Editorials

New treatments for inflammatory bowel disease

David S. Rampton and D.Phil

Subject headings Crohn's disease; ulcerative colitis; inflammatory bowel disease; corticosteroids; mesalazine; immunosuppressive drugs; cytokines

INTRODUCTION

Although inflammatory bowel disease (IBD) is apparently still relatively rare in the East, evidence from Hong Kong suggests that over recent decades the incidence of both ulcerative colitis (UC) and Crohn's disease (CD) may be rising there[1-3]. Indeed, it seems likely that as the prevalence of enteric infections falls, and urbanisation and diagnostic awareness increase, IBD will become increasingly common in Asia, as it has in the last fifty years in Europe and North America. It therefore seems appropriate to review advances in the medical therapy of these often refractory diseases.

In this paper, I shall not attempt to review extensive earlier evidence about the efficacy of corticosteroids, aminosalicylates or, in patients refractory to these drugs, immunosuppressive agents; nor shall I discuss the role of surgery. Furthermore, rather than describing the management of the "whole" patient with IBD[4,5], I shall concentrate primarily on drugs which have recently gained an established place in, or appear very promising for, the treatment of IBD. I shall also outline the use of liquid formula diets in active CD, and mention the possible but unproven place of traditional medical modalities.

At the outset, it is worth emphasizing some of the problems encountered in the evaluation of new treatments for IBD. UC and CD have fluctuating courses which depend on both site and extent of disease, as well as, in CD, previous surgery and the time since the most recent relapse. In both diseases, objective measurement of disease activity and definition of trial endpoints is difficult. In CD, for example, measures of disease activity, such as the Crohn's disease activity index (CDAI), colonoscopic appearances and laboratory variables, do not always move in parallel[6].

Dr. David S. Rampton, D. Phil. P., Reader and Consultant Gastroenterologist, Gastrointestinal Science Research Unit and Digestive Diseases Research Centre, St Bartholomew's and Royal London School of Medicine and Dentistry, London E1 2AD, UK.
Correspondence to Dr. DS Rampton, D Phil, FRCP, Department of Gastroenterology, Royal London Hospital, London E1 1BB, UK
Tel. +44·171·7442, Fax. +44·171·7441
E-mail:drampton@mds.pmw.ac.uk
Received 1998-07-21

In addition to these difficulties, the design, conduct and interpretation of trials in IBD is complicated by the size and variablity of the placebo response[7], the too frequent use of small numbers of patients with consequent Type II statistical errors, and the confounding effects of concurrent or recently discontinued therapy.

Finally, none of the numerous experimental animal models of bowel inflammation resembles human IBD sufficiently closely to enable valid extrapolation of results in such studies to the clinical arena. A possible exception to this generalisation is the spontaneous colitis to which the cotton-top tamarin in captivity is prone[8], but the animal's rarity and expense prevents its utilisation for large scale therapeutic trials. In this review, therefore, attention with be focussed primarily on results obtained in human studies.

AETIOPATHOGENESIS OF IBD

Although the aetiology of IBD remains obscure, recent studies have begun to shed light on its pathogenesis. In brief, it appears that an initiating factor, for example a microbial or dietary product or antigen, triggers an inappropriately severe and prolonged intestinal mucosal inflammatory response in genetically predisposed individuals[9]. The inflammatory response is amplified and perpetuated by recruitment of leucocytes from the gut vasculature which, with upregulation of the expression of nuclear transcription factors such as NFkB[10]. leads to excessive release locally of cytokines[9], eicosanoids[11], reactive oxygen metabolites[12] and other mediators. In CD, in particular, a procoagulant diathesis and multifocal granulomatous intestinal microinfarction may occur early in the disease process[13]. Elucidation of the pathogenesis of IBD has improved our understanding of the possible modes of action of conventional treatment (Table 1) and has led to the development of entirely mew therapeutic approaches, to be discussed in the second half of this review (Table 2).

NEW FORMULATIONS AND APPLICATIONS OF EXISTING DRUGS

Corticosteroids (Table 1)

Corticosteroids are the most useful conventional agents in the treatment of active IBD, whether given orally, intravenously or topically[4,5]. They have multiple potentially beneficial actions on the

Table 1 New formulations and applications of existing therapies for IBD

Treatment	References
Corticosteroids	
Budesonide	14-18
Aminosalicylates	
Mesalazine (enteric-coated pH-released & slow-release), olsalazine, balsalazide	4,5,19-22
Immunomodulatory agents	
Azathioprine & 6-mercaptopurine	23-29
Cyclosporine	30,31
Methotrexate	32,33
Mycophenolate mofetil	34
Antibiotics	
Metronidazole	35-37
Other	38
Liquid formula diet	39,40

Table 2 Potential new treatments for IBD aimed at specific pathophysiological targets

Target	Agent	References
Colonic bacterial flora	Non-pathogenic *E coli*	41,42
Epithelium	Short chain fatty acids*	43-46
Leucocytes		
Reduce numbers	Apheresis, anti-CD4 antibodies, bone marrow transplant	47-50
Reduce migration	Adhesion molecule antibodies or antisense oligonuleotide	51
Cytokines		
Reduce pro-inflammatory cytokines	NFkB antisense oligonucleotide	10
Antagonise inflammatory cytokines	Anti-TNF antibodies*, IL-1 receptor antagonist	52-55
Increase anti-inflammatory cytokines	IL-10* , interferon alpha or beta, IL-11, TGF beta	56
Mediators	Cytoprotective prostaglandins	11
	COX2 inhibition	
	Synthesis inhibitors and receptor antagonists of leucotrienes, thromboxanes, PAF	11,57-60,67
	Antioxidants	12,61
	Inducible NOS inhibition	62
	Fish oil (EPA)	63-66
Vasculature	Heparin*	67,68
Enteric nerves	Local anaesthetics*	69-71
Unknown targets	Nicotine (UC)*, stopping smoking (CD)*	72-75

*Denotes current or imminent option

inflammatory process, but which of these is, or are, of predominant importance in IBD is unclear. The anti-inflammatory actions of steroids include inhibition of leucocyte migration and activation; inhibition of the expression of cellular adhesion molecules; suppression of synthesis of cytokines (interleukins-1, -2, -6, -8 and tumour necrosis factor(TNF)), at least in part by inhibition of the activation of NFkB; reduction of release of lipid mediators (leucotrienes, thromboxanes, prostaglandins and platelet activating factor (PAF)); and inhibition of phospholipase A2, cyclo-oxygenase 2 and inducible nitric oyide synthase.

The numerous side-effects of systemic corticosteroids, particularly when given longterm (e. g. moon face, acne, purpura, dysphoria, opportunistic infection, hypertension, diabetes mellitus, weight gain, osteopaenia and growth retardation in children), have prompted a search for safer for mulations. To this end, a number of corticosteroid preparations have recently been assessed which when given orally are either poorly absorbed from the gut or very rapidly metabolised in the intestinal wall or liver: one of these, budesonide, has so far achieved clinical application.

When given in an oral controlled ileal release (CR) formulation to patients with active ileocaecal CD, budesonide was not significantly less effective than prednisolone in inducing remission in one study[14] and substantially better than placebo in another[15]. Side-effects were much fewer in patients given budesonide CR than prednisolone, as was adrenal suppression assessed by measurement of plasma cortisol levels[14]. When evaluated for maintenance of remission over 12 months in CD, budesonide CR delayed the onset of relapse when compared to placebo, but overall relapse rates at 1 year (60-70%) were, disappointingly, not improved[16,17]. In a trial in patients with UC, an oral colonic release preparation of budesonide showed benefit similar to that obtained with prednisolone in patients with active disease; particularly if extensive, disease; improved efficacy for patients with left-sided disease may depend upon the development of formulations providing even more delayed release of the active drug, or the use of higher doses[18]. Further studies are needed to clarify the role of oral budesonide in IBD. In particular, we require reassurance that to achieve a clinical result equivalent to that of prednisolone, it will not be necessary to use so great a dose of budesonide as to produce an incidence of systemic side-effects and adrenal suppression similar to that caused by conventional steroids.

Aminosalicylates (Table 1)

Suphasalazine is firmly established in the management of active colitis (both UC[4] and CD[5]), and in the maintenance of remission in UC[4]; the same applies to its sulphapyridine (and therefore relatively side-effect) free derivatives, whether in bacterially-liberated (olsalazine, balsalazide), enteric-coated pH-released [Asacol, Claversal, Salofalk (mesalazine e. c.)] or slow-release [Pentasa (mesalazine s. r.)] formulations.

Like corticosteroids, aminosalicylates have a wide variety of anti-inflammatory effects, although which of these explain their efficacy in IBD is not known. These actions include inhibition of leucocyte migration and cytotoxicity; reduced activation of NFkB; inhibition of the synthesis of lipid mediators (leucotrienes, thromboxanes, prostaglandins, PAF) and of interleukin-1; reduction of prostaglandin degradation; antioxidant

effects; TNF antagonism; and in epithelial cells, induction of heat shock proteins and inhibition of apoptosis and MHC Class II expression.

In active ileocaecal CD, recent interest has focussed on the use of mesalazine slow-release (Pentasa), a preparation which delivers high concentrations of 5-aminosalicylic acid to the small bowel as well as colon. In one study, this preparation, given in high dose (4 g/ day) for 16 weeks, resulted in a remission rate of 43% in patients with active ileocaecal CD, while lower doses (1 g and 2 g) were no more effective than placebo (remission rates 18% - 24%)[19].

While several individual studies in the last 10 years have suggested that aminosalicylates may also have a role in maintaining remission in inactive CD, a recent meta-analysis has shown this effect to be minimal, with a reduction in relative risk of symptomatic relapse at 1 year in patients on mesalazine as opposed to placebo of only 6%, and in post-operative patients of 13%[20]. Cost-benefit issues in relation to longterm use of these relatively expensive drugs in inactive CD clearly need resolution.

Aminosalicylates have a dose-related therapeutic role in moderately active (although not acute severe) UC and, particularly, in patients with inactive disease, in whom they reduce annual relapse rates to about 25% compared with 75% in placebo-treated patients. In patients with left-sided active UC, clinical trials support the theoretical proposal that drugs delivering 5 aminosalicylate (5-ASA) primarily to the colon (olsalazine, balsalazide) may be more effective than those from which 5-ASA is released more proximally, e. g. Asacol[21,22].

Immunomodulatory drugs (Table 1)

Azathioprine and 6-mercaptopurine The benefits of azathioprine and its metabolite, 6-mercaptopurine, as second-line agents in the management of chronic IBD are now widely accepted[23]. These agents inhibit purine nucleotide biosynthesis and appear thereby to modify Tlymphocyte function.

Azathioprine is useful in maintaining remission of both UC[24] (in patients failing to respond adequately to aminosalicylates) and CD[25], and as a steroid-sparing drug in the minority of patients with either disease who relapse repeatedly on steroid withdrawal[23]; it may also play special roles in accelerating remission and healing ileal lesions when given in combination with prednisone in active CD[26,27], and in Crohn's patients with perianal disease[23].

Apart from their side-effects (nausea, vomiting, headache, joint pains, rash, fever, and, more seriously, bone marrow depression, acute pancreatitis, chronic hepatitis and possible malignancy in longterm users), the main disadvantages of a zathioprine and 6-mercaptopurine are that they take up to 4 months to act when given orally. Trials to assess the possibility of accelerating the clinical response in active CD using intravenous azathioprine are in progress[28]. If results prove successful, use of this route of adminstration will demand prior assay of red blood cell concentration of 6-thiopurine methyltransferase (6-TPMT), homozygous deficiency of which can be fatal as a result of failure of inactivation of 6-mercaptopurine.

A French report showed that, in patients with inactive CD, the risk of relapse after 4 years of successful treatment with azathioprine (or 6-mercaptopurine) was similar whether the immunosuppressive agent was continued or stopped; The authors suggested that, in view of the potential toxicity of long-term use of azathioprine, its withdrawal should be considered in patients who had remained in remission after 4 years' treatment[29].

Cyclosporine Cyclosporine inhibits helper-and cytotoxic T-lymphocyte function and proliferation, mainly through inhibition of interleukin-2 gene transcription. It also reduces interferon-gamma, interleukin-3 and interleukin-4 production.

Interest in the use of intravenous cyclosporine in active CD was stimulated by Brynskov's provocative report in 1989[30], but subsequent trials have cast a dampener on the use of this agent, at least in low dose, in Crohn's.

In contrast, in a single small controlled study[31], the results of which have been largely confirmed by subsequent experience elsewhere, intravenous (4 mg/ kg·day) followed by oral (5 - 8 mg· kg/ · day) cyclosporin, given in addition to continuing corticosteroids, averted colectomy in the acute phase in about 80% of patients with acute severe UC who had failed to respond to 5-7 days of intravenous steroids.

Enthusiasm for this approach, however, needs to be tempered both by the frequency of relapse necessitating colectomy (up to 50%) that follows withdrawal of cyclosporine, and by its serious side-effects. Acutely, these include opportunistic infections, particularly pneumocystis carinii pneumonia; renal impairment including a 20% reduction in glomerular filtration rate in most patients, and an often irreversible interstitial nephritis in up to 25% patients; hypertension, hepatotoxicity, epileptic fits, hyperkalaemia, hyperuricaemia, hypertrichosis and paraesthesiae. Longterm oral use may predispose to lymphoma. The side-effects of cyclosporine necessitate frequent

monitoring of cyclosporine blood levels and serum biochemistry in treated patients. At present, use of cyclosporine in acute severe UC should probably be restricted to clinical trials and specialist centres familiar with its use. Further studies are needed to define which patients should be given the drug intravenously, and what continuing oral therapy, for example cyclosporin, azathioprine or 6-mercaptopurine, they should be prescribed thereafter. It is possible, however, that intravenous cyclosporine, perhaps given with prophylactic trimethoprim/sulphamethoxazole, may turn out to be very useful, in the minority of patients with steroid-refractory acute severe UC, for buying time for improving their nutrition prior to, and/or preparing them psychologically for surgery.

Methotrexate Methotrexate is an immunosuppressive agent widely used in difficult rheumatoid arthritis and psoriasis. A North American group reported that this drug, given once a week as a 25 mg intramuscular injection, was superior to placebo in improving symptoms (remission rates at 16 weeks 40% and 20%, respectively) and reducing requirements for prednisone in steroid-dependent CD[32]. In chronic steroid-dependent UC, in contrast, a lower dose of methotrexate (12.5 mg), given orally once weekly, was no more effective than placebo in the induction of remission or its maintenance over a 9 month period[33]. Whether use of methotrexate in IBD becomes widespread will depend on the success of rival agents with fewer side-effects.

Mycophenolate mofetil Very recently, a preliminary study suggested that mycophenolate mofetil, a T-cell inhibitor used increasingly in the prevention of transplant rejection, may be of value in refractory Crohn's disease[34]. This drug appears to be relatively non-toxic, although expensive, and is currently undergoing controlled trial in CD.

Antibiotics (Table 1)

Metronidazole Metronidazole acts not only against a range of anaerobes and protozoa, but also has immunomodulatory effects. Controlled trials have shown that oral metronidazole (800 mg/ day) has moderate benefit in ileocolonic CD[35], and in preventing recurrence after ileal resection[36], while open studies indicate that it may also be effective in perianal CD[37]. Treatment needs to be given for up to 3 months, and may be complicated by nausea, vomiting and unpleasant reactions when combined with alcohol; more importantly, it may induce a peripheral neuropathy not always reversible on its discontinuation.

Other antibiotics Anecdotal reports and uncontrolled trials have suggested possible roles for clarithromycin and ciprofloxacin in CD, the latter particularly for perianal disease, and for trimethoprim/sulphamethoxazole in acute severe UC. Tobramycin given orally in addition to steroids and sulphasalazine improved remission rate in active UC[38], and some gastroenterologists use this or another broad-spectrum antibiotic as prophylaxis against bacteraemia and endotoxic shock in severely ill patients with acute severe UC.

DIETARY THERAPY (Table 1)

There is no specific dietary therapy for patients with UC, although a few (< 5%) may improve with avoidance of cow's milk, and some with proctitis and proximal constipation may benefit from fibre supplementation. Patients with stricturing small bowel CD should avoid high residue foods (e. g citrus fruit segments, nuts, uncooked vegetables) which might cause bolus obstruction. All patients with IBD, particularly if it is active or extensive, are at risk of nutritional deficiencies which need replacement as necessary.

Over the last 20 years, it has become clear that in children with CD, as well as in adults with extensive small bowel disease and in those who respond poorly to, or prefer to avoid corticosteroids, an alternative therapy is a liquid formula diet. This can either be elemental (aminoacid-based), protein hydrolysate (peptide-containing) or polymeric (containing whole protein and not therefore hypoallergenic), and is given for 4-6 weeks as the sole nutritional source[39,40]. This approach is probably as effective as corticosteroid therapy in the short-term, about 60% patients achieving remission. Unfortunately, after the resumption of a normal diet, many patients relapse (50% at 6 months): whether this can be prevented by selective and gradual reintroduction of particular foods to which indivual patients are not intolerant, or by the intermittent use of further enteral feeding for short periods, remains to be proven.

The success of enteral nutrition as a primary treatment for CD is also limited by its cost, the unpleasant taste of some of the available preparations, the need often to give the feed by nasogastric tube, and the poor compliance of many patients in adhering to it. Such therapy does, nevertheless, offer a valuable alternative in the well-motivated minority of patients for whom it is appropriate.

NEW THERAPIES AIMED AT SPECIFIC PATHOPHYSIOLOGICAL TARGETS (Table 2)

Elucidation of the pathogenesis of IBD has led to

the evaluation in experimental animal models, and to a lesser extent in the human disease, of several different therapeutic approaches aimed at specific pathophysiological targets (Table 2). Where substantial data in humans, will now be briefly discussed.

Non-pathogenic escherichia coli

There is some evidence that patients with UC have increased proportions of adhesive and enterohaemorrhagic *E coli* in their large bowel. Two preliminary reports suggest that oral administration of capsules containing non-pathogenic *E coli* may have a role in maintaining remission in patients with inactive UC[41,42], but further work is required to confirm the efficacy of this or other
(e.g. , lactobacillus) probiotic approaches.

Short chain fatty acids (SCFA)

Normal colonic epithelial cells depend for their energy metabolism on a luminal supply of SCFA, derived from bacterial flora. In UC, colonocytes inadequately utilise SCFA; low luminal SCFA levels in UC exacerbate this metabolic defect[43]. Efforts to remedy the defect by treatment of patients with distal UC with enemas containing SCFA, principally butyrate, have unfortunately not proved uniformly successful[44-46]; furthermore, the appeal of this very safe therapy is restricted by the unpleasant smell of the enemas.

Modifying leucocyte numbers and function

Depleting leucocyte numbers, by use of leucocyte apheresis, antiCD4 antibodies or bone marrow transplantation, has been shown in uncontrolled reports to suppress activity of CD[47-49]; a similar effect is seen in AIDS when the CD4 count falls[50]. Furthermore, trials are in progress to assess the clinical efficacy in IBD of inhibiting leucocyte migration into the gut mucosa using antibodies or antisense oligonucleotides to adhesion molecules such as ICAM-1[51]. As with other major immunomodulatory therapies, it is not yet clear whether the benefits of such approaches will outweigh their cost, complexity and, particularly, toxicity in relation to the risks of infection and malignancy.

Modulation of cytokine activity

Recognition of altered cytokine expression in IBD has prompted therapeutic trials using interleukin-1 receptor antagonist, interferon-alpha and gamma, anti-TNF-alpha antibody and interleukin-10 (IL-10): of these, the last two are the most promising.

Anti-TNF-alpha antibody Controlled trials have shown that intravenous infusions of either mouse/human chimeric (cA2) or 95% humanised (CDP571) anti-TNF-alpha antibody induced remission in active refractory CD[52,53] and healed Crohn's fistulae[54]; uncontrolled studies suggest efficacy in UC too[55]. The published results are impressive, mucosal lesions healing completely in many instances. However, the relative merits of cA2 and CDP571 require clarification in relation to their efficacy, safety and cost. Reassurance is needed that repeated usage will not lead to adverse effects as a result of host antibody induction, or of immunosuppression with consequent opportunistic infection or malignancy. Definition of which patients are most likely to benefit from this very specialist treatment is also needed: this may relate not only to their disease phenotype (e. g. , fistulating disease), but also their genotype (e. g. , TNF microsatellite subtype).

Interleukin-10 IL-10 is an anti-inflammatory and immunosuppressive cytokine. A recent placebo-controlled trial of recombinant human IL-10 gave promising results in steroid-refractory CD[56], and further reports are imminent.

Antisense oligonucleotide to NFkB. The upregulation of NFkB in IBD tissue may play a central role in its pathogenesis as a result of stimulation of the synthesis of proinflammatory cytokines such as TNF, IL-1 and IL-6[10]. It remains to be seen whether trials of antisense oligonucleotides to NFkB will prove as effective and safe in human IBD as they appear to be in experimental colitis in mice[10].

Modifying the effects of lipid mediators

Reducing synthesis of proinflammatory prostaglandins with non-selective non-steroidal anti-inflammatory drugs (NSAIDs) has an adverse rather than beneficial effect in IBD, perhaps because of the concomitant suppression of cytoprotective prostaglandins[11]. The efficacy and safety of selective cyclooxygenase-2 (COX2) inhibitors have not yet been formally assessed in IBD. Trials with inhibitors of the synthesis of the extremely potent inflammatory mediator, leucotriene B4, in UC have shown at best a very modest benefit[57,58]. Ridogrel, a dual thromboxane synthesis inhibitor and receptor antagonist[59], has been shown to induce remission in over 40% patients with moderately active UC[60], and is under trial in active Crohn's. Antagonists to platelet activating factor (PAF) have been ineffective in active UC.

Antioxidants

While enhanced mucosal production of reactive

oxygen metabolites is well established[12], published trials of antioxidant therapy in human IBD are limited to one open study of patients with steroid-resistant CD who appeared to benefit from intramuscular injections of superoxide dismutase[61]. Despite the lack of controlled data available, many patients with IBD in the West use over the counter antioxidant drugs in an effort to ameliorate their disease.

Although increased mucosal generation of nitric oxide may contribute to the pathogenesis of IBD[62], there is no data yet to support the hypothesis that selective inhibition of inducible nitric oxide synthase may be beneficial.

Fish oil (eicosapentaenoic acid, EPA)

EPA, the active ingredient of fish oil capsules, decreases synthesis of leucotriene B4, thromboxane A2, prostaglandin E2, platelet activating factor and interleukin-1. Although these actions should make it a useful anti-inflammatory agent, trials in UC have shown that high doses produce only modest clinical improvement[63-65]: in addition, the strong fishy odour on the breath associated with consumption of EPA preparations is likely to inhibit their widespread use.

More recently, an enteric-coated fish oil preparation, which is better tolerated than standard formulations, although is not yet commercially available, has been reported to reduce substantially the relapse rate in patients with inactive CD (relapse rate at 1 year 28% on fish oil, 69% on placebo)[66]. This exciting result, if confirmed by other groups, could become a very useful and, probably, safe form of maintenance therapy in CD: the apparently beneficial cardiovascular effects of EPA would contribute to its popularity with patients.

Modulation of procoagulant state

Active IBD is characterised by a procoagulant diathesis which may contribute not only to the increased risk of systemic thromboembolism characteristic of the disease[59,67], but also to the intramucosal inflammatory process[13]. Several recent pilot studies suggest that intravenous heparin may have a beneficial effect on disease activity in both UC and CD[68], and controlled studies are in progress. Mechanisms of action of heparin in IBD are likely to include interference with leucocyte-endothelial cell adhesion and of platelet activation as well as its anticoagulant effects[68].

Modulation of enteric nerve function

Neuronal hyperplasia, hypertrophy and degeneration, together with abnormalities of neurotransmitter content, have been described in the gut mucosa of patients with IBD. In open studies, Bjorck *et al* have reported clinical and sigmoidoscopic improvement in 90% of UC patients treated with lidocaine enemas for up to 12 weeks[69]; similar uncontrolled results using ropivacaine gel rectally have been published more recently[70]. This approach needs to be validated by controlled trials; whether any beneficial effect of lidocaine or other local anaesthetics is due to modulation of enteric nerve function or to inhibition of production by mucosal leucocytes of inflammatory mediators[71] is unclear.

Smoking: Nicotine

Smoking is rare is patients with UC and anecdotal reports have suggested that some individuals can control their disease by judicious indulgence in this otherwise undesirable habit. Two controlled studies have confirmed that nicotine patches can induce remission in active UC[72,73], although, surprisingly, cannot maintain it[74]. Studies are in progress to assess the efficacy of alternative formulations of nicotine (for example in oral pH-release capsules or enemas) which, by allowing first-pass hepatic metabolism of nicotine will avert the systemic side effects produced by skin patches, and allow the use of higher doses. The mechanism of the therapeutic effect of nicotine in UC, some of the pharmacological effects of which appear to be pro-inflammatory, is unknown: possibilities include increased colonic mucus secretion, alterations of cell-mediated immunity, and reductions in gut permeability, prostaglandin E2 production and rectal mucosal blood flow.

Smoking has an adverse effect on the natural history of CD[75], including the reoperation rate: patients with CD who smoke should be advised to stop.

TRADITIONAL MEDICINE

In the West, a substantial minority of patients with IBD, dissatisfied with conventional pharmacological treatment, resort to alternative therapies including herbal medications such as aloe vera, relaxation, aromatherapy, acupuncture and homeopathy (Lakeman M & Rampton DS, unpublished)[76,77]. Unfortunately, however, there appear to be very few reports of the efficacy of such therapy, at least in the English language literature[78]: controlled studies of traditional medical treatment of IBD are urgently needed.

CONCLUSIONS

There is still no entirely effective, safe, cheap treatment for the suppression of IBD, let alone its cure.

Amongst the conventional alternatives, the

major recent advances are the development of oral corticosteroids, such as budesonide, with few systemic side-effects, and of new aminosalicylates, such as mesalazine slow-release for CD and balsalazide for UC. The side-effects of existing immunomodulatory agents, with the possible exception of azathioprine, make them unlikely to achieve a major role in patients with uncomplicated disease. Liquid formula diets are effective and safe in patients with active small bowel CD, but the value of traditional medical treatment in IBD is as yet unproven.

Of the drugs designed to rectify specific pathophysiological abnormalities in IBD, short chain fatty acids and lidocaine enemas are occasionally useful in patients with refractory distal UC. Injections of anti-TNF antibody and interleukin-10 may prove to be a major step forward in patients with difficult IBD, but their safety in the long- as well as short-term requires confirmation. Other "designer-drugs" have proved disappointing to date, perhaps because their effects on the complex inflammatory response are, unlike those of corticosteroids and aminosalicylates, too accurately focussed on specific, but redundant mediator pathways. We still need to learn what makes the inflammatory response in the mucosa of patients with UC and Crohn's persist chronically: it is possible that identification of this key abnormality will, in the absence of the discovery of a reversible primary cause, offer the best hope of developing an effective new therapy for patients with IBD.

REFERENCES

1 Sung JY, Chan KL, Hsu R, Liew CT, Lawton JWM. Ulcerative colitis and antineutrophil cytoplasmic antibodies in Hong Kong Chinese. *Am J Gastroenterol*, 1993;88:864-869

2 Lai CL, Wu PC, Wong KL *et al.* Clinical features of ulcerative proctocolitis in Hong Kong Chinese: a review of three decades. *Am J Proctol Gastroenterol Colon Rectal Surg*,1985;1:14-19

3 Sung JJY, Hsu RKK, Chan FKL, Liew CT, Lau JWY, Li AKC. Crohn's disease in the Chinese population. An experience from Hong Kong. *Dis Colon Rectum*, 1994;37:1307-1309

4 Kornbluth A, Sachar DB. Ulcerative colitis practice guidelines in adults. *Am Gastroenterol*, 1997;92:204-211

5 Hanauer SB, Meyers S. Management of Crohn's disease in adults. *Am J Gastroenterol*,1997;92:559-566

6 Modigliani R, Mary JY, Simon JF *et al*. Clinical, biological and endoscopic picture of attacks of Crohn's disease: evaluation on prednisone. *Gastroenterology*, 1990;98:811-818

7 Meyers S, Janowitz HD. "Natural history" of Crohn's disease. An analytic review of the placebo lesson. *Gastroenterology*, 1984;87:1189-1192

8 Chalifoux LV, Bronson RT. Colonic adenocarcinoma associated with chronic ulcerative colitis in cotton top marmosets. *Gastroenterology*, 1981;80:942-947

9 Podolsky DK. Inflammatory bowel disease. *New Eng J Med*, 1991;325:928-937 & 1008-1016

10 Neurath MF, Pettersson S, Meyer Zum Buschenfelde KH, Strober W. Local ad ministration of antisense phosphothiolate oligonucleotides to the p65 subunit of NF-kB abrogates established experimental colitis in mice. *Nature Medicine*, 1996;2:998-1004

11 Rampton DS, Hawkey CJ. Prostaglandins and ulcerative colitis. *Gut*, 1984; 25: 1399-1413

12 Simmonds NJ, Rampton DS. Inflammatory bowel disease'a radical view. *Gut*, 1993;34:865-868

13 Wakefield AJ, Sankey EA, Dhillon AP. Granulomatous vasculitis in Crohn's disease. *Gastroenterology*, 1991;100:1279-1287

14 Rutgeerts P, Lofberg R, Malchow H. A comparison of budesonide with pred nisolone for active Crohn's disease. *New Eng J Med*, 1994;331:842-845

15 Greenberg GR, Feagan BG, Martin F. Oral budesonide for active Crohn's disease. *New Eng J Med*, 1994;331:836-841

16 Greenberg GR, Feagan BG, Martin F. Oral budesonide as maintenance treatment for Crohn's disease: a placebo controlled, dose ranging study. *Gastroenterology*, 1996;110:45-51

17 Lofberg R, Rutgeerts P, Malchow H. Budesonide prolongs time to relapse in ileal and ileocaecal Crohn's disease. A placebo-controlled one year study. *Gut*, 1996;39:82-86

18 Lofberg R, Danielsson A, Suhr O. Oral budesonide versus prednisolone in patients with active extensive and left-sided ulcerative colitis. *Gastroenterology*, 1996;110:1713-1718

19 Singleton JW, Hanauer SB, Gitnick GL. Mesalamine capsules for the treatment of active Crohn's disease: result of 16 week trial. *Gastroenterology*, 1993;104:1292-1301

20 Comma C, Giunta M, Rosselli M, Cottone M. Mesalazine in the maintenance trea tment of crohn's disease: a meta-analysis adjusted for confounding variables. *Gastroenterology*, 1997;113:1465-1473

21 Courtney MG, Nunes DP, Bergin CF. Randomised comparison of olsalazine and mesalazine in prevention of relapses in ulcerative colitis. *Lancet*, 1992; 339:1279-1281

22 Green JRB, Lobo AJ, Holdsworth CD. Balsalazide is more effective and better tolerated than mesalamine in the treatment of acute ulcerative colitis. *Gastroenterology*,1998;114:23-28

23 Pearson DC, May GR, Fick GH, Sutherland LR. Azathioprine and 6-mercap topurine in Crohn's disease: a meta-analysis. *Ann Intern Med*, 1995;122: 132-142

24 Hawthorne AB, Logan RFA, Hawkey CJ. Randomised controlled trial of aza thioprine withdrawal in ulcerative colitis. *BMS*, 1992;305:20-22

25 O'Donoghue DP, Dawson AM, Powell-Tuck J, Bown RL, Lennard-Jones JE. Double blind withdrawal trial of azathioprine as maintenance treatment for Crohn's disease. *Lancet*,1978;2:955-957

26 Ewe K, Press AG, Sing CC. Azathioprine combined with prednisone or monotherapy with prednisone in active Crohn's disease. *Gastroenterology*, 1993; 105:367-372

27 D'Haens G, Geboes K, Ponette E, Penninckz F, Rutgeerts P. Healing of severe recurrent ileitis with azathioprine therapy in patients with Crohn's disease. *Gastroenterology*,1997;112:1475-1481

28 Sandborn WJ, van Os EC, Zins BJ. An intravenous loading dose of azathioprine decreases the time to response in patients with Crohn's disease. *Gastroenterology*, 1995;109:1808-1817

29 Bouhnik Y, Lemann M, Mary JY. Long-term follow-up of patients with Crohn's disease treated with azathioprine or 6-mercaptopurine. *Lancet*, 1996; 347:215- 219

30 Brynskov J, Freund L, Rasmussen SN. A placebo-controlled, double-blind randomised trial of cyclosporine therapy in active chronic Crohn's disease. *New Eng J Med*, 1989;321:845-850

31 Lichtiger S, Present DH, Kornbluth A. Cyclosporine in severe ulcerative colitis refractory to steroid therapy. *New Eng J Med*, 1994;330:1841-1845

32 Feagan BG, Rochon J, Fedorak RN. Methotrexate for the treatment of Crohn's disease. *New Eng J Med*, 1995;332:292-297

33 Oren R, Arber N, Odes S. Methotrexate in chronic active ulcerative colitis: a double blind, randomised, Israeli multi-centre trial. *Gastroenterology*, 1996;110:1416-1421

34 Neurath MF, Duchmann R, Peters M. Mycophenolate mofetil / cortisone versus azathioprine / cortisone for treatment of active inflammatory bowel disease: preliminary results of a prospective randomised study. *Gut*, 1997;41(suppl3): A224

35 Rosen A, Ursing B, Alm T. A comparative study of metronidazole and sulphasalazine for active Crohn's disease: the Cooperative Crohn's Disease Study in Sweden. II Result. *Gastroenterology*, 1982;83:550-562

36 Rutgeerts P, Hiele M, Geboes K. Controlled trial of metronidazole for preven tion of Crohn's recurrence after ileal resection. *Gastroenterology*, 1995; 108:1617-1621

37 Bernstein LH, Frank MS, Brandt LJ, Boley SL. Healing of perineal Crohn's disease with metronidazole. *Gastroenterology*, 1980;79:357-365

38 Burke DA, Axon ATR, Clayden SA, Dixon MF, Johnston D, Lacey RW. The efficacy of tobramycin in the treatment of ulcerative colitis. *Aliment Pharmacol Therap*, 1990;4:123-129

39 Fernandes Benares F, Cabre F, Esteve-Comas M, Gassull MA. How effective is enteral nutrition in inducing clinical remission in active Crohn's disease: a meta-analysis of the randomised clinical trials. *J Parent Enteral Nutr*,1995; 19:356-364

40 Griffiths AM, Ohlsson A, Sherman PM, Sutherland LR. Meta-analysis of en teral nutrition as a primary treatment of active Crohn's disease. *Gastroenterology*, 1995;108:1056-1067

41 Rembacken BJ, Snelling AM, Hawkey PM, Axon ATR. A double-blind trial of non pathogenic *E coli vs* mesalazine for the treatment of ulcerative colitis. *Gut*, 1997;41(suppl 3):A70

42 Kruis W, Schutz E, Fric P, Fixa B, Jud, aier G, Stolte M. Double-blind compari son of an oral Escherichia coli preparation and mesalazine in maintaining remission of ulcerative colitis. *Aliment Pharmacol Therap*, 1997;11:853-858

43 Roediger WE. The colonic epithelium in ulcerative colitis: an energy deficiency disease. *Lancet*, 1980;2:712-715

44 Breuer RI, Soergel KH, Lashner BA. Short chain fatty acid rectal irrigation for left sided ulcerative colitis: a randomised, placebo-controlled trial. *Gut*, 1997;40:485-491

45 Scheppach W, Sommer H, Kirchner T. Effect of butyrate enemas on the colonic mucosa in distal ulcerative colitis. *Gastroenterology*, 1992;103:51-56

46 Vernia P, Marcheggiano A, Caprilli R. Short-chain fatty acid topical treatment in distal ulcerative colitis. *Aliment Pharmacol Therapy*, 1995;9:309-313

47 Stronkhorst A, Radema S, Yong S-L. CD4 antibody treatment in patients with active Crohn's disease: a phase I dose finding study. *Gut*, 1997;40:320-327
48 Lopez-Cubero SO, Sullivan KM, McDonald GB. Course of Crohn's disease after allogeneic marrow transplantation. *Gastroenterology*, 1998;114:433-440
49 Bicks RO, Groshart KD. Editorial: the current status of T-cell lymphocyte apheresis(TLA)treatment of crohn's disease. *J Clin Gasterenterol*,1989;11: 136-138
50 James SP. Remission of Crohn's disease after human immunodeficiency virus infection. *Gastroenterology*, 1988;95:1667-1669
51 Koizumi M, King N, Lobb R, Benjamin C, Podolsky DF. Expression of vascular adhesion molecules in inflammatory bowel disease. *Gastroenterology*, 1992;103:840-847
52 Targan SR, Hanauer SB, van Deventer SJH. A short-term study of chimeric monoclonal antibody cA2 to tumour necrosis factor alpha for Crohn's disease. *New Eng J Med*,1997;337:1029-1035
53 Stack WA, Mann SD, Roy AJ. Randomised controlled trial of CDP571 anti body to tumour necrosis factor alpha in Crohn's disease. *Lancet*, 1997;349: 521-524
54 Van Deventer SJH, van Hogezand R, Present DH. Controlled study of anti-TNF-alpha for enterocutaneous fistulae complicating Crohn's disease. *Gut*, 1997;41(suppl 3):A2
55 Evans RC, Clarke L, Heath P, Stephens S, Morris AI, Rhodes JM. Treatment of ulcerative colitis with an engineered human anti-TNF-alpha antibody CDP571. *Aliment Pharmacol Therapy*, 1997;11:1031-1035
56 Van Deventer SJH, Elson CO, Fedorak RN. Multiple doses of intravenous interleukin 10 in steroid refractory Crohn's disease. *Gastroenterology*, 1997; 113:383-389
57 Laursen LS, Lauritsen K, Bukhave K. Selective 5 lipoxygenase inhibition by Zileuton in the treatment of relapsing ulcerative colitis: a randomised double-blind, placebo-controlled multicentre trial. *Eu J Gastroenterol Hepatol*, 1994; 6:209-215
58 Hawkey CJ, Dube LM, Rountree LV. A trial of Zileuton versus mesalazine or placebo in the maintenance of remission of ulcerative colitis. *Gastroenterology*, 1997;112:718-724
59 Rampton DS, Collins CE. Thromboxanes in inflammatory bowel disease-pathogenic and therapeutic implications. *Aliment Pharmac Therapy*, 1993; 7:357-367
60 Wright J, Schenowitz G, Adler G, Schneider H. Ridogrel for the treatment of mild to moderate ulcerative colitis: a placebo-controlled trial. *Gut*, 1996;39 (suppl 3):A188
61 Emerit J, Pelletier S, Tosoni-Verilgnue D, Mollet R. Phase II trial of copper-zinc superoxide dismutase (Cu Zn SOD) in the treatment of Crohn's disease. *Free Rad Biol Med*, 1989;7:145-149
62 Boughton-Smith NK, Evans SM, Hawket CJ. Nitric oxide synthase activity in ulcerative colitis and Crohn's disease. *Lancet*, 1993;342:338-340
63 Stenson WF, Cort D, Rodgers J. Dietary supplementation with fish oil in ulcerative colitis. *Ann Inter Med*, 1992;116:609-614
64 Aslan A, Triadafilopoulos G. Fish oil supplementation in active ulcerative colitis: a double blind, placebo controlled crossover study. *Am J Gastroenterol*, 1992;87:432-437
65 Hawthorne AB, Daneshmend TK, Hawkey CJ. Treatment of ulcerative colitis with fish oil supplementation: a prospective 12 month randomised controlled trial. *Gut*, 1992;33:922-928
66 Belluzi A, Brignola C, Campieri M, Pera A, Boschi S, Miglioli M. Effect of an enteric coated fish-oil preparation on relapses in Crohn's disease. *New Eng J Med*, 1996;334:1557-1560
67 Collins CE, Rampton DS. Platelet dysfunction: a new dimension in inflamma tory bowel disease. *Gut*, 1995;36:5-8
68 Evans RC, Shim Wong V, Morris AI, Rhodes JM. Treatment of corticosteroid-resistant ulcerative colitis with heparin'a report of 16 cases. *Aliment Pharmacol Therapy*, 1997;11:1037-1040
69 Bjorck S, Dahlstrom A, Ahlman H. Treatment of distal ulcerative colitis with lidocaine. *Can J Gastroenterol*, 1993;7:179-181
70 Arlander E, Ost A, Stahlberg D, Lofberg R. Ropivacaine gel in active distal ulcerative colitis and proctitis'a pharmacokinetic and exploratory clinical study.*Aliment Pharmac Therapy*, 1996;10:73-81
71 Sinclair R, Eriksson AS, Gretzer C, Cassuto J, Thomsen P. Inhibitory effects of amide local anaesthetics on stimulus-induced human leucocyte metabolic activation, leucotriene B4 release and interleukin-1 secretion in vitro. *Acta Anaesthiol Scand*, 1993;37:159-165
72 Pullan RD, Rhodes J, Ganesh S. Transdermal nicotine for ulcerative colitis. *New Eng J Med*, 1994;330:811-815
73 Sandborn WJ, Tremaine W, Offord KP. Transdermal nicotine for mildly to moderately active ulcerative colitis: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med*, 1997;126:364-371
74 Thomas GAO, Rhodes J, Mani V. Transdermal nicotine as maintenance therapy for ulcerative colitis. *New Eng J Med*, 1995;332:988-992
75 Sutherland LR, Ramcharan S, Bryant, Fick G. Effect of cigaretter smoking on recurrence of Crohn's disease. *Gastroenterology*, 1990;98:1123-1128
76 Rawsthorne P, Cronin CC, Shanahan F, Anton PA, Lofberg R, Bernstein CN. An international survey of the use and attitudes regarding alternative medicine by patients with inflammatory bowel disease. *Gastroenterology*, 1998; 114:A1067
77 Moody GA, Eaden JA, Phakta P, Sher K, Mayberry JF. The role of complementary medicine in European and Asian patients with inflammatory bowel disease. *Public Health*, 1998; in press
78 Chen Z. Treatment of ulcerative colitis with acupuncture. *J Tradit Chin Med*, 1995;15:231-233