim for that.
Mr. Kmiot (Q.): In the case with extremely gross inflammatory changes there was no response to metronidazole. Since the patient responded slowly to steroids and salazopyrin, was this not occult Crohn's you were looking at?
Professor Tytgat (A.): Why should I think so? This patient has had bona fide ulcerative colitis with all the standard classical criteria. Why should I now reconsider and look for another disease because he has severe pouchitis? The literature is filled with this sort of reasoning.
Professor Keighley (Q.): It does occur. Would you not agree?
Professor Tytgat (A.): I have not seen one case. I doubt it very much. It is very, very rare.
Professor Keighley (Comment): We have two very well documented cases. There is no doubt that the histopathological changes in the excised pouch indicated Crohn's disease, despite the fact that review of all the previous sections, the colectomy, and the subsequent rectal excision suggested ulcerative colitis.
Professor Tytgat (Q.): Well, what did the pathology show on the excised pouch to be typical of Crohn's disease?
Professor Keighley (A.): Lesions which were typical of Crohn's disease. Granulomas, transmural inflammation, fissures, etc.
Professor Tytgat (Q.): But any diseased mucosa, depending on the intra-luminal pressure, can cause ulceration cracks and fissuring. I doubt very much that this is a true specific pathognomonic sign of Crohn's disease.

Clinical diagnosis

R. J. Nicholls

The reported incidence of pouchitis has ranged from less than 5% to over 50%. It seems very unlikely however that the criteria used by the various authors have been the same. Some degree of inflammation in the reservoir is very common and other circumstances, e.g. outlet obstruction, can

lead to frequency of defaecation. It is probable that when both are present, some may make the diagnosis of pouchitis. It is also possible that most colitics suffer a degree of low-grade pouchitis. Thus pouchitis has probably been over diagnosed.

Nevertheless certain patients manifest an obvious clinical syndrome which is associated with endoscopic and histopathological inflammation of a severe degree. The symptoms include frequency of defaecation, watery stool, sometimes malaise and occasionally an activation of extra-alimentary disorders, e.g. arthropathy if previously present.

The histological grading system developed by Neil Shepherd has enabled some objectivity to be introduced. Richard Moskowitz personally examined 55 patients by sigmoidoscopy and recorded on a scale 0–6 the degree of macroscopic inflammation. Two correlations emerged. Macroscopic inflammation score was firstly related significantly to the frequency of defaecation (Fig. 13). Secondly it was also related to the histological grade of acute inflammation (also graded 0–6) in biopsies taken at the same time as the sigmoidoscopic assessment. In this last correlation there was a cluster of six cases with both severe (Grade 4–6) macroscopic and histological inflammation who on symptoms alone had already been considered to have pouchitis (Fig. 14). This gives a prevalence of 11% in the series but as with the Kock reservoir there is likely to be a cumulative incidence with the passage of time. These findings led us to feel that pouchitis should be diagnosed only by a combination of clinical, endoscopic and histopathological criteria with severity of inflammation being the essential feature.

There appears to be an important distinction between acute and chronic inflammation, the former only being diagnostic of pouchitis. In a larger group of 90 patients (including 77 with ulcerative colitis and 13 with familial adenomatous polyposis), 78 (87%) showed some degree of chronic and only 27 (30%) acute inflammation. While cases with severe chronic inflammation tended to have acute inflammation also, only those with acute changes manifested symptoms.

Possible risk factors for pouchitis have been studied at the Mayo Clinic, Leeds and St. Mark's Hospital. These can be summarised as follows. No mechanical factor, e.g. type of reservoir, emptying properties or compliance, or the presence of quantitatively assessed bacterial species can be related to the condition. Indeed the only positive association is with the original diagnosis. Pouchitis is almost unheard of in patients with familial adenomatous polyposis, almost all cases occurring in those with ulcerative colitis. Even in the absence of pouchitis,

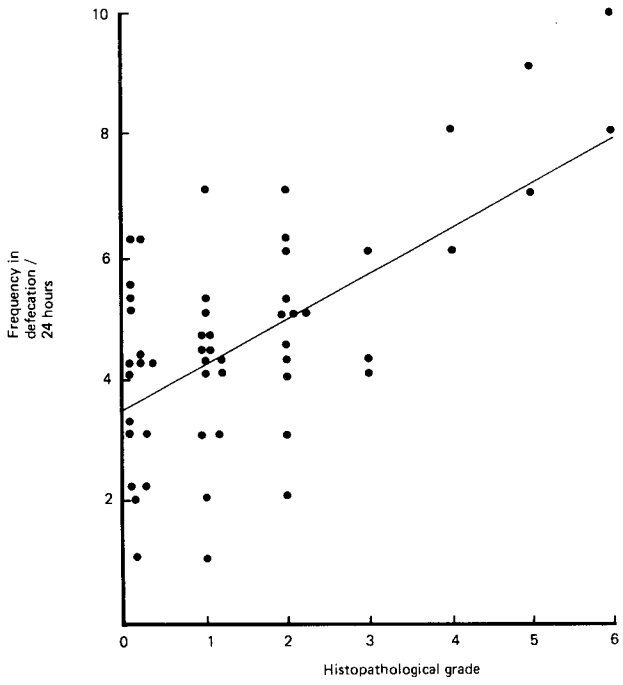

Fig. 13. Frequency of defaecation and histological grade of inflammation in 55 patients examined by one clinician. (Correlation coefficient of linear regression $r=0.65$; $p<0.001$)

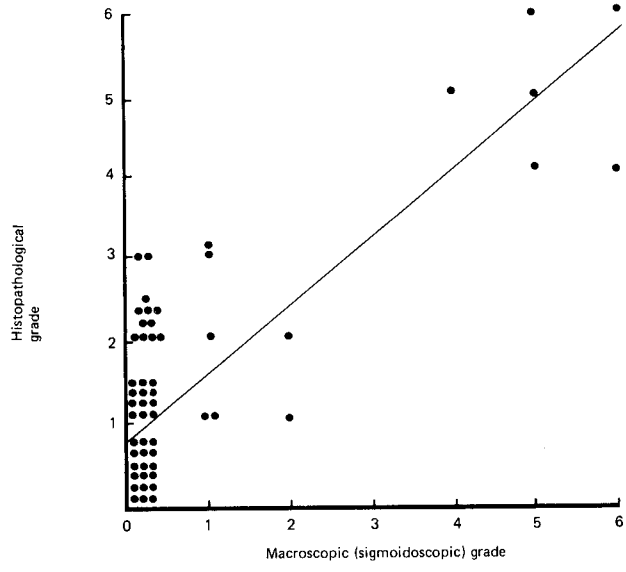

Fig. 14. Histological grade of inflammation and macroscopic grade on sigmoidoscopy in 55 patients examined by one clinician. (Correlation coefficient of linear regression $r=0.77$; $p<0.001$) (Figs. 13 and 14 taken from Moskowitz et al., Int J Colorect Dis 1:167–174)

colitics tend to have higher grades of histological inflammation in pouch biopsies. We also have evidence to suggest that patients who are most at risk are those originally having total rather than left sided colitis. In a study of 83 patients with ulcera-

tive colitis, there were 14 cases with pouchitis. All occurred in the 68 patients with total colitis and none in the 15 with left sided colitis. No correlation between pouchitis and backwash ileitis has been found.

Is pouchitis ulcerative colitis in the small intestine? There are the diagnostic correlations and similar histological appearances. Furthermore pouchitis seems to take the forms of a persisting chronic disorder or one that demonstrates exacerbations and remissions, similar to ulcerative colitis.

With regard to treatment the picture is confusing. There is no doubt that metronidazole can, sometimes dramatically, induce a remission. We do not however know how often it is effective or which type of patient is likely to respond. Are the failures of metronidazole treatment more likely to respond to conventional ulcerative colitis treatment? Again we do not know.

Our knowledge so far can be summarised as follows. Pouchitis should be diagnosed on the basis of clinical endoscopic and histological features, a histological grading system being strongly recommended. We are ignorant of its cause but a combination of disease-related susceptibility (UC), possibly with a bacteriological factor (response to metronidazole) should give useful clues. Treatment needs to be assessed through properly designed clinical trials.

Discussion

Professor Tytgat (Q.): Did you notice any correlation as to whether the patients had after elective or emergency colectomy developed pouchitis? What about the influence of postoperative pelvic sepsis?
Mr. Nicholls (A.): I cannot answer either question.
Mr. Marks (Q.): In the treatment of metronidazole, if it does not help what else have you tried?
Mr. Nicholls (A.): One tries steroids either locally or systemically but we do not know objectively how effective they are.
Mr. Mortensen (Q.): Can we ask Professor Tytgat about the newer kinds of salazopyrin substitutes? Is there any evidence they work better?
Professor Tytgat (A.): It does something. Primarily in the sense in passive therapy, it does something.
Mr. Mortensen (Q.): Especially when used in the form in which you can leave it in the pouch?
Professor Tytgat (A.): It is impossible to say that it is better, or equivalent to oral medication.
Dr. O'Connell (Comment): One of the patients I have come across responded to erythromycin, not to metronidazole.
Mr. Nicholls (A.): I think we desperately do need a proper clinical trial of several different agents in this kind of situation. You have got to have the patient base to start, though.
Mr. Mortensen (Comment): Getting a definition everybody agrees about, too. You have got to get that group of patients and everybody agrees about who they are.
Mr. Everett (Comment): I find augmentin as effective as metronidazole. I have several patients who need to take antibiotics more or less continuously, and they can get peripheral neuritis from metronidazole as you know, and so I have put them on augmentin. They take one tablet three times a day for a month and then reduce it, but they usually stay on just one tablet and that seems to suit them all right.
Mr. Nicholls (A.): There are some patients who, when you give them metronidazole get better and you stop it. Months later perhaps they get another attack. Other patients as indicated respond to the metronidazole agent but need to maintain a low dose therapy. There are other patients you try it on and nothing happens at all.
Professor Tytgat (Q.): Do you know of any study where lactobacilli have been used to try and modify the faecal flora?
Mr. Nicholls (A.): No.
Mr. Mortensen (Comment): Anecdotally, we have tried yoghurt every now and then.
Professor Tytgat (Q.): What sort of yoghurt?
Mr. Mortensen (A.): Active yoghurt.
Professor Tytgat (Q.): There are no viable bacilli. It is only certain brands of yoghurt which have live bacilli.
Mr. Mortensen (A.): It would be live.
Professor Tytgat (Q.): But there are now good preparations for the first time and you can truly modify the faecal flora with these newer products.
Mr. Nasmyth (Q.): In active ulcerative colitis there is a change in the pH of the stool. Has anybody looked at the pH of the stool in patients with pouchitis, and perhaps when they have recovered to see if there is any change there?
Mr. Nicholls (A.): Not that I know of.
Professor Keighley (Q.): Has anybody seen *Clostridium difficile* in pouches because we certainly have, and I am a little bit worried about longterm antibiotic therapy for that reason. It is interesting that the mucosa of these pouches does become colonified, and I suspect it is therefore an organ that can become affected by *Clostridium difficile* toxins.
Mr. Nicholls (A.): We do look for it. We have had one case with *Clostridium difficile*. He was quite ill

and finally lost the pouch. So we have had one case. We may well have missed others but we do look for it.

Professor Tytgat (Q.): In pouchitis defunctioning should cause it to heal up unless there is faecal contamination. If it does not then you should worry that something else is going on, for example chronic ischaemia or Crohn's disease. But normally a severely inflamed pouch, if you bypass stool and rinse it well, should improve.

Bacteriology (I)

D. G. Nasmyth

In the normal individual bacterial counts increase along the small intestine. In the ileum the ratio of anaerobes to aerobes remains approximately equal, although the type of anaerobic flora changes and there are increased numbers of Coliforms, Bacteroides and Clostridia [5]. The effect of further changes in the bacterial flora on the structure of ileal mucosa was investigated in patients who have undergone proctocolectomy for ulcerative colitis (conventional ileostomy $n=12$, pouch-anal anastomosis $n=11$).

Fourteen genera of faecal bacteria were identified and quantitated. Anaerobic bacterial fermentation of carbohydrate in the colon or ileum results in the production of volatile fatty acids (VFA). To determine whether there is a association between VFA and pouch mucosal change, faecal VFA from pouches and ileostomies were measured by gas liquid chromatography [6].

It might be expected that incomplete emptying of the pouch would be associated with an increased predominance of anaerobes and their metabolites in the pouch flora. This hypothesis was investigated by measuring the completeness of pouch evacuation with a synthetic stool labelled with ^{51}Cr sodium chromate [7].

Biopsies of ileal mucosa were taken at the same time as faecal samples. Four components of mucosal inflammation were assessed by scoring each on a scale from 0 (absent) to 3 (severe). Villous atrophy was assessed by measuring the ratio of mucosal surface length (MS) to the area of the lamina propria (LP) using the Kontron IBAS 1 image analyser [6].

When compared with faecal samples from ileostomies, those from pouches showed greater anaerobe predominance, and greater numbers of Bacteroides and Bifidobacteria. There were also greater concentrations of faecal propionate and butyrate in the pouches (Table 2).

Table 2. Concentration of organisms in faeces from patients with an ileal reservoir and permanent ileostomy

Median and range	Pouch	Ileostomy	
Anaerobes/aerobes *	100 (18 621–1)	4 (120–0.1)	
Bacteroides **	9.8 (0–11.9)	5.7 (0–10.1)	$\log^{10}$ cfu
Bifidobacteria *	8.7 (0–11.9)	0 (0–9.6)	$\log^{10}$ cfu
Propionate *	6 (0–10.4)	0.4 (0–10.7)	mmol/kg
Butyrate **	2.1 (0.4–29.2)	0.5 (0.1–15.6)	mmol/kg

* $p<0.05$; ** $p<0.01$

There was no significant correlation between the score for mucosal inflammation and the number of bacteria isolated, or the concentration of faecal VFA. However, the greater the number of Bacteroides the more severe was the villous atrophy ($r_s=-0.93$, $p<0.01$). Conversely, the higher the concentration of faecal butyrate the less severe was the villous atrophy ($r_s=0.68$, $p<0.05$). No association was demonstrated between the completeness of pouch emptying and faecal bacteria or mucosal change but the concentration of faecal propionate was higher in those pouches in which there was greater retention of ^{51}Cr ($r_s=0.82$, $p<0.01$) [6].

These associations do not demonstrate cause and effect, but they do suggest mechanisms by which bacteria may affect mucosal structure. Villous atrophy in the pouch has recently been shown to be associated with an increased crypt cell production rate. This study has shown that the higher the concentration of butyrate the less severe the villous atrophy; in other words a higher concentration of butyrate is associated with a lower turnover of epithelial cells. This fits in with studies in vitro in which butyrate has been associated with an arrest of cell proliferation [8]. It is also consistent with findings in the colon in which colonic neoplasia has been associated with low concentrations of butyrate [9]. It might seem paradoxical that the more severe villous atrophy should be associated with increased numbers of Bacteroides yet one of the products of anaerobic bacterial fermentation, butyrate, is associated with less severe villous atrophy. There is no paradox because very few species of Bacteroides produce significant amounts of butyrate, and it might be speculated that in vivo butyrate suppresses the growth of Bacteroides. The

association between pouch emptying and faecal propionate suggests that when the transit time of pouch contents is increased by incomplete emptying there is increased anaerobic fermentation, especially by bacteria that produce propionate.

Bacteriology (II)

M. J. Hill and F. Fernandez

Chronic inflammation in the reservoir occurs in almost every case; acute inflammatory changes, often severe and associated with diarrhoea (pouchitis) occur in some colitic patients but not in those with polyposis. The clinical features of pouchitis respond to metronidazole, suggesting a bacterial aetiology. We therefore decided to study the bacterial flora of pouch effluent in pouchitis patients compared with colitic and polyposis patients without pouchitis.

Samples of faeces were collected from 6 colitic patients with pouchitis, 20 colitics without pouchitis and 7 polyposis patients. The faecal samples were emulsified in a cryoprotective transport broth, frozen at −40 °C and transported to the laboratory for analysis. The bacteriological investigation took two forms, first a search for putative pathogens such as *Clostridium difficile, Yersinia* spp., *Campylobacter* spp., *Salmonella, Shigella, Vibrio* and enterotoxigenic *Esch. coli;* and secondly a study of the bacterial flora profile. To achieve these two aims the samples were plated on non-selective media for total counts and on a range of selective or diagnostic media for the counts of specific organisms.

We were unable to detect any of the pathogens sought and conclude that pouchitis is unlikely to be caused by such organisms or their toxins.

In general the bacterial counts in pouch patients were only a little higher than those seen in ileostomy effluent and were 4 logarithm (base 10 units) lower than those normally seen in faeces. This suggests that either the period of stasis in the pouch is low or that conditions are unfavourable for bacterial growth. Nevertheless the relative proportions of the major genera in pouch faeces were more similar to those seen in "normal" faeces than in ileostomy effluent (e.g. *Bifidobacterium* spp. were as numerous as *Bacteroides* spp.; lactobacilli were a major component).

Trends in the composition of the flora from colitic pouches with and without pouchitis suggested that both aerobic and anaerobic organisms were more numerous in pouchitis patients than in healthy pouches, but there was no difference in the relative proportions of anaerobes and aerobes. None of the trends in differences in individual genera were statistically significant but this could have been simply due to the small number of pouchitis patients.

It is unlikely that a known intestinal pathogen is the cause of pouchitis, but it is possible that the disease is caused by an at present unidentified abnormality in the floral profile or in the immune response to that profile.

Discussion

Mr. Mortensen (Q.): How happy are you with grading of histological biopsies? How easy is it to do it reliably and efficiently, and if you gave the same biopsy to 25 histologists were they all graded equally?
Mr. Nasmyth (A.): Well, I have to confess this was only done with one histologist. Obviously, one took the advice of the histopathologist on how to do it and this was the grading system that they recommended. All sections were submitted to the pathologist blind. Probably, on occasions it was fairly obvious that I was showing him sections from an ileostomy as opposed to a pouch, simply because of the technique of taking the biopsy, but he had no relevant clinical information when he scored them.
Dr. Hill (Q.): Have you looked at how much variation in bacteriological counts there is from day to day?
Mr. Nasmyth (A.): We did duplicate samples. Quantitative bacteriology is quite expensive in terms of the numbers of plates you need to do, so we only repeated a few. Qualitatively, the results were fairly similar on follow-up. Quantitatively, there were occasionally quite big differences.
Dr. Hill (Q.): And the same applies to your volatile fatty acids?
Mr. Nasmyth (A.): Yes.
Dr. Shepherd (Q.): Why did you use lamina propria fibrosis as a parameter and how often did you see it?
Mr. Nasmyth (A.): We saw it very rarely. There were one or two where this change was obvious but only one or two.
Dr. Shepherd (Q.): What do you think this represents?
Mr. Nasmyth (A.): Presumably the late stage of chronic inflammation and more than that I cannot say.
Dr. Shepherd (Q.): Or ischaemia?
Mr. Nasmyth (A.): Possibly.

Mr. Nicholls (Q.): The bacteriological differences between an ileostomy and pouch are significant. Agreed?
Dr. Hill (A.): Yes.
Mr. Nicholls (Q.): In which case the only difference that immediately comes to mind is the fact that one is freely evacuated and the other one is not. So there is an element of stasis is there not?
Dr. Hill (A.): Yes. I wouldn't argue with that at all and it is interesting that the changes that we have seen in our study were entirely manifested in terms of anaerobic flora, so there was obviously quite a lot of fermentation going on which would tie in well with the fatty acid pictures that were obtained. But is is not the sort of longterm festering stasis that causes the production of large amounts of toxic substances that might well induce pouchitis. On the other hand, if you wanted to propose a protective substance then you might well be able to argue that.
Dr. O'Connell (Q.): Were any of the patients in your series early "S" pouches from the St. Mark's group who have stasis and intubate? If so, do you know whether that influenced the bacterial appearance in the pouches?
Dr. Hill (A.): There was a mixed bag of pouches, so to speak and there was no pouch-related difference in the bacteriology.
Mr. Mortensen (Q.): There was a paper from the Mayo Clinic suggesting that a proportion of patients did have a syndrome related to proximal small bowel overgrowth and I wonder if there is any information on that.
Dr. O'Connell (A.): Yes. We identified a group of people who had jejeunal bacterial overgrowth and this was related to a high stool volume and a poor result, and it exactly mirrored what Kelly had found in a group of Kock pouch patients some 5 years earlier, also with pouch dysfunction.
Professor Hultén (Q.): In the Blind Loop Syndrome you have a bacterial contamination and a high flow from the intestine, but you rarely see mucosal inflammation as seen in pouchitis. How about that?
Dr. Shepherd (A.): I think the major change you see, as George Nasmyth suggested, was villous atrophy. You do see chronic inflammation. You don't tend to see acute inflammation unless you have got an additional mechanical factor which will cause local ulceration, such as in sigmoid diverticulosis with a faecolith or something like that. The changes tend to be just villous atrophy and chronic inflammation.
Mr. Nasmyth (Comment): There are two points here which are quite important. One is perhaps the length of time for which the pouch has been constructed and what influence that has, and the second is to classify what one is looking at. In our study we were not looking at patients with pouchitis. Some, at least two, had had documented episodes of pouchitis but at the time they were studied they did not have it. I expected when I started this that we would find a significant correlation between our index of mucosal inflammation and villous atrophy. We didn't. Maybe we didn't have enough numbers. In the small bowel the change is predominantly villous atrophy and not inflammation. From the observations on the Kock pouch 10 years out, marked infiltration of the lamina propria with both acute and chronic inflammatory cells occurs early on. Later this levels off and remains stable so that the difference at 5 years and 10 years is minimal. However there might be quite a marked difference between one year and 5 years. In our flush of enthusiasm to study these patients we looked at them fairly early after the pouch had been constructed and it may well be that some of the conclusions we have drawn might have to be re-interpreted in the light of long-term follow-up.
Mr. W. H. F. Thomson (Q.): Did the patient who had a clinical pouchitis treated with metronidazole successfully have the faeces scrutinised bacteriologically before and after?
Mr. Nasmyth (A.): We did not study this, it is obviously something that needs to be done.
Mr. Nicholls (Q.): Have the Mayo done it?
Dr. O'Connell (A.): Not that I know of.
Mr. Kmiot (Q.): Do you think we should be looking at adherent mucosal flora?
Mr. Nasmyth (A.): Looking at the literature the bacteria isolated from the mucosa do not differ significantly from those in the lumen.
Dr. Hill (Comment): I agree that, qualitatively, they are very similar. The relative proportion is however very different; there are many fewer anaerobic flora. We looked bacteriologically at biopsy specimens from colitics with and without pouchitis and could not see any differences between them.
Mr. Nicholls (Q.): Having not established very much so far from a lot of work, do you feel there is still a role or place for study of bacteriology, perhaps in a more functional way?
Dr. Nasmyth (A.): I think part of the problem is that we don't understand the aetiology of colitis and that represents the main difficulty. The pouch offers a system which might be more amenable to study than the colon, particularly in looking at products of bacterial metabolism, if they are important. Perhaps the chance to look at the effects of treatment of pouchitis, particularly by antibiotics and to follow changes in the flora, might give us a

clue as to which bacteria we should look at in relation to the aetiology of colitis.
Dr. Hill (A.): I am sure we should continue to look at it. It is a problem knowing how to go about it. We have been doing a study on colitis with a group of clinicans in Salisbury, Swindon and Wolverhampton looking at the initial stages of colitis. So we were looking at the flora in patients first diagnosed with colitis, then patients in remission. This has yielded a bacterial library of patients in remission and we are just watching and waiting for them to go into relapse and see what changes we can see.
Mr. Nasmyth (Comment): Concerning the action of metronidazole, it is fairly well established that it has a genuine immunosuppressive action and undoubtedly affects T-cell function. It may therefore be that it is the mucosal response to the bacterial flora that is significant rather than the change in the flora itself.
Dr. Hill (A.): Yes, it may well be. Metronidazole seems to have an increasing profile of activities and its effect on the immune system is just one of them. However the antibacterial action of metronidazole is rapid but when used as an anti-tumour agent it is very much more slowly active. I do not know what I would expect as far as its anti-immune reaction would be.
Professor Keighley (Q.): If the butyrate hypothesis on the aetiology of ulcerative colitis is right, one would expect that those individuals who cannot handle butyrate are going to be those who developed pouchitis.
Dr. Hill (A.): The colonic mucosa has an absolute requirement for luminal butyrate as a nutrient. It is its main energy source. Most organisms are very good butyrate producers and will be very sensitive to metronidazole, so when you treat with metronidazole there will be a massive decrease in the amount of butyrate. Therefore I do not think it is a matter of patients not being able to handle butyrate.
Professor Tytgat (Q.): But if butyrate is the main energy source for colonic mucosa and *Bacteroides* suppresses the butyrate producers then levels will be low.
Mr. Nasmyth (A.): Well, that was pure speculation. I am just hypothesising.
Professor Tytgat (Q.): You said something like that.
Mr. Nasmyth (A.): No, what I said was that the situation in which the *Bacteroides* proliferate might well be one in which the organisms which are producing butyrate do not.
Dr. Hill (Q.): Yes, there is a limited amount of nutrient and so if you have a person whose flora is dominated by bacteroides it must be at the expense of something else. So it must be at the expense of well-known butyrate producers. If you have got very large numbers of *Bacteroides* then maybe you have decreased numbers of the others. So that would fit to some extent.
Professor Tytgat (Q.): But it would not explain why pouchitis improves if you bypass faecal flora from the inflamed pouch.
Dr. Hill (A.): No, that would not fit at all.
Professor Tytgat (Q.): Because butyrate production decreases dramatically as soon as you bypass?
Dr. Hill (A.): Yes, that wouldn't fit, nor would the effect of metronidazole.

Inflammatory mediators in ulcerative colitis

D. J. Gertner and D. S. Rampton

Eicosanoids, 20-carbon fatty acids derived from arachidonic acid, have been implicated as mediators in several inflammatory conditions. Since Gould first described increased prostaglandin excretion in stools in patients with ulcerative colitis, there have been numerous reports of increased eicosanoid synthesis and release in the inflamed colon [10].

What physiological role do eicosanoids play in normals and might they play a role in the pathogenesis of ulcerative colitis or pouchitis? Oral and parenteral PGE_1 and $PGF_2\alpha$ provoke watery diarrhoea in humans, probably by effects on intestinal water and electrolyte transport and gut motility. Splanchnic blood flow may also be altered by prostaglandins. Prostaglandins stimulate mucus production and, in the stomach, exert a "cytoprotective" effect; whether this occurs in the colon is not clear. Leukotrienes increase vascular permeability and are highly chemoattractant for leucocytes. Eicosanoids could therefore explain many of the features of ulcerative colitis [10].

The clinical problem in colitis is twofold. Firstly the cause of colitis is unknown and secondly, curative therapy is lacking. Moreover the mechanism of action of drugs currently used in colitis is not well understood.

Our experiments have been designed, firstly, to examine those factors which stimulate the inflammatory response and thereby improve our understanding of the pathogenesis of colitis, and secondly, to attempt to inhibit the inflammatory response and thus develop novel therapeutic agents. We have used an in vitro method in which

rectal biopsies are incubated in oxygenated Tyrode's medium which is changed every 20 min. The release of PGE_2 and LTB_4 into the medium, before and after the addition of potential trigger factors or drugs, is measured by radioimmunoassay. We have shown that eicosanoid release by colitic mucosa is increased compared with normal and correlates with disease activity. Exogenous arachidonic acid amplifies LTB_4 and PGE_2 release indicating enhanced 5-lipoxygenase and cyclo-oxygenase activity in inflamed mucosa [11] (Fig. 15).

Why are these two enzyme systems switched on? Of the potential initiating factors currently under investigation (e.g. FMLP, a bacterial derived peptide, bacterial endotoxin, bile acids and PAF), two (FMLP and bile acids) are known to be capable of producing colitis in experimental animals [12, 13].

Attempts to inhibit these enzyme systems with specific pharmacological agents have not yet proven effective in colitis [10]. Indomethacin and flurbiprofen, potent cyclo-oxygenase inhibitors, do not improve colitis and may worsen it. 5-lipoxygenase inhibition with benoxaprofen was ineffective; newer, more potent 5-lipoxygenase inhibitors are currently being evaluated. Dietary therapy could also be efficacious. A fish-oil diet rich in polyunsaturated (w-3) fatty acids inhibits 5-lipoxygenase and results in the synthesis of PGE_3 and LTB_5, which are thought to be less pro-inflammatory than PGE_2 and LTB_4. Conventional treatment may or may not act by modification of arachidonic acid metabolism. Experimentally, corticosteroids inhibit the release of membrane bound arachidonic acid and therefore limit the availability of free substrate for these two enzymes. Sulphasalazine and its metabolites exert diverse and dose-dependent effects: prostaglandin synthesis and degradation are reduced as are thromboxane and leukotriene synthesis; these agents have also been shown to act as free-radical scavengers [10].

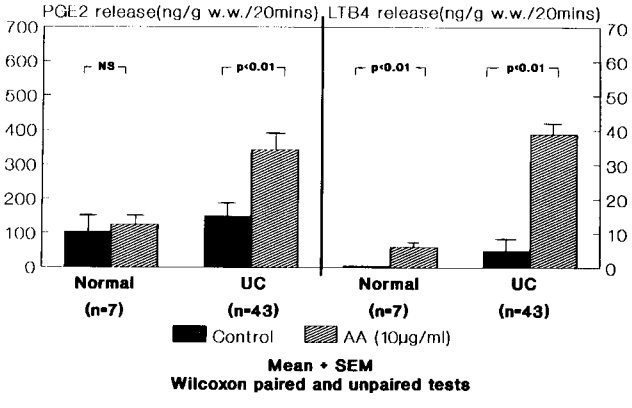

Fig. 15. Effect of exogenous arachidonic acid on eicosanoid release by normal and colitic mucosa

Pouchitis appears to occur only in patients in whom the operation was performed for ulcerative colitis. The histological abnormalities are similar to those found in ulcerative colitis. The beneficial effect of metronidazole in pouchitis contrasts with that in ulcerative colitis and might suggest a bacterial aetiology perhaps mediated by FMLP or endotoxin. Data on inflammatory mediators in pouchitis are currently lacking. Studies on eicosanoid synthesis and release in this iatrogenic condition may provide further clues to the aetiology and therapy not only of pouchitis but also of ulcerative colitis.

Discussion

Professor Tytgat (Q.): We have just finished a study measuring the PAF content in biopsies from normals, patients with ulcerative colitis, pouch patients with and without pouchitis, and the actual content of PAF in all these four categories was exactly the same. There was certainly no increase in PAF in pouchitis mucosa. That does not mean that the generation capacity may be different but the actual content was indistinguishable.

Dr. Gertner (A.): We have actually tried to look at the PAF release and production in colitis and it is quite a difficult chemical to get out.

Professor Tytgat (Q.): But that was generation capacity and that is what you expect in a mucosa with so many inflammatory cells. That doesn't mean a thing, and the actual content I think is much more important.

Dr. Gertner (A.): One of the problems with this is that this could all be an epiphenomenon. We aren't sure if it is perhaps just an aftereffect of the inflammatory infiltrate switching on all these enzyme mechanisms. What we don't know is what actually switches it on in the first place and this is an attempt to get a handle on that really.

Mr. Nicholls (Q.): Where do these reactions occur?

Dr. Gertner (A.): Membrane bound arachidonic acid is released by phospholipase into the cytosol, and these mediators are produced within the cytosol and then released.

Professor Hultén (Q.): The neurohumoral regulation of blood flow differs very much in the stomach, small intestine and colon. It is only in the stomach and colon that we have vaso-dilatator fibres. You focus your interest on prostaglandins. What about the bradykinin mechanism?

Dr. Gertner (A.): I could show you a slide with 10 other cascades, all of which involve different pathways such as the kinins, for example. They may all be important in inflammatory mechanisms but we do see a particular correlation between these pro-inflammatory mediators, the leucotrienes, and the disease condition in colitis. That is not to say that these other cascades are not also important. We just do not know.

Faecal bile acids in pouch and pouchitis patients

M. J. Hill and R. W. Owen

In previous studies we have reported on the faecal bile acids in patients with chronic ulcerative colitis and in familial adenomatous polyposis (FAP) patients. In the former group of patients there was a relationship between the faecal bile acid concentration and the severity of epithelial dysplasia and the risk of colorectal cancer. The latter group were characterised by a lack of bacterial metabolites despite the bacterial flora having a normal composition and having normal bile acid degradative activity in vitro. These results suggested that in FAP there was an inhibitor of bacterial metabolism present in the colon and secreted either by the colonic mucosa or in some small intestinal secretion (e.g. bile).

It has been demonstrated that bile acids are toxic to the intestinal mucosa and are responsible for cholerrheic diarrhoea. It was therefore decided to study the faecal bile acids in pouch and pouchitis patients to determine whether the diarrhoea and severe inflammation in pouchitis could be due to an abnormally high intestinal bile acid concentration. In addition, by comparing the faecal steroids of pouch patients treated for FAP with those treated for UC, evidence of the cause of the lack of steroid metabolism in FAP patients might be obtained.

The faecal steroids in the 20 healthy UC-Pouch patients, the 7 healthy FAP-Pouch patients and the 6 UC-Pouch patients with pouchitis were assayed by the method of Owen et al. [14].

In contrast to ileostomy patients, the faecal steroids were mainly deconjugated (68% in UC-Pouch and 81% in FAP-Pouch). The hydrolase enzyme produced by the gut flora is highly active and evidently even the brief transit time in the pouch patients was sufficient to facilitate the reaction. Similarly, whereas in ileostomy patients the bile acids excreted have usually undergone only slight dehydroxylation, in the pouch patients 23% of the free bile acids had undergone dehydroxylation. The extent of dehydroxylation was as high in FAP-Pouch patients as in UC-patients.

Table 3. Mean bile acids (mg/g faeces)

	UC $n=20$	UC pouchitis $n=6$	FAP $n=7$
Total bile acids (TBA)	7.68	5.65	7.15
Total conjugates (% TBA)	2.68 (35%) **	0.52 (9%) **	1.56 (22%)
Tauro-conj	0.44 *	0.17 *	0.46
Glyco-conj	2.24	0.35	1.10
Total free bile acids	5.0	5.14	5.60
CA	1.94	2.87	2.35
DCA	0.51	0.24	0.90
CDCA	2.04	1.86	1.73
LCA	0.51	0.18	0.54

UC, ulcerative colitis; FAP, familial adenomatous polyposis; * Significantly different, $p < 0.025$; ** significantly different, $p < 0.05$

There is no evidence from this study that the faecal bile acid concentration is high in pouchitis; in fact the reverse appears to be true since the faecal bile acid concentration in pouchitis patients was 13.98 m*M* compared to 17.27 and 18.42 m*M* respectively in the FAP-Pouch and the UC-Pouch patients. It can be seen in Table 3 that the pouchitis patients had significantly lower levels of glycoconjugates in the faeces than colitics without pouchitis.

The bile acids do not appear to have a cholerrheic role in the causation of pouchitis. Interestingly, the results on the pouch patients with no pouchitis provide useful evidence that the lack of metabolic activity in the colonic flora of FAP patients is dependent on the presence of the colon and may be caused by a colonic secretion.

Discussion

Professor Hultén (Q.): Which of the different bile acids are the most cytotoxic?
Dr. Hill (A.): Lithocholic and deoxycholic are both highly cytotoxic but lithocholic seems to be marginally more so.
Professor Tytgat (Q.): If there is less fermentation of fibre there should be less dilution of bile salts.
Dr. Hill (A.): The food residues are of such low molecular weight that they don't have much osmotic effect, so they won't really affect the degree of diet hydration.
Professor Tytgat (Q.): Therefore, there should be less dilution.
Dr. Hill (A.): Yes, but I am not talking about aqueous dilution, I am talking about solid dilution.

Professor Tytgat (Q.): I was talking about aqueous. Could it be that some of the bile salts are sequestered by the fibres?
Dr. Hill (A.): Yes.
Professor Tytgat (Q.): And you extract it in your extraction procedure?
Dr. Hill (A.): Yes. We are happy that we can extract any bile acids that would have absorbed to solid surfaces.
Mr. Kmiot (Q.): Over how many days did you collect the faecal sample? There has been some recent work which suggests that to get a valid result you need at least 7 days and some people say more than 7 days.
Dr. Hill (A.): That is if you are going to look at an individual not if you want to look at populations. If you are looking at populations, then you can use single samples. If you are looking at individuals then you must have at least a 3-day collection.
Mr. Kmiot (Q.): Could a single sample have picked out a person when they were just secreting a low amount of bile acid at that time point of sampling?
Dr. Hill (A.): Well, we have never seen tremendous diurnal variation even from day to day. If you look at the concentrations, we haven't seen the variations that others have reported. We found an error of plus or minus 10% by taking a single sample rather than a 3-day collection.
Professor Keighley (Q.): We know that transit is grossly abnormal in these pouch patients, and solid lumps of food are there. This must be a factor. Did you standardise diet in this study? They were not all starved? Because it makes such a difference to what you collect?
Dr. Hill (A.): We reckoned that since these patients didn't have to be starved to get pouchitis we ought to look at their steroids under normal dietary circumstances.
Professor Keighley (Q.): But because eating food has such an impact on the faecal composition surely you should standardise it somehow?
Dr. Hill (A.): I think that in a perfect study we would have had diet standardised.
Professor Keighley (Q.): Have you studied ileostomy patients who have had a large segment of terminal ileum resected?
Dr. Hill (A.): No. We haven't looked at that.
Mr. Nicholls (Q.): Is there any difference in bile salt concentrations in polyposis patients with an intact colon and those that have had a colectomy with ileorectal anastomosis?
Dr. Hill (A.): If they have had a colectomy they behave from the metabolic point of view as if they have an ileostomy. There is no metabolism at all. But there is no metabolism in a colitis patient who has had a colectomy either, neither is there in a polyposis patient with a complete colon. We have explained the lack of metabolism in the ileorectal ones as being due to very short transit. When we analysed these patients by type of pouch, we had much greater metabolism in the ones who needed to catheterise. So it is a bit of a blow to hear that those with the artificial emptying didn't have any longer stasis than the others. But for some reason or other they do have more metabolism.
Professor Williams (Q.): How much can you rely on the fact that you have only got six subjects? We heard the suggestion that diet is important. What about age, length of time since surgery, length of bowel remaining? How reproducible are these measurements?
Dr. Hill (A.): We could have improved the study a great deal by standardising the diet first of all and obviously by getting greater numbers. We could improve it by taking longer collections instead of single samples. We would possibly get different results in patients with a pouch that had been done many years previously rather than a few months. There must be some period of stabilisation.
Professor Williams (Q.): Is there any difference in body weight, age and sex?
Dr. Hill (A.): Yes. The faecal bile acid output increases with increasing body weight. It is higher in women than in men and it increases with age. There is a relatively small increase with age.

Pouchitis: defining an objective method of diagnosis

W. A. Kmiot and M. R. B. Keighley

The reported incidence of pouchitis varies from 7–43% in patients following restorative proctocolectomy, although it is not clear if different series are describing the same condition. Recent work has documented an incidence of 11% on the basis of specifically defined clinical, sigmoidoscopic and histological criteria of acute inflammation. Despite this, the definition of pouchitis remains unclear and the diagnosis difficult due to the relapsing and remitting nature of the disorder and its patchiness at a macroscopic and microscopic level.

To define a more objective diagnostic method we have used the specific inflammatory cell seen in pouchitis, i.e. the neutrophil, and performed isotope scans after labelling it with ^{111}Indium.

Twenty-two patients have had the radiolabelled neutrophil scans performed at a median of 22 (range 7–46) months following pouch formation.

The study groups were stratified into three; (1) pouchitis on clinical, microscopic and sigmoidoscopic criteria ($n=9$); (2) poor functional result without evidence of pouchitis ($n=7$); (3) good functional result ($n=6$).

Sixty ml. of venous blood was removed from each patient and 15 ml layered over 7 ml of Ficoll-Hypaque in four separate tubes. Following centrifugation at 400 g for 60 min a distinct neutrophil band was visible which was aspirated. After a single wash in saline, the cells were labelled with 5 MBq of Indium oxime and resuspended in platelet free plasma. This was centrifuged for a final time, the supernatant counted to determine labelling efficiency, and the cell pellet injected into each patient following a further resuspension in plasma.

All patients had gamma camera scans 4 and 24 h following cell reinjection and a 4-day stool collection counted isotopically, along with specific clinical, haematological and sigmoidoscopic assessment. All nine subjects in the pouchitis group had a 1-month course of metronidazole. All patients were re-studied 1 month later and those with a positive scan initially were rescanned.

Two out of nine scans in the pouchitis group were unsuccessful and of the remaining seven, four were positive. After treatment, repeat scans showed reduced pouch activity in each case. All other patients had a negative scan.

Faecal granulocyte excretion was positively correlated with scan activity and was decreased in each re-scanned case. The 24-h defaecation frequency in patients with a positive scan significantly improved from a pre-treatment value of 8 (7–11) times per 24 h (median and range) versus a post-treatment value of 6 (4–8), a difference not detected in the negative scan group.

Histological grade and sigmoidoscopic appearance improved following therapy only in those patients with a positive scan.

Haematological and biochemical indices of inflammation tested, namely haemoglobin, white cell count, ESR, CRP, AGP and albumin were not significantly different between the three study groups. Absolute values did not correlate with a positive scan.

This pilot study demonstrates that ^{111}Indium granulocyte scanning is a sensitive method of assessing acute pouch inflammation. The absence of positive scans in asymptomatic patients refutes the existence of a syndrome of subclinical pouchitis. Specificity however is less, with the three false negatives reflecting the inconsistent response of the condition to metronidazole and its intermittently active nature.

Therefore use of this technique in conjunction with the other three diagnostic criteria may enable improved detection of active pouchitis.

Discussion

Mr. Nicholls (Q.): There must be polymorphs in the pouches, even in the negative ones. Is it a matter of the method being too insensitive to pick them up?

Mr. Kmiot (A.): The amount of neutrophils in each patient in the pouchitis group was similar. The labelling in patients with positive and negative scans in that group was similar as well. I think this may be a question of neutrophil kinetics, perhaps the cells are not entering the mucosa in a patient with a negative scan. One presumes that this disease is in fact in remission at the time.

Dr. Shepherd (Q.): Isn't it more likely to be a reflection of the presence of ulceration? If you look at ulceration histopathologically there are thousands of polymorphs.

Mr. Kmiot (A.): Well, if that was the case you would expect it to be picked up on the faecal excretion.

Mr. Bartolo (Q.): Did you employ any method for counting the neutrophils before you put them back into the patient?

Mr. Kmiot (A.): Yes, they were all Coulter counted. The median values were between 10^7 and 10^8.

Mr. Bartolo (Q.): Did you assess how accurate your labelling was before putting them back into the patient?

Mr. Kmiot (A.): We did. We centrifuged the neutrophils after labelling and then measured the activity in the supernatant; the labelling efficiency was around 66%.

Professor Williams (Q.): I have patients who have urgency of defaecation who I would classify as having pouchitis because on biopsy they have an acute inflammatory reaction, but frequency is only four times a day. Other patients are very well for 3 or 4 months and then they get an acute attack of what I again would classify as pouchitis. So one wonders about in your poor result group. Did any of these go on and have this sort of cyclical type of problem that some patients get, and indeed in the so-called pouchitis group, were you looking at them during an acute attack?

Mr. Kmiot (A.): Both the positive controls and the study group had this history. They were selected exactly for that reason. So in fact, you might suspect pouchitits in them, even though there was nothing on biopsy or on the sigmoidoscope for you to confirm your preliminary diagnosis.

Mr. Nicholls (Q.): In the group with poor result but no pouchitis what do you think the dysfunction was due to?
Mr. Kmiot (A.): Two of the seven patients were found to have jejeunal bacteriological overgrowth. Of the other five one had thyrotoxicosis and the other four were labelled as functional diarrhoea.
Mr. O'Connell (Q.): We had this morning a virtual agreement that pouchitis occurs only when you have had an antecedent history of ulcerative colitis. It seems to occur chiefly in patients with pancolitis, and I suggest that it also seems to occur mainly in patients who have had extracolonic manifestations of their disease, because those who have recurrent pouchitis are those who complain of arthralgia, uveitis, general malaise and a high ESR. We have such a spectrum of the disease that perhaps if we can define those about whom none of us would disagree, that would be a starting point.
Mr. Bartolo (Q.): When we diagnose someone with ulcerative colitis we use clinical and endoscopic features and histology. Pouchitis could well be ulcerative colitis occurring again in colonic metaplasia in the small bowel. Why can't we just use those same features that we use to diagnose ulcerative colitis?
Mr. Kmiot (A.): On the basis that, in our patients for which we used those criteria, three did not have any clinical response to metronidazole.
Mr. Nicholls (Q.): We do not know anything like enough about drug treatment in this condition to be able to accept that as a diagnostic criterion. It has been suggested that there are at least two different forms of pouchitis, that it is a heterogeneous condition. There is a bacteriologically related one which may respond to metronidazole and there is one which does not respond which might do so to steroids.
Mr. Hawley (Q.): I would support that. For me pouchitis is a clinical diagnosis, but not all cases respond to metronidazole. I have got about six patients who have had to go back on steroids and they are totally cured with a small dose of steroids.
Professor Williams (Comment): You should not even close your mind to two causes of it. This is probably a multi-factorial problem.

Evacuation and pouchitis

P. R. O'Connell

Construction of an ileal pouch reservoir produces stasis within the distal small bowel. This is desirable in patients with an ileal pouch-anal anastomosis or a Kock continent ileostomy, as post operative stool frequency is directly related to the maximum capacity of the ileal reservoir [15, 16]. The corollary is that the ileal reservoir must evacuate efficiently to maximise benefits of a large reservoir and to minimise biological effects of stasis within the distal ileum [17]. The importance of efficient pouch evacuation to clinical outcome has been clearly demonstrated in patients with ileal 'S' pouch anal anastomosis [4]. Impairment of ileal pouch evacuation resulted in ileal pouch intubation at least once per day in 50% of patients. Animal studies confirmed that the 'S' pouch reservoir with a long efferent limb empties poorly, perhaps by overflow [18]. Contrast radiology confirmed that a long ileal pouch efferent limb was obstructive [19]. These observations led to changes in ileal pouch design with shortening of the obstructive efferent limb in 'S' pouches and to development of other non-obstructive ileal pouch designs.

Conventional contrast radiological studies of the ileal pouch reservoir provide excellent detail and are useful in establishing anastomotic integrity before closure of a protective loop ileostomy. Evacuation proctography is also useful in investigation of patients considered to have inefficient ileal pouch evacuation. However neither technique provides a quantitative measurement of ileal pouch emptying which is needed for comparative studies of ileal pouch design and clinical outcome. Furthermore, the radiation dosage of conventional radiological methods make control and sequential studies difficult to justify.

Several non-radiological and scintigraphic methods which quantify ileal pouch evacuation have been developed. To simulate physiological evacuation, the media employed must have a consistency which resembles semisolid ileostomy stool. Methyl cellulose paste [20], porridge [2], aluminium magnesium silicate gel [21, 22] and radiolabelled egg albumin [23] have been used. Using silicate gel containing the colourmetric marker phenolsulphonpthalein, Stryker found a direct relationship between the efficiency of ileal 'J' pouch evacuation and functional result [21]. Later scintigraphic studies have shown that ileal pouch emptying is similar to that of the healthy rectum and that little difference exists in the efficiency of evacuation of the various ileal pouch designs [22, 23].

Pouchitis occurs in approximately 14% of patients following ileal pouch-anal anastomosis [24]. An antecedent history of ulcerative colitis and stasis within an ileal reservoir are prerequisite to development of the condition. The aetiology is widely

believed to be due to stasis within the ileum leading to bacterial overgrowth and mucosal inflammation. To study this hypothesis, we investigated 20 patients following ileal pouch-anal anastomosis. Ileal and jejeunal bacterial growth and efficiency of ileal pouch evacuation were correlated with clinical outcome. Enteric bacteriology and ileal pouch evacuation were not different in patients with recurrent pouchitis ($n=6$) when compared to patients with a good clinical outcome ($n=8$). Of interest was identification of jejeunal bacteriological overgrowth in patients with a poor clinical outcome ($n=6$) associated with a large stool volume [24].

Our observations regarding ileal pouch evacuation and its relationship to pouchitis are supported by those of Moskowitz [2] and Heppell [23]. These cast doubt on the theory that pouchitis is due simply to stasis with quantitative bacterial overgrowth within the ileal pouch. Whether a qualitative change in ileal pouch flora is responsible is as yet uncertain. An attractive alternative is that, in certain individuals, intraluminal microbial antigens produce an inflammatory response within ileal pouch mucosa which closely resembles the antecedent colitis [17]. Investigation of this hypothesis may provide answers to many questions regarding the pathophysiology of ulcerative colitis.

Discussion

Mr. Bartolo (Q.): Were your patients in the left lateral position, and were you evacuating from the neorectum or were you using a radio-opaque balloon?
Dr. O'Connell (A.): The material was inserted with the patient was in the left lateral, but then we had a plastic commode on which the patient sat. Lateral views only were found to be useful. The balloon was used to look at angles not for quantifying emptying.
Professor Tytgat (Q.): Do you instruct the patients to press when they empty their pouches?
Dr. O'Connell (A.): We just left them beside the gamma camera and went off to one side and said "Evacuate just as you would normally when you want". We left the machine on continuous acquisition for 3 minutes and when they said they were finished we went back in.
Professor Hultén (Q.): Do you instruct your pelvic patients to strain?
Dr. O'Connell (A.): No, I don't give any specific instructions. I would certainly think I would dissuade somebody from staining a lot because prolapse might occur.
Professor Keighley (Q.): Have you looked at pouch emptying in your jejeunal overgrowth syndrome? What about transit?
Dr. O'Connell (A.): The transit work from the Mayo Clinic was specifically aimed to see whether the ileal pouch-anal anastomosis affects the ileal break phenomenon, and it is still intact. They have not yet looked at patients with jejeunal bacterial overgrowth.
Professor Keighley (Q.): What would you predict?
Dr. O'Connell (A.): Proably there will be a slower transit in those with overgrowth.
Professor Hultén (Q.): Is there a relationship between incomplete emptying and pouchitis? In the continent ileostomy most patients become continent eventually. Many irrigate the pouch with saline after every evacuation but the patients who do that have a similar risk of pouchitis as the others.
Dr. O'Connell (A.): Today has reinforced my opinion that pouchitis is not due to stasis per se. Stasis may be part of the whole, it creates the whole milieu, but it is not just stasis.
Mr. Nicholls (Q.): Have you studied the species of bacteria in patients with jejeunal overgrowth?
Dr. O'Connell (A.): No. In the cost-conscious Mayo they decided to do Gram stains only.
Mr. Nicholls (Q.): Were they quantitative?
Dr. O'Connell (A.): No, we quantified the various growths and sub-divided those on the basis of the Gram strain. We could say whether they were Gram negative bacilli, but we couldn't go into the subspecies. It would cost $ 1500 a specimen to process in greater detail.
Professor Hultén (Q.): Were there correlations between defaecation frequency and pouchitis?
Dr. O'Connell (A.): Some people with pouchitis have a greater stool frequency than when they don't have pouchitis.
Professor Hultén (Q.): How did you define pouchitis in Rochester?
Dr. O'Connell (A.): We defined it as a clinical syndrome.
Mr. Nicholls (Comment): We might leave that till the end. I do not wish to interrupt but I think that in fact that might be germane to the final 10 minutes of discussion, and we are all ears to know how they define pouchitis in Rochester. But thanks very much indeed.

Ileal pouch motility

D. Kumar and N. S. Williams

The diagnosis of pouchitis is made either on clinical symptoms of excessive stool frequency and malaise

or macroscopic/microscopic inflammation of the ileal reservoir. However, there is a significant overlap in pouch function or dysfunction between the inflamed and normal pouches. Also our current understanding of pouch motility is based on static measurements of pouch pressure independent of small bowel motility proximally and anal canal motor activity distally. In order to define patterns of pouch motility and establish relationships between motility of the ileal reservoir, the small bowel and the anal canal on one hand and pouch function morphology on the other, we have studied anal manometry, reservoir capacity and compliance and mucosal morphology in 15 patients [7] and ambulatory measurements of small bowel motility, pouch motility and anal canal motility in 8 patients. Static measurements (anal manometry, pouch capacity and compliance) were made using a water filled balloon connected to a pressure transducer and a latex balloon attached to an 8 FG catheter respectively. Ambulant measurements of small bowel, pouch and anal canal manometry were made by a fine (OD 2 mm) catheter-mounted microtransducers. The signal was recorded on audio tape on a portable tape-recorder. The patients were fully ambulant during the study.

Resting anal canal pressure was significantly lower ($p < 0.01$) in pouch patients but the maximum squeeze pressure was unaltered. Patients with minor leakage had significantly lower resting pressures ($p < 0.05$) than those who were fully continent. Patients with urgency of defaecation had significantly lower squeeze pressures ($p < 0.05$) than those who could defer defaecation for more than 30 min. Similarly patients who could defer defaecation had greater pouch compliance and larger pouch capacity. None of the pouches showed macroscopic inflammation when examined endoscopically. However, on microscopic examination, both fibrosis and moderate to severe infiltration of the lamina propria with acute and chronic inflammatory cells was evident. There was no significant correlation between the degree of mucosal inflammation and either frequency or urgency of defaecation.

Prolonged manometry of the pouch showed two types of motor activity. First, there were large (> 50 mm Hg) amplitude contractions which lasted for 0.5 ± 0.1 min (mean $\pm$ SEM) duration and had no relation to pouch filling. These giant contraction waves were significantly ($p < 0.05$) more frequent in pouches with a capacity of 300 ml (mean) or less. They occurred with similar frequency during the day and at night. When three or more such contractions appeared over a period of 5 min, the patients felt an urge to empty the pouch. The second type of contraction occurred with a frequency of 6–8/min. This type of activity was predominantly seen after meals. Giant contraction waves were also seen in association with 6–8 per minute activity in the postprandial period. The anal canal showed slow contractile activity at a frequency of 2–3/min. The upper anal canal immediately adjacent to the anastomosis showed complete inhibition of motility in response to pouch distension; the mid and lower anal canal were not affected in a similar manner. On the other hand, small bowel motility in patients with ileal reservoirs was characterised by a significantly ($p < 0.05$) shorter cycle length (42.5 ± 11.4 min) when compared with healthy controls. The contractile frequency, phase I, and phase II activity in the small bowel in ileal pouch patients was similar to that seen in healthy controls. Whether this is the effect of colectomy or pouch formation on small bowel motor activity has yet to be determined.

Prolonged monitoring of ileal reservoirs has provided us with a pouch motility marker (giant contraction waves) which can be easily measured to give us an indication of pouch function, i.e. giant contractions occur more frequently in smaller capacity pouches and are related to the frequency of bowel action. Although these types of contractions do not reflect the aetiology of pouch dysfunction, they may provide a useful guide to its severity.

Discussion

Professor Hultén (Q.): How about motility in the pouch with inflammation?
Mr. Kumar (A.): I wish I knew how to classify them into the two separate groups of no pouchitis and definite pouchitis. However, the patients with inflammation would tend to have a frequency of more than 6 per minute, whereas those who have a good result tend to show a lower frequency of these contractions.
Mr. Kmiot (Q.): We still don't really know why patients with pouchitis evacuate so frequently. Is it increased motility or is it excessive secretion?
Mr. Kumar (A.): I am not sure what you mean when you say "pouchitis" and what Leif Hultén means when he says "pouchitis". There are one or two patients in my practice who get absolute classic colitis-type symptoms and have everything else there, but I also have patients who are asymptomatic for periods of time and are fine, then suddenly they have an attack of increased frequency. Furthermore, I have patients who have frequency

of bowel action but they don't have much in the way of inflammation.

Mr. Nicholls (Q.): All pouch dysfunction is not pouchitis, and indeed your relationship between sphincter relaxation, sphincter performance and urgency suggests a separate functional disorder, not pouchitis.

Professor Williams (A.): Well, just to be controversial, with the Kock ileostomy you are dealing with a pouch which has an egress to the surface. There is a sphincter of sorts but it is not a real sphincter and also it is not in the pelvis. It is simplistic to rule out other factors and to say just because there is inflammation and poor function, then the patient has pouchitis. I suspect that most such patients have not been fully evaluated in motility terms.

Professor Hultén (Q.): I think you are making it more complicated than it is in practice. If you have got a pouch patient with a steady frequency of about 3 to 5 per day, who then develops increased frequency with bloody stools and malaise, there is no difficulty on seeing a red bloody mucosa there to say that patient has got pouchitis.

Professor Keighley (Q.): We know there is a tremendously variable response to modalities of medical treatment and we are probably talking about a spectrum of disordered pouch function. One of the components is something that is associated with a lot of diarrhoea, it may be sudden or insidious, and you see inflammation when you put the sigmoidoscope in. The histopathologist sees a lot of acute inflammatory cells as opposed to the normal villous atrophy that is almost normal in these patients. Those taken together with a clinical symdrome ought to be the criteria for the diagnosis.

Mr. Nicholls (Q.): So we have gone full circle back to this morning. We are looking at a clinical disorder which, like all diseases, can be defined by appearances, both macro and micro, plus the clinical features.

Professor Williams (Q.): We are looking at a syndrome, aren't we? We are not looking at a disease entity but a pouchitis syndrome for which there may be a variety of causes.

Dr. Kamm (Q.): The problem is similar to others in inflammatory bowel disease in terms of nature and definition. Using the Crohn's disease activity index, especially in following therapy, you cannot include treatment as one of the parameters, but you can use a complex of symptoms, signs and laboratory data and come up with a final figure.

Mr. Nicholls (Q.): It seems that we are talking about a syndrome of clinical, histological and macroscopic features, the cause of which is obscure because the cause of ulcerative colitis is obscure because we have so far not unearthed any aetiological factors that can be related to the condition.

Mr. Mann (Q.): If you tried to define ulcerative colitis as a syndrome in terms of bowel frequency, urgency and incontinence and everything else, it would be extremely difficult. The only objective data that are relatively independent of subjective influences are the histological criteria and I would make a plea that we do observe this as very much part of our appreciation of what we mean by pouchitis.

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