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ASSESSMENT OF DRUG THERAPY IN INFLAMMATORY BOWEL DISEASE

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Introduction

Ulcerative colitis and Crohn's disease (regional enteritis) are chronic relapsing inflammatory conditions affecting the gut. In their initially described typical manifestations they were clearly distinct from each other, ulcerative colitis causing bloody diarrhoea due to inflammation confined to the colon, and Crohn's disease presenting with pain, diarrhoea and weight loss due to terminal ileal disease. The realisation that Crohn's disease could in addition or alternatively affect the colon has blurred this distinction, and it now seems uncertain whether they are two entirely distinct conditions, or poles of a clinical spectrum. Whilst their aetiology remains unknown this is unlikely to be resolved.

The age of onset of both conditions is variable, but may frequently present in young adults. Whilst countrywide figures are not available, it seems likely that in the UK there are between 12 and 25,000 individuals with diagnosed Crohn's disease (based on figures from Mayberry *et al.*, 1979 and Miller *et al.*, 1974), and a greater number with ulcerative colitis. Most patients require life-long medical supervision, even if for many this is only a twice-yearly out-patient assessment, so these diseases form an important part of gastroenterological practice. They are associated with significant morbidity and some mortality—for example a two-fold increased risk of dying amongst patients with Crohn's disease compared with matched controls in one recent study (Prior *et al.*, 1981). The variety of therapies in use and on trial, particularly for regional enteritis, emphasises how far we are from achieving ideal treatment, let alone cure of these conditions. This article is concerned with the assessment of drug therapy for inflammatory bowel disease, and is almost wholly concerned with the problems of assessing responses in individual patients. The design of trials will receive little attention, and for a discussion of problems arising with analysis of data from prolonged observation of individual patients the reader is referred to Peto *et al.* (1977). The term 'inflammatory bowel disease' is used to encompass both ulcerative colitis and Crohn's disease.

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Aetiological considerations

Clinicians and pathologists can, in the majority of cases, assign patients with non-specific inflammatory bowel disease to the categories of either ulcerative colitis or Crohn's disease. However studies on the aetiology and pathogenesis of the gut inflammation in these conditions do not currently support this distinction. One powerful argument for considering the two diseases as part of a spectrum comes from family studies. Up to 30% of patients presenting with inflammatory bowel disease may have affected relatives, and there are many examples of kindreds containing some individuals with ulcerative colitis and others with Crohn's disease (Singer *et al.*, 1971; Farmer *et al.*, 1981).

Initially each disease was differentiated clinically from an infectious disease, ulcerative colitis as a cause of bloody diarrhoea distinct from bacillary dysentery, Crohn's disease an inflammation of the terminal ileum distinct from tuberculosis. Since then there have been many attempts to implicate specific pathogens as the cause of inflammatory bowel disease, ranging from specific strains of *E. coli*, cell-wall deficient bacteria, and atypical mycobacteria to conventional viruses and 'transmissible agents' identified by cytotoxic effects in tissue culture. None have yet convincingly survived critical scrutiny in other laboratories (for example, Philpotts *et al.*, 1980) although it is clear that the altered milieu of inflamed gut favours the growth of many microorganisms.

As no infectious agent has been identified, the theory that immunological mechanisms are involved has gained ground. Some immunological theories consider inflammatory bowel disease a primary autoimmune disease, a manifestation of specific anti-gut immune responses such as anti-colon antibodies (Broberger & Perlmann, 1959) and lymphocyte cytotoxicity for colonic epithelium (Shorter *et al.*, 1969). Others emphasise the evidence for immune responses against antigens normally present in the gut lumen, such as bacteria, to suggest that local expression of the immune responses will damage the gut mucosa as an 'innocent bystander' (Monteiro *et al.*, 1971). There is a great wealth of evidence for immune

responses which potentially could cause gut inflammation, with virtually identical observations in both ulcerative colitis and Crohn's disease (Hodgson, 1980). Most of these could be unimportant consequences of gut inflammation.

As the primary cause remains unknown, specific curative therapy cannot be planned. This brief review of current aetiological theories would suggest that treatment should be aimed either at suppressing immune responses, or non-specifically at the inflammatory process; it would also suggest that the same drugs should be effective in both diseases.

Aims of therapy

The clinical state of a patient with active inflammatory bowel disease reflects many different factors. There is the primary disease process of gut inflammation, confined to the mucosa in ulcerative colitis, spreading through the thickness of the wall in Crohn's disease. There are metabolic consequences, such as protein-losing enteropathy and hypoalbuminaemia, anaemia, hypokalaemia, hypocalcaemia and hypomagnesaemia. Structural abnormalities arise such as strictures, perforations, fistulae or abscesses. The treatment of the patient will involve, and usually as a priority, treatment of these consequences of inflammation by transfusion, replacement of losses, minerals, vitamins and so on. In this discussion however, we are concerned with management of the primary disease process, as early as we can define it, the inflammation in the gut. Drug therapy in these chronic conditions, with characteristic episodes or relapse and remission, may be directed either at control of active inflammation or at the maintenance of remission.

Ulcerative colitis

Despite the familial and aetiological evidence which bring ulcerative colitis and Crohn's disease together, to most gastroenterologists clinically typical ulcerative colitis is easy to recognise, categorise and treat. The results of drug trials are usually clear-cut. It is worth identifying why this is so, to point out the contrast of the altogether different state of affairs in Crohn's disease.

Clinico-pathological correlations

Patients present with diarrhoea which is often bloody. Tenesmus reflecting rectal inflammation may be present. Colonic pain is usually mild. About 20% of patients have extra-intestinal manifestations, those of skin, joint and eye waxing and waning with gut disease, those of liver and spine much less related.

The pathological process is superficial mucosal inflammation, almost invariably present in the rectum and spreading for variable distances proximally. In pancolitis a small segment of ileum may also be inflamed. A distinction was formerly drawn between idiopathic proctitis confined to the rectum, and proctocolitis, but the basic disease processes seem identical. Over 10 years about 10% of patients with idiopathic proctitis will suffer proximal extension of their disease. The cases of 'right-sided' ulcerative colitis in text books prior to the 1960s work would now be classified as colonic Crohn's disease (Lockhart-Mummery & Morson, 1964).

There is a close correlation, both intuitively and in practice, between the pathological process of gut inflammation and the symptomatology. Furthermore patients with ulcerative colitis form a homogeneous group, in which the only significant variables are the activity of disease at the time of assessment, and the extent of colonic involvement. The homogeneity has been mathematically formalised by Hywel-Jones *et al.* (1973). As symptoms are rapidly assessed, and material for histopathological study is (relatively) accessible, there is little surprise that the disease has lent itself to clinical trials of drug therapy. It is only in the small group of patients with fulminant colitis, in whom general management problems such as transfusion and electrolyte management take urgent priority, combined with the early recourse to surgery, that clinical trials become difficult (Truelove & Jewell, 1974).

Clinical assessments

The major trials defining the sheet-anchors of ulcerative colitis therapy—sulphasalazine and corticosteroids, were performed in the 1950s and early 1960s using simple clinical indices and virtually identical assessments are in use today.

Active disease trials

Truelove & Witts (1955) defined active ulcerative colitis as an attack of bloody diarrhoea without specific pathogens, and assessed the result of cortisone therapy into one of three categories:

(i) clinical remission (1–2 stools daily, no fever, normal pulse, no anaemia, normal ESR).
(ii) no change or worse.
(iii) other—i.e. improved but not in remission.

That this remarkably simple assessment was a useful tool reflects in part the effectiveness of corticosteroid therapy, as minor degrees of clinical improvement might well not have emerged on such a simple scale.

Truelove & Witts (1955) defined three categories of disease activity, to assess the effectiveness of therapy in various severities of attack, *viz*:

	Severe	*Mild*
Bowel frequency	≥ 6 daily	≤ 4 daily
Blood in stool	++	±
Fever	> 37.5°C on 2 days out of 4	normal
Pulse rate (beats/min)	> 90	normal
Hb (allow for transfusion)	≤ 75%	normal or nearby
ESR	> 30 mm/h	< 30 mm/h

Moderate activity was intermediate between these two.

This simple assessment is remarkably robust, and is useful not only in assessing drug therapy but in correlating laboratory observations with disease activity. Nonetheless it has one major problem: although all the features mentioned worsen during severe attacks of ulcerative colitis, they do not necessarily move in unison, and patients may therefore hover between two categories, or even three. Thus the investigator is allowed a certain amount of 'discretion'. This index also involves two pieces of laboratory data, and the best laboratory correlate of disease activity is discussed later.

Similar clinical indices have been used by a number of authors; that of Dearing *et al.* (1969) prejudges an important issue by adding to the 'quiescent' category 'no activity as judged by proctologist and radiologist'; 'slight activity' judged by these two for 'mildly active' disease, and so on for each category. As it is unlikely that all clinical, sigmoidoscopic and radiological features will move together, and to avoid the undue exercise of 'discretion' in assigning an overall category, many workers define a number of clinical and other parameters and consider changes in each parameter separately. Additional clinical features such as urgency (the number of minutes for which the patient can resist the urge to stool), incontinence, general well-being and ability to work have been added (Buckell *et al.*, 1978). Additional data has been generated by the use of diary cards to record bowel frequency by day and night, the amount of rectal bleeding, the degree of urgency, and incontinent episodes (Heatley *et al.*, 1975; Buckell *et al.*, 1978). Such diary cards at least offer the patient a means of occupying his time whilst waiting in the follow-up clinic, and the data thereon correlate well with clinical indices, and with a 'global' clinical assessment by the patient of 'excellent', 'good', 'fair', 'bad' or 'terrible.' In practice there seems little to choose between any of these, and the clinical scale of Truelove & Witts (1955) does not seem to have been significantly bettered.

Sigmoidoscopic assessment

Direct inspection of the mucosa to assess inflammation might more pertinently reflect the results of anti-inflammatory treatment than clinical features. In patients with localised proctitis for example, this inflamed area is often associated with motility disorders in the adjacent bowel and resulting constipation, thus removing one of the cardinal symptoms of colitis. A number of studies have used sigmoidoscopic appearances ('proctoscopic findings by a qualified proctologist' (Dearing *et al.*, 1969)) to categorise patients. Baron *et al.* (1964) examined the observer variation in sigmoidoscopic assessment, emphasising that some features are readily classified (e.g. bleeding) whilst others (e.g. granularity) are not. The following grading has been suggested as likely to have less inter-observer disagreement (Heatley *et al.*, 1975):

Grade I – normal mucosa
Grade II – hyperaemic mucosa with loss of vascular pattern
Grade III – bleeding on light contact or spontaneously
Grade IV – severe changes with an excess of mucus, pus, mucosal haemorrhage and occasional ulceration

The correlation between sigmoidoscopic changes and clinical assessments, though good, is by no means absolute. For example 12 out of 46 patients who had achieved clinical remission after 4 weeks of corticosteroid therapy still showed active sigmoidoscopic appearances (Truelove & Witts, 1955). Conversely, in extensive ulcerative colitis treated with local corticosteroid preparations, the sigmoidoscopic appearances of the locally treated area may improve ahead of the rest of the colon. Whilst colonoscopy offers a way of assessing the appearance of the whole colon, it is not a suitable technique either for frequent use on the same patient, or for use in severe cases because of the risk of perforating the bowel.

Histological assessment

At sigmoidoscopic examination, superficial mucosal biopsies can be safely taken and offer an objective assessment of inflammation. Serial biopsies can be coded and shuffled, to eliminate all bias. A number of cardinal features, such as the degree of inflammatory infiltration in the lamina propria, the transmigration of polymorphonuclear cells across epithelium, crypt abscesses etc. are graded as normal, moderate or

severe. There are often considerable delays in achieving histological remission, and abnormal histology with active inflammation can be found when clinical and sigmoidoscopic appearances appear normal (Morson & Dawson, 1979). For example in Campieri *et al.* (1981) trial of 5-aminosalicyclic acid enemas, after 2 weeks clinical remission had been reached in 93% of cases, but histological in only 77%.

Radiological examination

Plain abdominal X-rays, though helpful clinically in acutely ill patients, lack precision. The barium enema, even with double contrast, is far less sensitive than endoscopic and histological examinations for identifying and defining disease extent; in particular the relatively ahaustral descending colon seen in some normal individuals is difficult to distinguish from mild distal colitis. Thus though improvement can be documented by radiological appearances on a 'better, worse, no change' scheme, this is insensitive, and indeed the changes noticed may not correlate with clinical changes: 6 out of 20 barium enemas in patients entering clinical remission after a month were unchanged or worse (Truelove & Witts, 1955). The radiation dosage (4–12 rads) also limits its use for repeated assessments.

Laboratory assessment

A simple blood test, reflecting the extent and severity of inflamed colon at the time of sampling, would offer many advantages. The ideal substance would be specific for inflammatory bowel disease, correlate with inflammatory activity, and be unaffected by treatment unless inflammation improved, in which case changes would be rapid.

Many blood tests have been tried, the original clinical index of Truelove & Witts (1955) incorporating haemoglobin and ESR.

Haemoglobin The Hb level, though clinically important, does not solely reflect inflammatory activity. Anaemia reflects length of history, whether or not supplements have been given, nutritional status and so on.

ESR An elevated sedimentation rate usually reflects increased concentration of alpha-globulins, fibrinogen and gamma-globulins. There is a good overall correlation with disease activity in ulcerative colitis; for example, using a clinical index, mean ESR was 18 mm/h in quiescent colitis, 43 in mildly, 62 in moderately and 83 in severely active disease. The scatter however was great, and amongst patients all of whom had severe bloody diarrhoea, weight loss, anaemia and fever, the range of ESR was 3 to 120 (Dearing *et al.*, 1969). In addition to this problem of scatter, with resulting overlap between groups, the ESR does not respond rapidly when patients improve. Clinical improvement often occurs within 24–48 h of corticosteroid therapy, but the ESR may not respond for a week or so, reflecting the relatively long half-life of the proteins that contribute to the sedimentation rate (Fagan *et al.*, 1982). These authors do show, however, that the ESR will not fall with corticosteroid therapy unless the patient's clinical condition improves.

Other acute phase reactants

The ESR reflects the serum concentration of a number of proteins some of which are acute phase reactants, and is also affected by packed cell volume and albumin concentration. It is more logical, though technically more demanding, to measure serum concentrations of a specific acute phase reactant. Seromucoids, a group of α_1-glycoproteins chemically separated from serum as perchloric-acid soluble, phosphotungstic acid insoluble materials, were first assessed by Cooke *et al.* (1958). The predominant protein is orosomucoid, α_1-acid glycoprotein. More recently a specific assay of α_1-acid glycoprotein has become available (Thaw & Albutt, 1980). The α_1-glycoprotein levels correlate with disease activity in ulcerative colitis, with a much lesser degree of overlap between the groups (Dearing *et al.*, 1969), and particularly good separation between mildly and moderately active patients judged clinically. The half-life of seromucoids measured by the precipitation assay is about five days, so that the speed of response in rapidly improving patients is no greater than the ESR. In a prospective study in which a purely clinical activity index was correlated with serum orosomucoids and ESR, there was a much better correlation with orosomucoids than ESR (Jensen *et al.*, 1976). Furthermore, there was a very good correlation between orosomucoid and protein loss into the gut, used by many workers as a 'gold standard' for gut inflammation, and discussed below.

Weeke & Jarnum (1971) analysed serum concentrations of 19 serum proteins in relation to disease activity in ulcerative colitis, and found significant elevations of orosomucoid, α_1-antitrypsin, easily precipitable glycoprotein, haptoglobin and haemopexin. Other proteins, such as complement components from classical and alternative pathways also react as acute phase reactants in this disease (Hodgson *et al.*, 1977). All these acute phase reactants increase proportionally to a clinical activity index, and none seem superior to orosomucoid. None is specific for the inflammatory process of ulcerative colitis or Crohn's disease. One classical acute phase reactant, C-reactive protein, which shows marked changes in Crohn's disease, was of little value in assessing patients with ulcerative colitis (Fagan *et al.*, 1982).

CEA

Although carcinoembryonic antigen achieved prominence as a marker of colorectal cancer, the finding of elevated serum levels in patients with ulcerative colitis raised the hope that this might be a relatively specific marker for inflammatory activity in the gut. However in serial studies, although an association of active disease and elevated CEA levels was found, even in pancolitis only 60% of patients had high levels during flare-ups of disease, and in patients with proctitis, only 12% had elevated levels (Gardner *et al.*, 1978).

Serum albumin and protein-losing and cell-losing enteropathy

Serum albumin levels have been incorporated into clinical indices (e.g. Burnham *et al.*, 1978) on the basis that albumin levels directly reflect gut inflammatory activity, falling as a result of a protein losing enteropathy. There is a close relationship between serum albumin levels and measured protein loss in inflammatory bowel disease (Bendixen *et al.*, 1970: Jensen *et al.*, 1976). Unfortunately this relationship only holds true of patients in a steady state, and several days (5–14) are required for studies of albumin metabolism, whether this is assessed by faecal excretion of labelled protein or by assessments of catabolic rate (Matthews, 1957; Bendixen *et al.*, 1968). A simple estimation of serum albumin gives information on extent and activity of disease over the preceding weeks, but does not rapidly respond to change.

A recent approach has been the use of ^{111}Indium labelled white cells (Saverymuttu *et al.*, 1981). Autologous labelled neutrophils after re-injection intravenously are rapidly localised in the gut mucosa, and a very high proportion of injected cells are excreted into the gut lumen from inflamed bowel, and can then be counted in faeces. In active ulcerative colitis, 2–30% of injected cells can be recovered within 72 h compared with $< 1\%$ in normals. This approach, initially introduced to localise diseased gut by external scanning, offers a more rapid assessment of the extent and severity of gut inflammation than protein loss; it is however technically demanding, requires a short-lived isotope, and involves a radiation dose if external scanning is to be performed of about 1 rad.

Other approaches

Identification and quantitation of prostaglandin metabolites in stool and urine of patients with ulcerative colitis, in amounts proportional to disease activity, raised the hope that this would offer an objective assessment of disease which might reflect one of the main mechanisms of inflammation (Gould *et al.*, 1981). However treatment with inhibitors of prostaglandin synthesis such as indomethacin lowered concentrations of prostaglandins without causing improvement in inflammatory activity (Rampton & Sladen, 1981).

Remission trials

Up to 75% of individuals who have recovered from an attack of ulcerative colitis will undergo relapse over a 12 month period (Misiewicz *et al.*, 1968). With this high spontaneous relapse rate, there has been little difficulty in demonstrating the effectiveness of maintenance therapy, by admitting patients in clinical remission 'on symptoms and sigmoidoscopic appearance,' and defining relapse on similar criteria, for example as 'a return of symptoms due to ulcerative colitis that required additional treatment' (Dronfield *et al.*, 1978).

Conclusions

In any trial of therapy in ulcerative colitis it is easy to assess both a number of clinically relevant symptoms, and sigmoidoscopic and histological appearances. Placing all these together into a 'global' index will lose some information, but effective therapy will be clear using any of these assessments. They should be adequate for elucidating the current problems in drug treatment of ulcerative colitis—the role of substituted sulphonamides, preparations of 5'aminosalicyclic acid derivatives, etc. It is relevant however that the value of these assessments was proved in trials of highly effective drugs. If two very similar treatments are compared, a real advantage in one, in speed of response for example, may not be apparent with these indices and laboratory supplementation may then add further information. Serum orosomucoid, or the specific α_1-acid glycoprotein analysis, would seem the best candidate for this.

Crohn's disease

Experience of the assessment of drug therapy in Crohn's disease contrasts sharply with that in ulcerative colitis, mainly reflecting the characteristics of the disease.

Clinico-pathological correlations

Crohn's disease may effect any area of the gut: approximately one third of patients have mainly colonic disease, one third disease confined to the small gut, particularly terminal ileum, and one third have mixed disease (de Dombal *et al.*, 1974). Gut inflammation is discontinuous and transmural and

associated with fibrosis, stenosis and fissuring, fistulae and abscesses. Symptoms differ strikingly according to disease site. Pure colonic disease may be indistinguishable from ulcerative colitis. Small intestinal disease depending on site and extent can present with malabsorption with oedema due to hypoalbuminaemia, with subacute obstruction, or with anaemia or growth retardation in patients with no gastrointestinal symptoms. Persistent perianal problems may be the only symptom. Extra-intestinal manifestations of eye, skin and joint disease show a less clear relationship between exacerbations and gut disease activity, probably reflecting persistent low grade inflammatory activity. The lack of correlation between symptoms and the process of gut inflammation is illustrated by frequent delays of several years between the first symptom of the disease and diagnosis; furthermore, clinically uninvolved areas of the gut in a patient with Crohn's disease often show inflammation or biochemical abnormalities if meticulously examined (Ferguson *et al.*, 1975; Goodman *et al.*, 1976).

Crohn's disease thus lacks the advantages of ulcerative colitis. The patients are heterogenous (mathematically expressed by Hywel-Jones *et al.* 1973); there is a poor correlation between gut inflammatory activity and symptoms in many individuals; tissue is not readily available for repeated biopsy unless the rectum is involved.

Clinical assessments

The various clinical indices of disease activity reflect these difficulties. De Dombal *et al.* (1974) produced a clinical index for classifying disease activity as a factor affecting short term prognosis, based on the Truelove and Witts ulcerative colitis criteria. Their assessment was as follows:-

Local features	*Mild*	*Severe*
Bowel actions	2–3/day	6+/day
Pain	occasional	continuous/severe
Rectal bleeding	negligible	macroscopic
Systemic symptoms		
Pulse (beats/min)	<90	>100
Temperature	<99°F	>99°F
Hb	>80%	<70%
Weight loss	<½ stone (3.3 kg)	>1 stone

Intermediate attacks were graded as moderate.

This assessment highlights the difficulties. The index is clearly suitable for colonic disease, but it is unlikely that a patient with small intestinal disease would appear in the 'severe' category on all seven counts: thus there is again an element of 'discretion' in allotting patients to a final category. One value of this index is that all the information is usually available retrospectively, and it is a useful tool for correlating immunological or other observations with disease activity. It is unlikely to be sensitive enough to follow responses of individual patients to therapy, particularly as therapeutic responses to drugs in Crohn's disease are often not dramatic.

Crohn's disease activity index

The best known attempt to assess clinical activity in Crohn's disease is the Crohn's disease activity index, CDAI, designed for the U.S. National Co-operative Crohn's Disease Study (NCCDS), initiated in 1970 at which time no regimes for Crohn's disease had been subjected to controlled clinical trial (Winship *et al.*, 1979).

The requirement for the CDAI illustrates further the difficulties of assessing drug therapy in Crohn's disease. The number of patients with active Crohn's disease are relatively small in any one centre. All the drugs subjected to this clinical trial, prednisolone, sulphasalazine and azathioprine, have dose-related side-effects. The clinical assessment had to be reproducible in different centres and quantifiable so that (i) a given degree of improvement could permit a reduction of the trial drug dose, and (ii) degrees of improvement could be subjected to ranking and statistical analysis (Summers *et al.*, 1979).

To construct the CDAI, a panel of gastroenterologists identified 18 parameters which could easily be assessed at an outpatient visit, which were thought to be important indicators of disease activity. These were measured in 116 patients, and an overall evaluation of the patient arrived at simultaneously, using the global categories of 'very well,' 'fair to good,' 'poor,' and 'very poor.' This last assessment was given a numerical value (y = 1, 3, 5 or 7 respectively) as the dependent variable, and then related to the 18 measured parameters, $x_1 - x_{18}$, the independent variables, by the formula $y = b_0 + b_1 \times_1 + b_2 \times_2 \ldots\ldots b_{18} \times_{18}$. Multiple regression analysis was used to delete the independent variables that contributed least to prediction of the global clinical state, so that 8 important predictive variables were identified, each of these weighted by a coefficient to achieve the best prediction of the dependent variable; and these coefficients were then standardised to whole numbers. (Best *et al.*, 1976, 1979). The calculation of the CDAI based on the eight surviving variables is illustrated in Table 1. The value of the CDAI can range from slightly negative to over 600. Table 1 also enumerates the 10 variables deleted either because they were inadequate predictors, or because the prediction appeared illogical.

It is apparent that subjective features play a major part in this index, notably of diarrhoea, pain, and sensation of well-being (recorded over a week in a diary card by the patient). 23% of the final index is contributed by the sensation of well-being alone (Best *et al.*, 1976). To define 'remission' an object of

Table 1 Crohn's disease activity index (CDAI). Best *et al.* (1976).

	Variables	
1.	No liquid or soft stools (each day for seven days)	× 2
2.	Abdominal pain (0=none – 3=severe, 1 and 2 intermediate)	× 5
3.	General well-being (0=well – 4=terrible, 1, 2 and 3 intermediate)	× 7
4.	Number of complications amongst (i) arthralgia/arthritis, (ii) iritis/uveitis, (iii) E. nodosum, pyoderma gangrenosum, aphthous stomatitis, (iv) anal fissure, fistula or abscess, (v) other fistula, (vi) fever over 100°F during past week.	× 20
5.	Taking opiates for diarrhoea 1=yes, 0=no	× 30
6.	Abdominal mass (0=none, 2=questionable, 5=definite)	× 6
7.	47 – haematocrit (males) 42 – haematocrit (females)	× 6
8.	% deviation from standard weight (+ or −)	× 1
		Total = CDAI

'Remission' < 150 Severely ill > 450

Thus a patient with 4 loose stools daily, mild daily abdominal pain, feeling 'poorly' with a perianal fistula, taking codeine phosphate, with a questionable right iliac fossa mass, a PCV 5% below normal, 5% under body weight would have a CDAI of (28 × 2) + (7 × 5) + (14 × 7) + (1 × 20) + (1 × 30) + (2 × 10) + (5 × 6) + (5 × 1) = 294.

Excluded variables (see text) 1. Average daily temperature, 2. Average hours of pain, 3. Days per week with blood in stool, 4. Nausea and vomiting, 5. Appetite, 6. Nocturnal bowel motions, 7. Abdominal tenderness, 8. Serum albumin, 9. Pain awakening patient, 10. Site of disease.

treatment, a CDAI of 150 was chosen. 90% of 'very well' patients score below 150, but also 6% of 'poor' patients are thus 'in remission.' A CDAI of 450 was interpreted as sufficiently severe disease to warrant withdrawal from a double-blind trial.

The CDAI has been widely discussed and not universally accepted. The major subjective element renders it particularly unsuitable for the assessment of drugs with euphoriant effects such as prednisone. It is cumbersome, requiring a week's diary card from the patient, and a complex calculation from the physician: on subsequent enquiry amongst the physicians involved in the NCCDS, 21% found it 'a real pain to calculate' (Best & Becktel, 1981). A simpler form of the CDAI, assessing diarrhoea, pain and well-being over 1 day only, and deleting consideration of opiates, haematocrit and weight, with only minor loss of predictive power, has been proposed by Best & Becktel (1981).

A large number of much simpler clinical indices have been proposed. Harvey & Bradshaw (1980a) proposed a one-day index scoring from 0–15, as shown in Table 2. This correlated well with the CDAI, not surprisingly, as many of the features measured are identical, with the patient's assessment of well-being, stool frequency and pain being the major determinants. An International Workshop at Oxford in 1981 drew up a list of 10 clinical features, each to be scored as present or absent, omitting the highly subjective variable of well-being: the 10 features are shown in Table 3. The Organisation Mondiale de Gastroenterologie surveyed over 20 centres worldwide and identified six objective variables closely related to severity (Myren *et al.*,

Table 2 Simple clinical index – Harvey & Bradshaw (1980a)

A. General well-being (0=very well, 1=slightly below par, 2=poor, 3=very poor, 4=terrible).
B. Abdominal pain (0=none, 1=mild, 2=moderate, 3=severe).
C. Number of liquid stools daily.
D. Abdominal mass (0=none, 1=dubious, 2=definite, 3=definite and tender).
E. Complications: arthralgia, uveitis, erythema nodosum, aphthous ulcers, pyoderma gangrenosum, anal fissure, new fissure, abscess (Score 1 per item).

Table 3 Oxford Assessment—Clinical index for Crohn's disease

1. Pain present.
2. Bowels open 6+ per day *or* blood and mucus in stools.
3. Perianal complications.
4. Fistula.
5. Other complications.
6. Mass present.
7. Wasting *or* emaciated.
8. Temperature above 38°C.
9. Tenderness present.
10. Haemoglobin below 10 g.

Score 1 for each of the ten features present.

1978). When information gathered from a large number of centres was analysed simultaneously by the CDAI, Harvey and Bradshaw's index, the OMGE index and the Oxford index (de Dombal *et al.*, 1982), there was a high degree of correlation between all of them.

Whilst the treatment of a patient with Crohn's disease is clearly aimed at overall clinical improvement, the majority of drugs in use are more specifically aimed at the inflammatory process. Use of the CDAI in such trials emphasises that the term Crohn's disease activity index is a misnomer: 'I wish we had called it an illness index' (Singleton, 1981). Many of the complications of Crohn's disease will elevate the CDAI or other clinical scores, yet do not reflect active inflammation. Frequency of diarrhoea following resection is one obvious example. Fibrotic obstruction needs a surgeon, not anti-inflammatory drugs. Interestingly Harvey & Bradshaw (1980b) commented that the combination of a high clinical score with a low ESR was a harbinger of early surgery in their patients.

In the design of trials, this implies the selection of patients for anti-inflammatory therapy on the basis that active inflammation is present and is contributing to the symptoms; admitting all comers on the basis of symptomatic disease with a high 'illness' score may obscure the effectiveness of such treatment. The alternative approach is to use combined clinical and laboratory indices with a greater reflection of inflammatory activity, or to resort to laboratory estimations in parallel with the clinical scores.

Combined clinical and laboratory indices

Of the relatively simple clinical indices, the CDAI involves measurement of the packed cell volume; a clinical index used by Burnham *et al.* (1978) scored haemoglobin, white blood count, ESR and serum albumin, each given a value of 0–2 on the basis of degree of abnormality, in addition to a clinical score on the traditional clinical features of well-being, pain, frequency of diarrhoea and rectal bleeding, plus physical signs of weight loss, fever, mass, tenderness, fistulae, perianal and extra-intestinal lesions.

Few of these laboratory measurements are related purely to inflammatory activity. Haemoglobin or packed cell volume reflects prior blood loss and haematinic deficiency as well. White blood counts may be affected by many drugs used in the treatment of Crohn's disease—prednisone, sulphasalazine and immunosuppressants. The role of albumin is discussed later. The ESR in Crohn's disease, as in ulcerative colitis, shows considerable overlap between groups, and in a group of patients assessed clinically using de Dombal's index, the median ESR was 18 in 36 patients with mild disease, and 17 in 40 moderately active patients (Fagan *et al.*, 1982).

The most ambitious combined clinical and laboratory index is that of van Hees *et al.* (1980). The index was drawn up by a similar process to that for the CDAI, except that clinical and laboratory data, rather than the patients themselves, were presented to three gastroenterologists, who drew up global index of 'inactive' to 'very severe.' Using multiple regression analysis again, an activity index was drawn up using 9 pieces of data, as shown in Table 4 with an example. The final Activity Index again involves a constant and coefficients for each variable, and gives a value of between 50 and 300.

Almost all the data in the van Hees index are objective, and in comparison with the CDAI (van Hees *et al.*, 1980) and with the other clinical indices referred to above which all correlate well with each other (de Dombal *et al.*, 1982) the van Hees index is the odd one out. The level of serum albumin contributes most to the van Hees index, based on the authors' belief that 'protein loss via the intestinal wall is the most reliable parameter to measure the inflammatory activity in the intestine' and the demonstration that serum albumin correlates better with gut protein loss that total protein ESR or haemoglobin (van Tongeren & Eekhout, 1976). This good correlation notwithstanding, serum albumin level is also affected by nutrition, and reflects the product of both inflammatory activity and the duration of active disease, and these considerations may explain the poor correlation with other indices. Whilst the van Hees index has been an effective tool to document clinical improvement during a clinical trial of salazopyrine (van Hees *et al.*, 1981) it is unlikely to respond very rapidly to changes in inflammatory activity.

Pure laboratory indices

The ideal laboratory index, specific, sensitive and rapid in response, does not exist. André *et al.* (1980) surveyed a number of candidate serum proteins

Table 4 Activity index for Crohn's disease. Van Hees *et al.* (1980)

Variables		*Coefficient*
Albumin (g/l)	×	− 5.48
ESR (mm/h)	×	0.29
Body mass index (Quetelet) $\frac{\text{weight (kg)} \times 10}{\text{H}^2\ (\text{m}^2)}$	×	− 0.22
Abdominal mass (1=no, 5=>12 cm diameter)	×	7.83
Sex (1=male, 2=female)	×	− 12.3
Temperature °C	×	16.4
Stool consistency (1=well formed, 3=watery)	×	8.46
Resection (1=no, 2=yes)	×	− 9.17
Extraintestinal lesions (1=no, 2=yes).	×	10.7
Constant		−209

Example: A female, afebrile, weighing 65 kg, height 1.78 m, who has had a resection previously, has no mass or extra-intestinal lesions, but loose motions, an ESR of 45 and an albumin of 29 g/L, has an activity index of (29 × −5.48) + (45 × 0.29) + (205 × −.22) + (1 × 7.83) + (2 × −12.3) + (37 × 16.4) + (2 × 8.46) + (2 × −9.17) + (1 × 10.7) − 209 = 199, corresponding to the clinicians' assessment of moderate activity.

(orosomucoid, C-reactive protein (CRP), albumin, individual immunoglobulins, alpha-1-antitrypsin) together with iron, haematocrit, ESR and a crude test for circulating immune complexes, and found that only the orosomucoid and CRP levels, and the ESR, significantly correlated with the CDAI.

In an extensive assessment of CRP in Crohn's disease, Fagan *et al.* (1982) found a much more impressive correlation between a clinical index of disease activity (de Dombal's) and CRP than was found in patients with ulcerative colitis. The serum CRP level (< 1 mg/ml in normal individuals) had a median value of 4 in mild disease, 15 in moderate and 85 in severe disease, although again there was considerable overlap between groups. There was however a very rapid fall in CRP level over 24–48 hours after the initiation of successful treatment (although corticosteroids did not lower the CRP if clinical improvement did not occur). The CRP level would therefore seem to be a sensitive and rapidly responding correlate of inflammation, though not specific for inflammatory bowel disease. A direct comparison of serial changes of CRP and orosomucoid would be of interest.

Figure 1 shows this index of inflammatory activity, the serum CRP correlated with the CDAI in a group of patients, and also shows the global ratings of mild, moderate or severe for the whole group. The CDAI

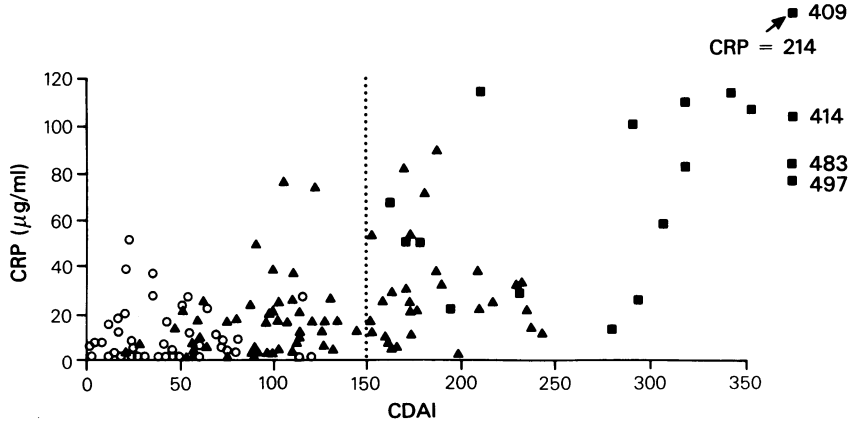

Figure 1 Simultaneous assessment of serum C-reactive protein (CRP, y axis) and CDAI (x axis) in 25 individuals each studied on a number of occasions. The clinical categories (de Dombal *et al.*, 1974) of mild O, moderate ▲, and severe ■, are also shown. T = 0.47, $P < 0.01$. (Fagan *et al.*, 1982).

correlates moderately with CRP level (Kendalls coefficient T = 0.47) but there are some patients in whom these are obviously discordant. Patients with surgical complications such as fibrous strictures would score high on CDAI, but low in CRP; conversely low CDAI with high CRP levels might represent indifference by the patient, or the euphoriant effect or prednisone; additionally patients who present with clinically longstanding disease despite a short history have probably passed through this stage.

The role of protein-loss estimation, and white cell scanning with faecal collection, are as already outlined in patients with ulcerative colitis. The white cell excretion correlates with CDAI level and with CRP levels in the majority of patients (Saverymuttu *et al.*, 1982), and in Crohn's disease its ability to identify areas of gut inflammation may be particularly useful. It is however not likely to become widely applicable for multicentre trials, although it may be useful in specialised centres using complex assessment protocols.

Histological assessment

Although subtle abnormalities can be found histologically in gut tissue taken from sites remote from clinical and radiological involvement in Crohn's disease, such abnormalities may need special cell counting techniques for detection (Ferguson *et al.*, 1975), are not specific for Crohn's disease (Hill *et al.*, 1979) and do not seem suitable for assessing the main inflammatory activity in a patient. Therefore it is only in patients with rectal involvement in whom repeated histological assessment could be made in trials of drug therapy; colonoscopy cannot be frequently repeated, does not regularly visualise the terminal ileum, and only provides very superficial fragments for assessment of this transmural disease process. Even when conventional rectal biopsies are taken through a rigid sigmoidoscope in patients with colonic involvement, characteristic histology for Crohn's disease is obtained in less than 20% of patients. Even more disappointingly when rectal biopsy appearances were classified in increasing degrees of abnormality, there was no correlation between severity of inflammation and clinical symptoms of diarrhoea and bleeding, or the Crohn's disease activity index, either in the whole group of patients investigated in the NCCDS, or even in patients with only colonic disease. The role of histology in Crohn's disease would appear to be to confirm the diagnosis, and extent of disease (Hill *et al.*, 1979).

Radiological assessment

The extensive radiological assessment of Crohn's disease in patients treated with placebo during the NCCDS demonstrated the erratic and unpredictable correlation between radiographic and clinical features. Despite the achievement of clinical remission of 60% of prednisone-treated patients after 4 months, within this group of patients overall no significant radiological improvement was noted; improvement was noted only in the group in whom radiological assessment was carried out after more than 6 months prednisone therapy (Goldberg *et al.*, 1979).

The poor correlation with clinical indices, the radiation risk, and the intra-observer error (Geffen *et al.*, 1968) all combine to make radiological assessment a cumbersome and inefficient means of assessing drug therapy, although its value in diagnosis and definition of disease site and extent is not in doubt.

Other forms of assessment

Present *et al.* (1980) responded to the heterogeneity of clinical features in patients with Crohn's disease by setting specific treatment goals for each individual—elimination of a mass, closure of a fistula, withdrawal of steroid therapy without relapse, prevention of obstruction. Whilst in a small group of patients with different treatment aims this results in difficulties in evaluating the result of a trial, the concept that patients with Crohn's disease cannot be treated as a whole, but should be stratified in terms of the manifestations of their disease, seems well-founded.

Trials in children

Assessment of disease activity presents particular problems in children, when subjective factors may be even more difficult than usual to analyse, and additional clinical features such as growth retardation may be particularly important.

Whittington *et al.* (1977) defined a global clinical rating (1 to 6) based mainly on chart review of patient's symptoms, physical examination, and ESR, haemoglobin, and serum albumin. Lloyd-Still & Green (1979) defined a much more complex clinical score, analogous to that used for grading patients with cystic fibrosis, assessing normal activities, diarrhoea, fever, physical examination, height and weight gain, radiological abnormalities, haematocrit, white cell count, ESR and albumin. The scores range from 10–80. As expected, the Whittington *et al.* (1977) score, that of Lloyd-Still & Green (1979) and the CDAI all correlate. The Lloyd-Still approach, in which height and weight gain form a major part of the assessments, seems intuitively to be best adapted to long-term assessments of drug therapy in children.

Conclusions

The extensive correspondence initiated by the

NCCDS has highlighted many problems, notably the effects of withdrawing previous drug therapy just before commencing a therapeutic trial, and the optimum time for assessment of therapeutic responses to drugs such as immunosuppressants. In addition, stratification of patients by disease site if clearly necessary (Summers *et al.*, 1979). There is no ideal clinical index, and laboratory measures of inflammatory activity often diverge from the clinical assessments. An ideal trial of therapy in Crohn's disease would study well-characterised patients, with similar disease sites, without surgical complications, after replacement of nutritional deficiences, with active inflammation, assessing response over a prolonged period of time by a number of purely clinical indices, and simultaneously by laboratory parameters of which the most helpful are the acute phase reactants, and the most specific the protein and white cell excretions. There may be some delay in realising this ideal.

References

ANDRE, C., DESCOS, L., LANDAIS, P. & FERMANIAN, J. (1980). Laboratory supplementation of Crohn's disease activity index. *Lancet*, **ii**, 594–595.

BARON, J.H., CONNELL, A.M. & LENNARD-JONES, J.E. (1964). Variation between observers in describing mucosal appearances in proctocolitis. *Br. med. J.*, **1**, 89–96.

BENDIXEN, G., JARNUM, S. & SOLTOFT, J. (1968). IgG and albumin turnover in Crohn's disease. *Scand. J. Gastroenterol.*, **3**, 481–489.

BENDIXEN, G., GOLTERMANN, N. & JARNUM, S. (1970). Immunoglobulin and albumin turnover in ulcerative colitis. *Scand. J. Gastroenterol.*, **5**, 441–443.

BEST, W.R., BECKTEL, J.M., SINGLETON, J.W. & KERN, F. (1976). Development of a Crohn's disease activity index. *Gastroenterology*, **70**, 439–444.

BEST, W.R., BECKTEL, J.M. & SINGLETON, J.W. (1979). Rederived values of the eight coefficients of the Crohn's disease activity index (CDAI). *Gastroenterology*, **77**, 843–846.

BEST, W.R. & BECKTEL, J.M. (1981). Crohn's disease activity index as a clinical instrument. In *Recent Advances in Crohn's Disease*, eds Pena, A.S., Weterman, I.T., Booth, C.C. & Strober, W. pp. 7–11. Amsterdam: Nijhoff.

BRAHME, F. & FORK, F.T. (1975). Dynamic aspects of colonic Crohn's disease. *Radiology*, **15**, 463–467.

BROBERGER, D. & PERLMANN, P. (1959). Auto antibodies in human ulcerative colitis. *J. exp. Med.*, **110**, 657–677.

BUCKELL, N.A., GOULD, S.R., DAY, D.W., LENNARD-JONES, J.E., & EDWARDS, A.M. (1978). Controlled trial of disodium cromoglycate in persistent ulcerative colitis. *Gut*, **19**, 1140–1143.

BURNHAM, W.R., LENNARD-JONES, J.E. & HECKETSWEILER, P. (1979). BCG vaccination in Crohn's disease. *Gut*, **20**, 229–233.

CAMPIERI, M., LANFRANCHI, G.A., BAZZOCCHI, G., BRIGNOLA, C., SARBI, F., FRAZER, G., BATTOCCHIA, A., LABO, G. & DAL MONTE, R.R. (1981). Treatment of ulcerative colitis with high dose 5-aminosalicylic acid enemas. *Lancet*, **ii**, 270–272.

COOKE, W.T., FOWLER, D.C. & COX, E.V. (1958). The clinical significances of seromucoids in regional ileitis and ulcerative colitis. *Gastroenterology*, **34**, 910–919.

DEARING, W.H., McGUCKIN, W.F. & ELVEBACK, L.R. (1969). Serum α_1-acid glycoprotein in chronic ulcerative colitis. *Gastroenterology*, **56**, 295–303.

DE DOMBAL, F.T., BURTON, I.L., CLAMP, S.E. & GOLIGHER, J.C. (1974). Short-term course and prognosis of Crohn's disease. *Gut*, **15**, 435–443.

DE DOMBAL, F.T., CLAMP, S.E. & SOFTLEY, A. (1982). *International Workshop on Crohn's Disease Activity*, Lyon, France.

DRONFIELD, M.W. & LANGMAN, M.J.S. (1978). Comparative trial of sulphasalazine and oral sodium cromoglycate in the maintenace of remission in ulcerative colitis. *Gut*, **19**, 1136–1139.

FAGAN, E.A., DYCK, R.F., MATON, P.N., HODGSON, H.J.F., CHADWICK, V.S. & PEPYS, M.B. (1982). Serum levels of C-reactive protein in Crohn's disease and ulcerative colitis. *Eur. J. clin. Invest.* (in press).

FARMER, R.G., MICHENER, W.M. & SIVAK, D.S. (1981). Studies of family history in inflammatory bowel disease. In *Recent Advances in Crohn's Disease*. ed. Pena, A.S., Wetterman, I.T., Booth, C.C. & Strober, W. pp. 213–218. Amsterdam: Nijhoff.

FERGUSON, R., ALLAN, R.N. & COOKE, W.T. (1975). A study of the cellular infiltrate of the proximal jejunal mucosa in ulcerative colitis and Crohn's disease. *Gut*, **16**, 205–208.

GARDNER, R.C., FEINERMAN, A.E. & KANTROWITZ, P.A. (1978). Seral CEA (carcino/embryonic antigen) blood levels in patients with ulcerative colitis. *Am. J. dig. Dis.*, **23**, 129–133.

GEFFEN, N., DARNSBOROUGH, A. & DE DOMBAL, P.T. (1968). Radiological signs of ulcerative colitis: assessment of their reliability by means of observer variation studies. *Gut*, **9**, 150–156.

GOLDBERG, H.I., CARUTHERS, S.B., NELSON, J.A. & SINGLETON, J.W. (1979). Radiographic findings of the National Co-operative Crohn's Disease Study. *Gastroenterology*, **77**, 925–937.

GOODMAN, M.J., SKINNER, J.M. & TRUELOVE, S.C. (1976). Abnormalities in the apparently normal bowel mucus in Crohn's disease. *Lancet*, **i**, 275–278.

GOULD, S.R., BRASH, A.R., CONNOLLY, M.E. & LENNARD-JONES, J.E. (1981). Studies of prostaglandins and sulphasalazine in ulcerative colitis. *Prostaglandins Med.*, **6**, 165–182.

HARVEY, R.F. & BRADSHAW, J.M. (1980a). A simple index of Crohn's disease activity. *Lancet*, **i**, 514.

HARVEY, R.F. & BRADSHAW, J.M. (1980b). Measuring Crohn's disease activity. *Lancet*, **i**, 1134.

HEATLEY, R.V., CALCRAFT, B.J., RHODES, J., OWEN, E. & EVANS, B.K. (1975). Disodium cromoglycate in the treatment of chronic proctitis. *Gut*, **16**, 559–563.

HILL, R.B., KENT, T.H. & HANSEN, R.N. (1979). Clinical usefulness of rectal biopsy in Crohn's disease. *Gastroenterology*, **77**, 938–942.

HODGSON, H.J.F. (1980). Immunological aspects of

inflammatory bowel disease. In *Inflammatory disease of the bowel*, eds BROOKE, B.N. & WILKINSON, A. pp. 38–52. Pitman Medical.

HODGSON, H.J.F., POTTER, B.J. & JEWELL, D.P. (1977). The humoral immune system in inflammatory bowel disease. 1. Complement levels. *Gut*, **18**, 749–753.

HYWEL-JONES, J., LENNARD-JONES, J.E., MORSON, B.C., CHAPMAN, M., SACKIN, M.J., SNEATH, P.H.A., SPICER, C.C. & CARD, W.I. (1973). Numerical toxonomy and discriminant analysis applied to non-specific colitis. *Quart. J. Med.*, **42**, 715–732.

JENSEN, K.B., JARNUM, S., KOUDHAL, G. & KRISTENSEN, M. (1976). Serum orosomucoid in ulcerative colitis. Its relation to clinical activity, protein loss and turnover of albumin and IgG. *Scand. J. Gastroenterol.*, **11**, 177–183.

LLOYD-STILL, J.D. & GREEN, O.C. (1979). A clinical scoring system for chronic inflammatory bowel disease in children. *Dig. Dis. Sci.*, **24**, 620–624.

LOCKHART-MUMMERY, H.E. & MORSON, B.C. (1964). Crohn's disease of the large intestine. *Gut*, **5**, 493–509.

MATTHEWS, C.M.E. (1957). The theory of tracer experiments with ^{131}I-labelled plasma proteins. *Phys. Med. Biol.*, **2**, 36–50.

MAYBERRY, J., RHODES, J. & HUGHES, C.E. (1979). Incidence of Crohn's disease in Cardiff between 1934 and 1977. *Gut*, **20**, 602–608.

MILLER, D.S., KEIGHLEY, A.C. & LANGMAN, J.S. (1974). Changing patterns in the epidemiology of Crohn's disease. *Lancet*, **ii**, 691–693.

MISIEWICZ, J.J., LENNARD-JONES, J.E., CONNELL, A.M., BARON, J.H. & JONES, F.A. (1968). Controlled trial of sulphasalazine in maintenance therapy for ulcerative colitis. *Lancet*, **i**, 185–188.

MONTEIRO, E., FOSSEY, J. & SHINER, M. (1971). Anti-bacterial antibodies in rectal and colonic mucosa in ulcerative colitis. *Lancet*, **i**, 249–251.

MORSON, B.C. & DAWSON, I.M.P. (1979). *Gastrointestinal pathology*. Oxford: Blackwell.

MYREN, J., BOUCHIER, I.A.D. & WATKINSON, G. (1978). Inflammatory bowel disease, an OMGE survey. *Scand. J. Gastroenterol.*, **14**, Suppl. 6, 1–28.

PETO, R., PIKE, M.C., ARMITAGE, P., BRESLOW, N.E., COX, D.R., HOWARD, S.V., MANTEL, N., McPHERSON, K., PETO, J. & SMITH, P.G. (1977). Design and analysis of randomised clinical trials requiring prolonged observation of each patient. *Br. J. Cancer*, **35**, 1–39.

PHILPOTTS, R.J., HERMON-TAYLOR, J., TEICH, M.M. & BROOKE, B.N. (1980). A search for persistent virus infection in Crohn's disease. *Gut*, **21**, 202–207.

PRESENT, D.H., KORELITZ, B.I., WISCH, N., GLASS, J.L., SACHAR, B.D. & PASTERNACK, B.S. (1980). Treatment of Crohn's disease with 6-mercaptopurine. *New Engl. J. Med.*, **302**, 981–987.

PRIOR, S., GYDE, S., COOKE, W.T., WATERHOUSE, J.A.H. & ALLAN, R.N. (1981). Mortality in Crohn's disease. *Gastroenterology*, **80**, 307–312.

RAMPTON, D.S. & SLADEN, G.E. (1981). Prostaglandin synthesis in ulcerative colitis: flurbiprofen compared with conventional treatment. *Prostaglandins*, **21**, 412–415.

SAVERYMUTTU, S.H., PETERS, A.M., LAVENDER, J.P., HODGSON, H.J.F. & CHADWICK, V.S. (1981). ^{111} Indium labelled autologous leucocytes in inflammatory bowel disease. *Gastroenterology*, **80**, 1273.

SAVERYMUTTU, S.H., PETERS, A.M., LAVENDER, J.P., HODGSON, H.J.F. & CHADWICK, V.S. (1982). Assessment of inflammatory bowel disease using ^{111} Indium labelled autologous leucocytes. *Eur. J. clin. Invest.* (in press).

SHORTER, R.G., CARDOZA, M., SPENCER, R.J. & HUIZENJA, K.A. (1969). Further studies of *In vitro* cytotoxicity of lymphocytes from patients with ulcerative colitis and Crohn's disease. *Gastroenterology*, **56**, 304–310.

SINGER, H.C., ANDERSON, J.G.D., FRISCHER, H. & KIRSNER, J.B. (1971). Familial aspects of inflammatory bowel disease. *Gastroenterology*, **61**, 423–428.

SINGLETON, J.W. (1981). *International Workshop on Crohn's Disease Activity, Oxford.* In discussion.

SINGLETON, J.W., LAW, D.H., KELLEY, M.L., HAGOP, S. & STURDEVANT, R.A.L. (1979). National Co-operative Crohn's Disease Study. Results of Drug Treatment. *Gastroenterology*, **77**, 870–882.

THAW, P.A. & ALBUTT, E.C. (1980). A critical evaluation of a serum seromucoid assay and its replacement by a serum α1 acid glycoprotein assay. *Ann. clin. Biochem.*, 140–143.

TRUELOVE, S.C. & JEWELL, D.P. (1974). Intensive intravenous regimen for severe attacks of ulcerative colitis. *Lancet*, **i**, 1067–1070.

TRUELOVE, S.C. & WITTS, L.J. (1955). Cortisone in ulcerative colitis: final report on a therapeutic trial. *Br. med. J.*, **2**, 1041–1044.

VAN HEES, P.A.M., VAN ELTEREN, P.H., VAN LIER, H.J.J. & VAN TONGEREN, J.H.M. (1980). An index of inflammatory activity in patients with Crohn's disease. *Gut*, **21**, 279–286.

VAN HEES, P.A.M., VAN LIER, H.J.J., VAN ELTEREN, P.H., DRIESSEN, W.M.M., VAN HOGEZAND, R.A., TEN VELDE, G.P.M., BARKER, J.H. & VAN TONGEREN, J.H.M. (1981). Effect of sulphasalazine in patients with active Crohn's disease. *Gut*, **22**, 404–409.

VAN TONGEREN, J.H. & EEKHOUT, A. (1976). Criteria to assess the severity of Crohn's disease and the effect of treatment. In: ed Weterman, I.T., Pena, A.S. & Booth, C.C. *The Management of Crohn's Disease*, Amsterdam: Elsevier.

WEEKE, B. & JARNUM, S. (1971). Serum concentrations of 19 serum proteins in Crohn's disease and ulcerative colitis. *Gut*, **12**, 297–302.

WHITTINGTON, P.E., BARNES, H.V. & BAYLESS, T.M. (1977). Medical management of Crohn's disease in adolescence. *Gastroenterology*, **70**, 439–444.

WINSHIP, D.H., SUMMERS, R.W., SINGLETON, J.W., BESK, W.R., BECKTEL, J.M., LENK, L.F. & KERN, F. (1979). National Co-operative Crohn's Disease: Study design and conduct of trial. *Gastroenterology*, **77**, 829–842.