¹¹¹Indium autologous granulocytes in the detection of inflammatory bowel disease

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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 ¹¹¹In 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 ¹¹¹In granulocytes over 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 ¹¹¹In granulocyte scan or a raised faecal excretion. These results show that investigations using ¹¹¹In 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 difficult^{1,2} 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 disease^{1,5} 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.

¹¹¹In leucocyte scanning and measurement of faecal ¹¹¹In 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 ¹¹¹In granulocyte preparation without compromising viability.¹⁰ Using this preparation we have prospectively evaluated the sensitivity of ¹¹¹In granulocyte scanning and faecal granulocyte excretion, contrast bowel radiology and rectal histology in detecting bowel disease.

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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.

¹¹¹IN GRANULOCYTES

Autologous granulocytes were separated on discontinuous plasma density gradients and labelled in plasma with ¹¹¹In tropolonate.¹⁰ 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 ¹¹¹In content of each aliquot measured on an ARMAC counter. The ¹¹¹In 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 ¹¹¹In 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 ¹¹¹In 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. ¹¹¹In 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 Index¹¹ less than 100). Faecal ¹¹¹In granulocyte excretion was raised in 29 of these patients. The single patient with normal faecal ¹¹¹In 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

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Table 1 Results of clinical impression, laboratory tests and diagnostic procedures in non-inflammatory bowel conditions

Diagnosis	Patients (no)	Clinical impression		
		Possible inflammatory	probable	definite
Irritable bowel syndrome	51	39	12	0
Diverticular disease	5	5	0	0
Postgastrectomy diarrhoea	2	2	0	0
Colonic polyps	3	3	0	0
Alcoholic liver disease	2	2	0	0
Drug induced	1	1	0	0
Lactose intolerance	1	1	0	0
Pernicious anaemia	1	1	0	0

Diagnosis	Abnormal laboratory tests	Radiology	Abnormal Histology	Scan	Faecal ¹¹¹ In ex
Irritable bowel syndrome	3	0	0	0	0
Diverticular disease	0	0	0	0	0
Postgastrectomy diarrhoea	0	0	0	0	0
Colonic polyps	0	0	0	0	0
Alcoholic liver disease	2	0	0	0	0
Drug induced	1	0	0	0	0
Lactose intolerance	0	0	0	0	0
Pernicious anaemia	0	0	0	0	0

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.

Table 2 Sensitivity of clinical impression, laboratory tests and diagnostic procedures in detecting patients with inflammatory bowel disease according to disease and distribution

Diagnosis	Distri- bution	Patients (no)	No. detected by	
			Clinical impression	Laboratory tests
Ulcerative colitis		6	5	5
Indeterminate colitis		3	2	2
Crohn's disease	Small bowel	10	6	6
	Large bowel	13	8	9
	Small and large bowel	1	1	1
Overall		33	22 (67%)	23 (70%)
Crohn's disease		24	15 (63%)	15 (63%)
Ulcerative colitis and indeterminate colitis		9	7 (78%)	7 (78%)

Radiology	Histology	Number detected by		
		Scan	Faecal ¹¹¹ In ex	
4	6	5	6	Ulcerative colitis
3	3	3	3	Indeterminate colitis
8	4	10	9	Crohn's - small bowel
10	9	12	13	large bowel
1	1	1	1	small & large bowel
26 (79%)	23 (70%)	31 (94%)	32 (97%)	overall
19 (79%)	14 (58%)	23 (96%)	23 (96%)	Crohn's disease
7 (78%)	9 (100%)	8 (89%)	9 (100%)	Ulcerative colitis & indeterminate colitis

Fig. 2 ¹¹¹In 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 ¹¹¹In granulocyte excretion and ¹¹¹In 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.¹ 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.² 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.¹ Although the diagnosis of ulcerative colitis or indeterminate colitis is usually easier, patients with just microscopic inflammation may provide problems.^{3 4 6}

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.

¹¹¹In 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 ¹¹¹In leucocyte scanning is becoming more popular than Gallium⁶⁷ citrate scanning for abscess localisation, however, it should become more widely available.^{12 13} Although ¹¹¹In 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 ¹¹¹Indium granulocytes are very difficult to estimate. The isotope ¹¹¹In 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 ¹¹¹In 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 ¹¹¹In granulocytes was estimated to be between 1–3 rads to the target organ, the spleen,^{14 15} 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 ¹¹¹In 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 ^{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 ^{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 distribution¹⁶ and permits some assessment of disease activity by scan grading using comparisons between the activity in bone marrow, liver, spleen and affected gut.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 activity¹⁸ 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^{2, 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,^{2, 14} however, it is often normal in small bowel Crohn's disease.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 cells²⁰ can be found in both disease states and normal subjects. ^{111}In granulocyte scanning and faecal ^{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.

References

- 1 Dyer NH, Dawson AM. Diagnosis of Crohn's disease. A continuing source of error. *Br Med J* 1970; **1**: 735-7.
- 2 Admans H, Whorwell PJ, Wright R. Diagnosis of Crohn's disease. *Dig Dis Sci* 1980; **25**: 911-5.
- 3 Read NW, Krejs J, Santaana CA, Morawski S, Fordtran JS. Chronic diarrhoea of unknown origin. *Gastroenterology* 1980; **78**: 264-71.
- 4 Elliott PR, Lennard-Jones JE, Bartram CI *et al.* Colonoscopic diagnosis of minimal change colitis in patients with a normal sigmoidoscopy and normal air content contrast barium enema. *Lancet* 1982; **1**: 650-2.
- 5 Isgar B, Harman M, Kaye MD, Whorwell PJ. Symptoms of the irritable bowel syndrome in ulcerative colitis. *Gut* 1983; **24**: 190-2.
- 6 Kingham JG, Levison DA, Ball JA, Dawson AM. Microscopic colitis - a cause of chronic watery diarrhoea. *Br Med J* 1982; **285**: 1601-4.
- 7 Saverymuttu SH, Peters AM, Lavender JP, Hodgson HJF, Chadwick VS. Indium-111-autologous leucocytes in inflammatory bowel disease. *Gut* 1983; **24**: 293-9.
- 8 Segal AW, Ensell J, Munro JD, Sarner M. Indium-111-tagged leucocytes in the diagnosis of inflammatory bowel disease. *Lancet* 1981; **2**: 230-2.
- 9 Stein DT, Gray MG, Gregory PB, Anderson M, Goodwin DA, McDougall I. Location and activity of ulcerative and Crohn's colitis by Indium-111 leukocyte scan. *Gastroenterology* 1983; **84**: 388-93.
- 10 Danpure HJ, Osman S, Brady F. The labelling of blood cells in plasma with Indium-111 tropolonate. *Br J Radiol* 1982; **55**: 247-9.
- 11 Best WR, Bectel JM, Singleton JW, Kern F. Development of a Crohn's disease activity index: National Cooperative Crohn's disease study. *Gastroenterology* 1976; **70**: 439-44.
- 12 Ascher N, Forstrom L, Simmons RL. Radiolabelled autologous leucocyte scanning for abscess detection. *World J Surg* 1980; **4**: 395-402.
- 13 Carrol B, Silverman PM, Goodwin DA, McDougall IR. Ultrasonography and indium-111 white blood scanning for the detection of intra-abdominal abscess. *Radiology* 1981; **140**: 155-60.
- 14 McDougall IR, Baumert JE, Lantieri RL. Evaluation of ^{111}In leukocyte whole body scanning. *Am J Roentgenol* 1979; **133**: 849-54.
- 15 Thakur ML, Lavender JP, Arnot RN, Silvester DJ, Segal AW. Indium-111 labelled autologous leucocytes in man. *J Nucl Med* 1977; **18**: 1014-21.
- 16 Saverymuttu SH, Peters AM, Hodgson HJF, Chadwick VS, Lavender JP. ^{111}In indium autologous leucocyte scanning: comparison with radiology for imaging the colon in inflammatory bowel disease. *Br Med J* 1982; **285**: 255-7.
- 17 Saverymuttu SH, Lavender JP, Hodgson HJF, Chadwick VS. Assessment of disease activity in inflammatory bowel disease: a new approach using ^{111}In granulocyte scanning. *Br Med J* 1983; **287**: 1751-3.
- 18 Saverymuttu SH, Peters AM, Lavender JP, Pepys MB, Hodgson HJF, Chadwick VS. Quantitative faecal ^{111}In indium labelled leucocyte excretion in the assessment of disease activity in Crohn's disease. *Gastroenterology* 1983; **85**: 1333-9.
- 19 Goodman MJ, Kirsner JB, Riddell RH. Usefulness of rectal biopsy in inflammatory bowel disease. *Gastroenterology* 1977; **72**: 952-6.
- 20 McK Watts, Thompson H, Goligher JC. Sigmoidoscopy and cytology in the detection of microscopic disease of the rectal mucosa in ulcerative colitis. *Gut* 1966; **7**: 288-94.