ADVANCED MEDICINE 20

Edited by
Anne Ferguson

Royal College of Physicians of London

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FOREWORD

This volume is based on a series of lectures given at the Royal College of Physicians in February 1984. The selection of topics reflects in part my own interests of gastroenterology, immunology and adolescence. Aspects of the prevention and long-term management of a number of common chronic diseases are considered, and there are chapters on 'new' diseases, and new approaches to the patient with cancer.

I am most grateful to my secretary, Mrs Doreen Orr, for her help at all stages in the organisation of the Conference and publication of this book; and I am grateful to my research staff for their assistance with the proof reading, and to our hospital librarians who have checked many references for me. The speedy publication of this volume reflects the conscientiousness of the participants, who provided manuscripts promptly, and the remarkable efficiency of Mrs Betty Dickens and her colleagues at Pitman Publishing Ltd.

Anne Ferguson
Western General Hospital Edinburgh
March 1984

CONTENTS

ASSESSMENT OF EXTENT AND ACTIVITY OF INFLAMMATORY BOWEL DISEASE

H J F Hodgson

The term 'Inflammatory Bowel Disease' is used here as a useful though inexact shorthand for ulcerative colitis and Crohn's disease. It is a spectrum of disease which affects the gastrointestinal tract in various sites, to varying extents, with an inflammatory process which waxes and wanes, both spontaneously and in response to treatment. As the distribution, the extent, and the activity of the inflammatory process all have important therapeutic and prognostic implications, their assessment has been extensively investigated. Currently there are a variety of techniques in use, many complementary and all in some way imperfect.

Another significant variable is just how accurately the physician or surgeon wishes to establish the extent and to grade the activity of disease. One obvious extreme is during the urgent medical management of a patient with acute ulcerative colitis, when the question to be answered is simply "Is the patient better than he was yesterday, and are we justified in continuing medical rather than surgical management?" In contrast, quite different assessments are required in a controlled clinical trial in Crohn's disease, testing a potentially dangerous drug which is not dramatically effective. In this case a wide variety of clinical, radiological and laboratory investigations have to be performed. As a simplification, the assessment of the disease activity of patients with ulcerative colitis is relatively easy and straightforward, whereas that of Crohn's disease is difficult.

Ulcerative colitis: methods of assessment

The assessment of ulcerative colitis is aided by the fairly close relationship between the pathology of the disease and the patient's symptoms. The diffuse mucosal inflammation readily explains the cardinal symptoms of diarrhoea, bleeding and tenesmus. The only significant variables amongst this fairly homogeneous group of patients are the proximal extent of the disease from the anal margin, and the activity of the inflammatory process. The affected tissue is readily available for inspection at endoscopy, and for histological sampling. In this condition, therefore, very straightforward clinical observations, established many years ago, remain the main tools for assessing disease activity.

Let us therefore consider the patient with known ulcerative colitis who presents with an exacerbation. We shall not consider further here the differential diagnosis, such as the necessity for excluding infectious colitis. A proper assessment of disease activity is vital, as the most important factor in the prognosis of an attack of ulcerative colitis is the clinical severity of the attack at the time the patient reaches hospital. Mortality figures in early years dramatically illustrated this, with a 30 per cent mortality of patients with severe ulcerative colitis admitted to hospital, compared with a virtual lack of mortality in those with only mild disease [1]. Mild attacks do not warrant hospital admission, but patients with severe attacks require admission and intensive therapy [2]. Such therapy, with an early decision being taken concerning colectomy, appears to have very significantly reduced the mortality in ulcerative colitis.

The distinction into severe, mild or moderate attacks of ulcerative colitis is made on six very simple observations, using information which can be obtained within an hour and a half of seeing a patient in casualty [3]:

	Mild	*Severe*
owel frequency	<4 daily	>6 daily
lood in stool	±	++
ever	normal	>37.5°C on 2 days out of 4
lse rate (beats/min)	normal	>90
(allow for transfusion)	normal or nearly	<75%
R	<30mm/h	>30mm/h

ch assessments will be combined of course with the other straightforward ical and radiological examinations which can safely be performed in a patient o may be severely ill with colitis.

noidoscopy

noidoscopy is necessary to define the presence of active ulcerative colitis, useful serially in assessing responses to therapy, but it is not of great value in ing the severity of a clinical attack. This of course is because it is not the ity of rectal involvement, but the extent of colonic involvement, which is najor determinant of whether or not a patient can develop a very severe k of colitis. A distal colitis, present in only the lower 20cm of the rectum, present with dramatic sigmoidoscopic findings, but is much less likely to a patient at risk than a total colitis.

ninal X-rays

abdominal X-rays are of vital importance in the assessment of an acute of colitis. They may indicate the presence of a complication such as ation, which places the patient in an immediate surgical group. Perfora- re notoriously difficult to diagnose in a patient on corticosteroids. Acute

dilatation of the colon, normally taken as a transverse diameter of over 6.5cm on plain film [4], may or may not be taken as an indication for immediate surgery, but is certainly an indication for the highest possible degree of medical and surgical vigilance. The plain X-ray will usually indicate the extent of colonic involvement by assessment of air-filled loops of colon, with widened or absent haustration and mucosal irregularity. Patients previously assessed as having a distal colitis on their enema may well have extended the disease proximally at the time of an acute presentation. Faecal hold-up on the right side of the colon may occur proximal to an affected segment of colitis, and this may have therapeutic implications. The presence of mucosal islands, with surrounding areas of bare mucosa – the equivalent of pseudo-polyps – is a radiological sign of considerable severity.

Figure 1. An ^{111} Indium labelled autologous WBC scan in a patient with colitis extending from the splenic flexure distally. Four hours previously labelled white cells were re-injected into the patient. The uptake in the liver is normal, but the inflamed descending colon is outlined

Other techniques

What of barium enema? The risk of formal barium enemas in patients with active colitis is well recognised, and the 'instant enema' is often used. It is my impression that this is rarely necessary, and contrast radiology is much more safely left until the patient has recovered from the relapse of disease. Obviously this also applies to colonoscopic examination of the colon which again is contraindicated in the presence of acute colitis. A non-invasive method of defining the extent of inflammation would obviously be a major advance, and recent studies have demonstrated that the use of labelled leucocytes can give extraordinary good pictures of the colon and define the extent of disease very accurately by a simple and non-invasive procedure which can be completed within four to five hours [5] (Figure 1). A particular use of such techniques is in patients who present for the first time with colitis. The scope of this investigation will be discussed later.

Prediction of response to treatment in ulcerative colitis

Acute attack

Lennard-Jones et al analysed a large number of cases looking for specific features which might be of value in defining whether an acute attack of colitis would respond to medical treatment [6]. A number of putative discriminants turned out to be of no value at all – these included whether or not this was a first attack, the sigmoidoscopic appearances, and the haemoglobin, white cell count and ESR. The most useful combination came from simple observations of the maximum temperature or pulse rate on any day, the observed bowel frequency on the day of admission (not the patient's own account of his bowel frequency!) and the plasma albumin level. The combination of more than nine bowel actions, a pulse rate of greater than 90/min, and a serum albumin of less than 30g/litre was associated with a 62 per cent chance of failing to go into remission.

Clinical trials

When formal therapeutic trials have been undertaken in ulcerative colitis, very simple tools similar to those in clinical use have been adequate to see whether drugs have been effective. In the treatment of ulcerative colitis, Truelove and Witts defined an 'attack' as being bloody diarrhoea without specific pathogens, and assessed the results of therapy into one of three categories:

1. Clinical remission (1–2 stools daily, no fever, normal pulse, no anaemia, normal ESR)
2. No change or worse
3. Other, i.e. improved but not in remission [3].

Evidence for the value of active treatment, and remission therapy, has been, and still is, obtained with these measurements. They seem more effective tools than either sigmoidoscopic appearances or histology findings. One problem with sigmoidoscopic assessment is the very considerable inter-observer variation. Thus

while some features such as bleeding observed at sigmoidoscopy can be readily agreed on, others such as 'granularity' are not. Heatley et al [7] have suggested that least inter-observer disagreement could be obtained with a grading system such as:

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 mucus, pus, mucosal haemorrhage and occasional ulcerations.

Another reason that sigmoidoscopic assessments do not appear to have been as successful as global clinical assessments is that there is in fact a poor correlation between the two. For example in Truelove and Witts' initial corticosteroid trial, 12 out of 46 patients who had reached clinical remission after four weeks of corticosteroid therapy still showed active sigmoidoscopic appearances. Furthermore, if local enema preparations are being tried for the treatment of ulcerative colitis, the readily inspectable portion of rectal mucosa may improve in response to a higher concentration of active therapeutic agent, while more proximal parts of the colon are still causing clinical disease.

Similar problems occur with histological assessment, as the histological appearances of inflammation tend not to have returned to normal at a time that a patient has entered clinical remission. For example with a trial of the recently introduced 5′ amino salicylic acid enemas, 93 per cent of patients were in clinical remission after two weeks but only 77 per cent in histological remission [8]. Radiological appearances are even more unsuitable. They are insensitive so that nearly a third of patients in one trial entering clinical remission had barium enemas which were unchanged or worse than during the period of clinical activity [3]; in addition, many individuals with active colitis do not have abnormal X-rays.

Crohn's disease: methods of assessment

Whilst, as outlined above, the immediate day-to-day assessment of a patient's acute colitis is relatively straightforward, the appreciation of less marked changes in activity, such as are required in therapeutic trials of long-term therapy, is much more difficult. This is seen most obviously in the management of Crohn's disease, and the use of laboratory and other assessments of inflammatory activity, although equally applicable in ulcerative colitis, will be discussed in this context.

Problems arise in Crohn's disease in sharp contrast to ulcerative colitis, because there is a very poor correlation between the pathological disease and the patient's symptoms. Partly this arises from the variability of distribution and extent of disease. The gut inflammation may be in small or large bowel, or elsewhere in the gastrointestinal tract; the inflammation is discontinuous and transmural, and is associated frequently with fibrosis, stenosis, fissuring, fistulae and abscesses. Symptoms differ strikingly according to disease site. Whilst pure colonic disease may be indistinguishable from ulcerative colitis, small intestinal

disease, depending on its site and extent, can present with malabsorption, with oedema and hypoproteinaemia, with sub-acute obstruction, or even with anaemia and growth retardation in patients with virtually no gastrointestinal symptoms at all. A lack of correlation between symptoms and the process of gut inflammation is exemplified by frequent delays of several years between the first symptoms of the disease and diagnosis, and compounded by the fact that clinically uninvolved areas of the gut in a patient with Crohn's disease often show inflammation or biochemical abnormalities if meticulously examined [9]. The patients are heterogeneous, there is a poor correlation between gut inflammatory activity and symptoms in many individuals, and unless the rectum is involved tissue is not readily available for repeated biopsy.

Clinical indices

These difficulties are illustrated by the forms of clinical index that have been used, in the hope that a simple assessment analogous to that for ulcerative colitis would emerge. De Dombal et al produced a clinical index for classifying disease activity as a factor affecting short-term prognosis in very similar form to that of the Truelove and Witts ulcerative colitis criteria [10]. 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 (3.3kg)	>1 stone

(*Intermediate* attacks were graded as moderate.)

It is clear from inspection of this classification that while it is highly suitable for patients with colonic disease, it is very unlikely that a patient with small intestinal disease will appear as severely affected on all seven counts. The attempt to make a more sophisticated assessment, versatile enough to cover inflammatory processes in various parts of the small and large intestine, has led to a large number of clinical indices. Many of these are cumbersome, and the best known – the Crohn's disease activity index designed for the United States National Cooperative Crohn's Disease study [11], has been amply summed up as "a real pain to calculate" [12]. It is worth considering in some detail why this is so.

"Crohn's Disease Activity Index"

The organisers of a multi centre controlled trial of Crohn's disease have a difficult problem. In addition to the problems implicit in Crohn's disease assessment

already referred to, the relatively small number of patients in any one centre requires a clinical assessment which can be reproducible in different centres, and quantifiable so that degrees of improvement can be subjected to ranking and statistical analysis. To construct this index for the US trial, a panel of gastroenterologists identified 18 parameters, which could easily be assessed at an outpatient visit and which were thought to be important indicators of disease activity. They measured these in a large number of patients, and simultaneously placed the patients into the overall categories of 'very well', 'fair to good', 'poor', and 'very poor'. This last assessment was given a numerical value, which was then related to the 18 measured parameters by a complex mathematical process of multiple regression analysis. Subsequently eight important predictive variables were identified, each weighted by a coefficient to achieve the best prediction of how 'well' the patient was thought to be; the result, after numerical simplification, is the calculation of the CDAI as illustrated:

Variables

1. Number of liquid or soft stools (each day for seven days)	x 2
2. Abdominal pain (0=none – 3=severe, 1 and 2 intermediate)	x 5
3. General well-being (0=well – 4=terrible, 1, 2 and 3 intermediate)	x 7
4. Number of complications amongst (i) arthralgia/arthritis, (ii) iritis/uveitis, (iii) erythema nodosum, pyoderma gangrenosum, (v) other fistula, (vi) fever over 100°F during past week	x20
5. Taking opiates for diarrhoea 1=yes, 0=no	x30
6. Abdominal mass (0=none, 2=questionable, 5=definite)	x 6
7. 47 – haematocrit (males) 42 – haematocrit (females)	x 6
8. % deviation from standard weight (+ or –)	x 1
	Total = CDAI

'Remission' <150 *Severely ill* >450

Thus a patient with four 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 five per cent below normal, five per cent under body weight would have a CDAI of (28 x 2) + (7 x 5) + (14 x 7) + (1 x 20) + (1 x 30) + (2 x 10) + (5 x 6) + (5 x 1) = 294. This numerical value can range from slightly negative to over 600. There have been many criticisms of this assessment. Firstly it is highly subjective – 23 per cent of the final index is contributed to by the sensation of well-being alone. Diarrhoea and pain also play major parts. It is necessary for the patient to record a diary card of features such as stool consistency, which encourages either introspection or prevarication. Most importantly, the CDAI is not in fact an assessment of the activity of Crohn's disease, if by 'activity' one means the inflammatory process present. In a patient whose clinical state is dominated by a fibrous stricture, a high index of