Indium autologous granulocytes in the detection of inflammatory bowel disease

S H SAVERYMUTTU, A M PETERS, M E CROFTON, H REES, J P LAVENDER, H J F HODGSON, AND V S CHADWICK

From the Departments of Medicine, Diagnostic Radiology, and Pathology, Royal Postgraduate Medical School, Hammersmith Hospital, London

SUMMARY 111Indium leucocyte scanning and measurement of faecal 111Indium leucocyte excretion are techniques which have recently been introduced for assessing patients with inflammatory bowel disease. The methodology has recently been made more specific for acute inflammation by labelling pure granulocytes rather than the mixed leucocyte preparation. To determine the accuracy of this modified technique in detecting inflammatory bowel disease, we have prospectively compared 111Indium granulocyte scanning and faecal 111Indium granulocyte excretion with rectal histology and contrast bowel radiology as screening procedures in 100 patients with suspected inflammatory bowel disease. Thirty three patients were shown to have inflammatory bowel disease – 24 with Crohn’s disease and nine with ulcerative colitis or indeterminate colitis. Overall the respective sensitivities for detecting inflammatory bowel disease were 97% for faecal 111Indium granulocyte excretion, 94% for 111Indium granulocyte scanning, 79% for radiology and 70% for rectal histology. The superiority of 111Indium granulocytes to radiology and rectal histology in detecting inflammatory bowel disease was, in the main, due to the difficulty in diagnosing Crohn’s with conventional techniques. Although three of the patients with ulcerative colitis and indeterminate colitis had normal sigmoidoscopic appearances – all had abnormal rectal histology. No patient with a non-inflammatory bowel disorder had a positive 111Indium granulocyte scan or a raised faecal excretion. These results show that investigations using 111Indium granulocytes are accurate in identifying inflammatory bowel disease and offer important advantages over conventional procedures for detecting Crohn’s disease.

The diagnosis of Crohn’s disease is frequently difficult1 2 and occasionally similar problems may be encountered in indeterminate and ulcerative colitis.3 4 There is no simple solution to this problem as there is considerable overlap in the clinical features between inflammatory and functional bowel disease1 5 while routine laboratory screening tests may be normal in the presence of extensive gut inflammation. The complete investigation of patients with suspected inflammatory bowel disease is therefore time consuming, involving both small and large bowel contrast radiology in addition to sigmoidoscopy and rectal biopsy. This rigorous approach is necessary as omission of any procedure may result in failure to diagnose extensive inflammatory bowel disease.3 4 6 To streamline the investigation of inflammatory bowel disease there is a need for a rapid screening procedure for bowel inflammation. 111Indium leucocyte scanning and measurement of faecal 111Indium leucocyte excretion are two procedures which have been used to assess patients with known inflammatory bowel disease.7 9 A major disadvantage of the conventional mixed leucocyte technique is the substantial platelet, red cell and lymphocyte contamination of the granulocyte fraction which reduces its sensitivity for detecting active inflammation particularly in subjects with a normal or low leucocyte count. Recently a method has been developed for preparing a 111Indium granulocyte preparation without compromising viability.10 Using this preparation we have prospectively evaluated the sensitivity of 111Indium granulocyte scanning and faecal granulocyte excretion, contrast bowel radiology and rectal histology in detecting bowel disease.
Methods

PATIENTS
One hundred and eight patients with suspected inflammatory bowel disease (IBD) were investigated either as inpatients (90) or outpatients (18). In 86 patients the presenting symptoms was chronic diarrhoea. All patients had symptoms for at least six weeks and an infective aetiology was excluded by stool cultures and serology. No patients received treatment before the completion of all investigations. The initial clinical impression of the diagnosis based on full history and examination including sigmoidoscopy but excluding results of laboratory tests was recorded retrospectively from a review of the notes and classified by one author (SHS) according to one of three categories – possible, probable and definite inflammatory bowel disease. Probable and definite impressions were taken to indicate inflammatory bowel disease. Haemoglobin (Hb), erythrocyte sedimentation rate (ESR) and serum albumin were measured in all patients – Hb<12 g/dl; ESR >20 mm in first hour and albumin <35 g/l were considered abnormal.

RADIOLOGY
Double contrast barium enema and either barium follow through (98) or small bowel enema (10) were carried out in all patients and reviewed 'blind' by a radiologist (MEC) with a special interest in gastrointestinal radiology. After review, eight patients were considered to have technically inadequate radiographs and were excluded from the study. The remaining 100 radiographs were classified into two categories – those showing positive evidence of inflammatory bowel disease and those showing no evidence of inflammatory bowel disease.

HISTOLOGY
Rectal biopsy was done in all patients and sections were reviewed blind by a histopathologist (HR). Adequate histology was available in every case.

\[ ^{111}\text{In granulocytes} \]

Autologous granulocytes were separated on discontinuous plasma density gradients and labelled in plasma with \[ ^{111}\text{In} \] troprolamine. After reinjection of the labelled cells, abdominal scans were performed from 40 minutes onwards and reviewed 'blind' by a nuclear medicine physician (JPL). Activity outside the normal distribution of spleen, liver, and bone marrow which was not fixed on later scans was considered abnormal indicating inflammatory bowel disease. Scans on 15 disease control patients with either gut malignancy or endocrine secretory diarrhoea showed only the normal distribution. A four day faecal collection in daily aliquots was started immediately after reinjection and \[ ^{111}\text{In} \] content of each aliquot measured on an ARMAC counter. The \[ ^{111}\text{In} \] content in the first day’s aliquot and the total four day collection was expressed as a percentage of the injected dose. From a study on the 15 hospital disease control patients the normal range for faecal \[ ^{111}\text{In} \] granulocyte excretion were defined. Values above 1% in the first aliquot or greater than 2% in the total four day collection were considered abnormal. No patient was excluded from the series because of an inadequate \[ ^{111}\text{In} \] granulocyte study.

Results

PATIENTS WITH EVIDENCE OF INFLAMMATORY BOWEL DISEASE ON RADIOLOGY OR HISTOLOGY (n=30)
Thirty of the 100 patients had features characteristic of IBD on either bowel radiology or histology. Considered individually, rectal histology detected 23 and radiology 26 of these patients with no false positives. All four patients in this group with normal radiology had colonic disease. On initial clinical impression 17 of the 30 patients were considered to have definite, and a further five thought to have probable, inflammatory bowel disease; while in the remaining eight patients the most likely diagnosis was thought to be the irritable bowel syndrome with inflammatory bowel disease being a possible diagnosis. The most useful clinical feature was the sigmoidoscopic appearance which was definitely abnormal in 14 patients including five of the six patients with ulcerative colitis, while probably abnormal in a further two of the patients but not in the remaining patient with ulcerative colitis. Twenty one out of 30 had one or more abnormal laboratory test. \[ ^{111}\text{In} \] granulocyte scanning was abnormal in 28 of these 30 patients. Both patients with normal scan had normal radiological studies and had mild symptoms at the time of the study (Crohn’s Disease Activity Index less than 100). Faecal \[ ^{111}\text{In} \] granulocyte excretion was raised in 29 of these patients. The single patient with normal faecal \[ ^{111}\text{In} \] granulocyte excretion had ileal Crohn’s disease and had clinically mild disease (CDAI 68). The sensitivity of faecal granulocyte excretion for detecting inflammatory bowel disease was the same whether the first aliquot (Fig. 1a) or the total four day excretion was measured (Fig. 1b).

PATIENTS WITH NO EVIDENCE OF INFLAMMATORY BOWEL DISEASE ON RADIOLOGY OR HISTOLOGY (n=70)
Seventy patients had normal good quality bowel radiographs and rectal histology. The diagnoses in
Indium granulocytes

Fig. 1a, 1b  Faecal granulocyte excretion in the first day collection (Fig. 1a) or the total four day collection (Fig. 1b). Solid circles represent results in patients with evidence of inflammatory bowel disease (IBD) on radiology or histology. Open circles represent results in the four patients with normal radiology and histology but with abnormal 111In granulocyte scan. Open and closed triangles represent results in patients in whom the final diagnosis was the irritable bowel syndrome (IBS) or the non-inflammatory bowel disorders (non-IBD). Horizontal bars represent the upper limit of normal for 111In granulocyte excretion – 1% in first day aliquot (Fig. 1a) and 2% in a four day collection (Fig. 1b).

66 cases are summarised in Table 1. No patient was considered on clinical impression to have definite inflammatory bowel disease but 12 were included in the probable category while the remainder possible inflammatory bowel disease. A further six patients had abnormal laboratory tests either because of cirrhosis or an associated arthritis (Table 1). All 66 cases had normal scans with faecal excretion values in the range of the disease control groups. In four cases, 111In granulocyte scan were abnormal – for example, Fig. 2, and faecal 111In granulocyte excretion was raised (Fig. 1). Two patients showed ileal localisation on scan and despite review again of the barium follow through examination with the knowledge of these findings, the radiographs were considered good quality normal studies. The repeat barium follow through in one case and small bowel enema in the other case showed ileal Crohn’s disease which was later confirmed histologically. One patient showed colonic localisation on scan, and, at colonoscopy the changes of Crohn’s colitis were found with sparing of the rectum. All three patients were thought on clinical impression to have possible inflammatory bowel disease. Both patients with ileal Crohn’s disease had abnormal laboratory tests but in one case the associated ankylosing spondylitis was thought to account for this. The patient with colonic Crohn’s disease had normal laboratory tests. The final patient showed jejunal localisation on scan, however, further investigations
were not undertaken as he returned to his referring hospital. In view of the incomplete investigations on this patient he has been excluded from the final calculations of results.

OVERALL RESULTS IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE

Based on the results of all the diagnostic procedures including the repeat studies, a final diagnosis of inflammatory bowel disease was made in 33 of the original 100 patients. The overall sensitivity of clinical impression, laboratory measurements, and the diagnostic procedures according to disease and distribution is shown in Table 2.

Although only 17 out of the 33 patients (52%) were definitely diagnosed on clinical impression this figure rose 22/33 (67%) when the probable category was also considered. Using the criteria of either an abnormal laboratory test or a probable/definite clinical impression 25 (76%) of the patients were identified but there were also 18 false positives.

![Granulocyte Scan](http://gut.bmj.com/content/gut/23/10/958/F2)

Fig. 2. In granulocyte scan in a patient with initially normal radiology who subsequently was shown to have small bowel Crohn’s disease. The scan shows in addition to the normal activity in spleen (top right) liver (top left) and bone marrow of lumbar spine and pelvis, activity in the right iliac fossa in loops of small bowel.
Faecal $^{111}$In granulocyte excretion and $^{111}$In granulocyte scanning had the highest sensitivities for detecting inflammatory bowel disease – 97% and 94% respectively. Rectal histology was the least sensitive procedure failing to detect 10 of the 24 patients with Crohn’s disease having an overall sensitivity of 70%. Bowel radiology had an intermediate detection rate with a sensitivity of 79%.

Discussion

The diagnosis of inflammatory bowel disease based solely on clinical grounds or laboratory measurements is difficult. Previous studies have shown the problems particularly associated with Crohn’s disease where the mean delay in diagnosis in one series reported in 1970, was 4-3 years with only 6% of patients correctly diagnosed after initial investigations and clinical assessment. These findings were confirmed by a later study in 1980 where only 21% of patients were clinically diagnosed with delays in some cases of up to 20 years before the correct diagnosis was established. In this study the ESR was raised greater than 20 mm in the first hour in 76% of patients as a whole but only 39% of cases with small bowel disease. Several reasons were suggested to account for failure of early diagnosis including incomplete investigation of the gastrointestinal tract in particular of the small bowel and the difficulty in separating any abdominal disease from the irritable bowel syndrome as the latter may mimic or coexist with organic lesions. Although the diagnosis of ulcerative colitis or indeterminate colitis is usually easier, patients with just microscopic inflammation may provide problems.

In the present series initial clinical impression was surprisingly good identifying 67% of patients with inflammatory bowel disease. Even considering Crohn’s disease alone, 63% were identified definitely (46%) or probably (17%). The combination of abnormal laboratory tests and clinical impression improved the detection rate to 76% at the expense of a 27% false positive rate. The major problem, however, was the 24% of patients (eight out of 33) in whom the diagnosis was thought to be non-inflammatory bowel conditions usually the irritable bowel syndrome. This figure is unacceptably high and indicates the need for an additional screening investigation.

$^{111}$In granulocyte scanning and measurement of faecal granulocyte excretion proved to be effective techniques for detecting inflammatory bowel disease in this study identifying all patients in whom an eventual diagnosis of inflammatory bowel disease was made. These techniques were superior to bowel radiology and rectal histology because they detected the 21% of patients with normal barium studies and the 30% of patients with normal rectal histology. Although the majority of examinations were performed as an inpatient we have encountered no major problem in carrying out scanning and a four day faecal collection measurements as an outpatient. The procedure can be simplified to a single 24 hour faecal collection in view of the demonstration that a one day collection is as accurate as a four day collection in discriminating between non-inflammatory and inflammatory bowel disease. Both abnormal scans and raised granulocyte excretion were specific for bowel inflammation as no patient with the irritable bowel syndrome or a wide range of non-inflammatory bowel disorders had positive results. Although examination of faecal smears for leucocytes has been used to diagnose inflammatory causes of diarrhoea; in preliminary studies we found a high incidence of false negative particularly in small bowel disease.

The choice of an additional screening investigation is influenced by a number of factors apart from accuracy including availability, cost, safety, patient acceptability and usefulness in clinical management. Radiology has the advantage of being a well established and widely available technique. As $^{111}$In leucocyte scanning is becoming more popular than Gallium$^{67}$ citrate scanning for abscess localisation, however, it should become more widely available. Although $^{111}$In granulocyte labelling requires more expertise in preparation than most nuclear medicine techniques, it can easily be accomplished by a technician and in our institution only one week’s training has been required. The comparative costs of radiology and $^{111}$In granulocytes are very difficult to estimate. The isotope $^{111}$In is expensive but this is offset by the majority of the procedures being done by a technician while contrast barium studies require the supervision of trained medical personnel. A major advantage of $^{111}$In granulocyte over radiology is that the technique is non-invasive, requires no bowel preparation and is safe in all patients including the acutely ill. Scanning requires no intubation and little cooperation thus unlike radiology the quality of the examination is not adversely affected by the frail, the elderly, the uncooperative patient or where there is poor bowel preparation. Radiation exposure for the $^{111}$In granulocytes was estimated to be between 1–3 rads to the target organ, the spleen, which was less than the radiation exposure to the spleen from a barium enema together with a barium follow through which is between 4–8 rads. A further advantage of $^{111}$In granulocytes over radiology is that it provides rapid results, screening both small and large bowel in the single examination while
there is a delay of up to 10 days between barium enema and barium follow through. As \textsuperscript{111}In granulocyte scanning involves the single procedure without bowel preparation or fasting, it was preferred by patients to bowel radiology, however, the faecal collection lessened its attractiveness.

Both \textsuperscript{111}In granulocyte scanning and faecal granulocyte excretion have been shown to be useful techniques in the assessment of inflammatory bowel disease. Scanning provides an accurate assessment of disease distribution\textsuperscript{16} and permits some assessment of disease activity by scan grading using comparisons between the activity in bone marrow, liver, spleen and affected gut.\textsuperscript{17} Faecal excretion measurements can be performed with just a quarter of the radioactive dose required for scanning and we have shown it provides an objective and accurate assessment of disease activity\textsuperscript{18}, which can be used to monitor response to treatment. Although scanning and faecal excretion measurements can be performed with the same cell preparation and are complimentary techniques they can be also used as separate procedures.

The limitations of contrast bowel radiology and rectal histology in detecting inflammatory bowel disease are illustrated in this series. Recent studies have shown that good quality double contrast barium enema can miss quite extensive inflammation\textsuperscript{2} \textsuperscript{14} and in the present study, five of the 23 cases with colitis had normal radiology. This figure would have been higher if expert review had not been performed. Rectal histology can be particularly useful in diagnosing colitis with normal radiology,\textsuperscript{2} \textsuperscript{14} however, it is often normal in small bowel Crohn’s disease.\textsuperscript{19} Difficulties arise in reporting both radiology and histology because interpretation is subjective. Furthermore certain abnormalities for example loss of haustral pattern on barium enema or a marginal increase in chronic inflammatory cells\textsuperscript{20} can be found in both disease states and normal subjects.\textsuperscript{11} In granulocyte scanning and faecal \textsuperscript{111}In granulocyte excretion are sensitive and accurate methods for detecting inflammatory bowel disease and provide clinically useful assessments of both disease distribution and disease activity. In this study they were diagnostically superior to conventional techniques.

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