Indium-111 Whole-Body Retention: A Method for Quantification of Disease Activity in Inflammatory Bowel Disease

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Quantification of disease activity in inflammatory bowel disease (IBD) has been by measurement of fecal excretion of ^{111}In-granulocytes. The difficulties of this method prompted us to evaluate quantification of whole-body ^{111}In retention, expressed as a percentage of whole-body activity at 3 hr following injection, as an alternative method. The patient stood in front of the uncollimated gamma camera at a distance of 4 m and counts were collected over 2 min. The geometric mean was taken of posterior and anterior counts and compared with a ^{111}In standard. The lower limit of the 95% confidence interval for whole-body retention in normals was 90%. Forty-five studies were performed on 33 patients with IBD. They were assessed in two groups, one to whom routine instructions for the collection of feces were given (Group A) but who did not always comply. The other group received oral and written instructions and were also monitored during the collection period (Group B) and reported full fecal collection. Although in Group A the correlation between fecal excretion and whole-body retention was good ($r = 0.7$, $n = 32$; $p < 0.001$), in Group B the relationship between fecal excretion and whole-body retention was significantly better ($r = 0.95$, $n = 18$; $p < 0.001$). On average, ^{111}In whole-body retention was consistent with findings obtained during imaging: ^{111}In excretion (100-whole-body retention) was 7.8% ± 4.9% in 5 normal scans, 10% ± 5.9% in 17 (+) scans, 22.3% ± 8% in 20 (++) scans and 57% ± 16% in 8 (+++) scans. We conclude that imaging is more sensitive than whole-body retention and fecal excretion in the detection of disease, but for quantification, whole-body retention is an accurate reliable alternative to fecal excretion.

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The principal uses of radiolabeled autologous leukocytes in inflammatory bowel disease (IBD) are for detecting bowel inflammation, both at initial presentation and when relapse is suspected, for determining distribution of disease and for quantification of disease activity. The latter application has particular potential in the assessment of new drug therapies (*1*). Although disease activity can be semi-quantified from scan appearances in scan imaging, it has been claimed that the most accurate way to quantify disease activity is to measure the radioactivity in a complete 4-day stool collection after injection of ^{111}In-labeled granulocytes (*2*). In normal individuals and patients with inactive IBD, no more than 2% of the injected dose is excreted in the feces, although this rises to levels as high as 60% in acute exacerbations of Crohn's disease or ulcerative colitis (*3*). However, the accuracy of this technique relies heavily on an adequate fecal collection. This is not always possible, particularly when assessing non-hospitalized patients who have frequent bowel actions (*4*). Furthermore, patients do not always report that fecal collection is incomplete. The unpleasantness of this technique for patients and for technical staff is also a major drawback of the method.

These disadvantages prompted us to evaluate a new, simple approach in which ^{111}In remaining in the patient is measured instead of the ^{111}In lost in the feces. This whole-body retention technique proved useful for evaluating disease activity in patients with bronchiectasis, in whom granulocytes from diseased lung are excreted via the sputum (*5*), and may represent a simple, accurate and acceptable method to quantify disease activity in patients with IBD.

This paper therefore reports the results of a comparison of the whole-body counting technique with quantification based on fecal ^{111}In counting.

METHODS

Patients

Thirty-eight patients (23 female and 14 male, aged between 18 and 65 yr) with IBD were studied. Twenty-four patients had Crohn's disease (localized in the large bowel in ten, small bowel in eight, and involving both large and small bowel in six patients), eight had ulcerative colitis, one collagenous colitis and five radiation enteritis. The diagnosis of IBD was based upon history, physical examination, radiologic, endoscopic and/or histopatho-

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logic features. None of the patients had respiratory or skin diseases that might be responsible for white cell loss. Ten patients were active smokers. A total of 50 ^{111}In radionuclide studies (imaging, fecal excretion and whole-body retention) were carried out in the 38 patients, since 12 patients were studied on two separate occasions. The study was approved by the local Ethics Committee and certification obtained from the Administration of Radioactive Substances Advisory Committee (ARSAC).

Clinical Assessment

Routine clinical assessment was carried out in all patients in addition to measurement of laboratory acute phase reactants, such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). In the 12 Crohn's disease patients who were studied on two occasions, ESR and CRP, together with the Crohn's disease activity index (CDAI), were assessed before each study. CDAI is the most widely used clinical score, with values >150 corresponding to active disease and <150 to inactive disease.

Cell Labeling

A "pure" population of autologous granulocytes was isolated from 102 ml venous blood (anticoagulated with 18 ml ACD-NIH A) with Metrizamide-autologous plasma-density gradient columns and labeled in plasma with ^{111}In-tropolonate (9–12 MBq) as previously described (*6*). By separating the cells in an aliquot of the injectate on a Percoll-saline density gradient column, no more than about 5% of the total injected cell-bound radioactivity was estimated to be present on non-granulocytic formed elements (*7*).

Imaging

Each patient was imaged at 3 and 20 hr after injection of labeled cells using a gamma camera (IGE 400A or 400T) fitted with a medium-energy, parallel-hole collimator. The images were inspected for evidence of IBD and subjectively graded by a nuclear physician (JPL), unaware of the whole-body retention or fecal excretion data, as negative (0), mildly positive (+), moderately positive (++) or markedly positive (+++) (Fig. 1). Bowel localization was compared to bone marrow and liver activity as part of the scan grading process. The grading system used in the study was based on visual analysis, and both intensity and extent of the disease were considerations in scan grading. This grading was done for 3- and 20-hr imaging, side by side.

Fecal Excretion

The fecal excretion of ^{111}In was estimated to quantitate disease activity (*2*). After the administration of ^{111}In-labeled granulocytes, all patients were asked to make a full 4-day stool collection. Results of fecal excretion measurement, however, may be influenced by the accuracy of stool collection. Therefore, we made a temporal separation of the patients into two groups: Group A was comprised of 20 patients who were given careful oral instructions for the collection of feces. Group B was comprised of 18 patients (including 4 inpatients) who received both oral and written instructions for fecal collection and were also contacted daily to assess their compliance with collection. A standardized questionnaire designed to evaluate the accuracy of fecal collection was administered to every patient when they handed over the samples. The total fecal ^{111}In content was counted in an ARMAC gamma counter and expressed as a percentage of the injected dose after correction for physical decay of ^{111}In as previously described (*2*). As already established (*2*), the normal fecal ^{111}In excretion was considered to be 2% or less of the injected dose.

Whole-Body Retention

As another way of quantifying disease activity, ^{111}In remaining in the patient was measured instead of evaluating the ^{111}In lost in the feces. Whole-body radioactivity was quantified as the counts collected in 2 min from the uncollimated gamma camera directed towards the erect patient at a distance of 4 m (*5*) (Fig. 2). A background count over 2 min was also performed, having ensured that there were no "hot" sources (such as ^{81m}Kr generator or radioactive patients) in the vicinity of the gamma camera. Counting was performed on the same camera for each patient either at the end of the day or early in the morning. As a result, variation in background was fairly low (s.d. 26% of the mean). The 15% energy windows were set on the two ^{111}In photopeaks (i.e., 170 and 247 keV). Following background subtraction, the geometric mean was taken of counts recorded with the patient respectively anterior and posterior to the camera. An ^{111}In standard (the activity of which was about one-third of the injected dose) was counted at the same distance. Counting was performed between 1 and 3 hr after injection of cells and again between 4–6 days later. It was assumed that no activity had been lost by 3 hr, so the whole-body retention at 4–6 days was expressed as a percentage of the 1–3 hr counts (*2*). Physical decay of the isotope was accounted for by comparison of whole-body counts with standard counts. Whole-body counts were also "directly" corrected for physical decay, using a decay constant of 0.0103 hr^{-1}. The average for the whole-body retention values respectively based on the standard and on correction for physical decay was then taken. In normals, whole-body retention is >90% (or <10% if expressed as excretion [100-whole-body retention]) (*5*).

In order to check that the uncollimated camera count rate was

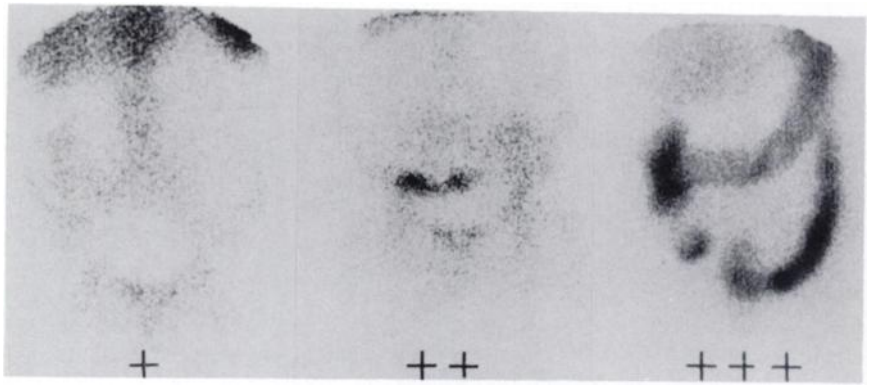

FIGURE 1. Representative examples of image grading. Three images from respective patients with IBD taken 3 hr after injection of labeled cells, scored (+), (++) and (+++), respectively.

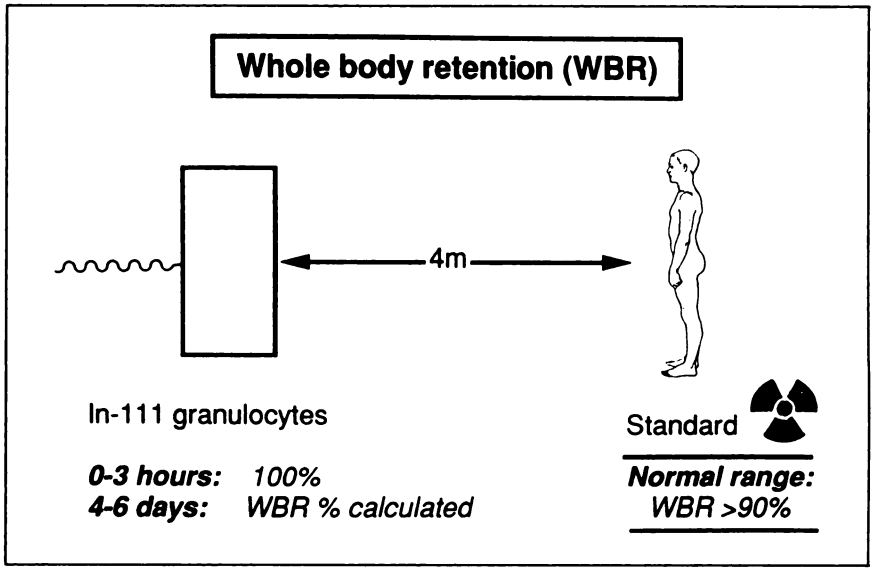

FIGURE 2. Diagramatic representation of the whole-body ^{111}In retention method.

independent of the vertical distribution of activity in the patient, a source of ^{111}In was counted at head, waist and foot levels from in front of and behind a subject who had been given no radioactivity and who was standing at a distance of 4 m from the camera.

Data Analysis

Results are expressed as means ± 1 s.d. Linear regression analysis was used to assess the correlation between whole-body retention, CDAI and fecal excretion. A p value of <0.05 was considered significant.

RESULTS

Disease Activity on Imaging

Forty-five of 50 studies had abnormal accumulation of activity; 17 were (+), 20 were (++) and 8 were (+++). The relationship between imaging and the disease activity index is shown in Figure 3 for 24 studies (in 12 patients with Crohn's disease). Among those with no or minimal (+) disease on imaging, five out of eleven studies had a CDAI of <150. Among those with a moderate (++) image, six out of nine studies also had CDAIs <150. All four studies with (+++) images had CDAIs >150.

Fecal Excretion

No patient was eliminated on the basis of incomplete collection. Ten of the 20 Group A patients (50%) and 17 of 18 Group B patients (94%) reported an accurate fecal collection. For Group A, fecal radioactivity was higher than normal in one of six patients with a (−) scan, in two of eleven with (+) scans, in seven of twelve with (++) scans and all five patients with (+++) scans. For Group B, the results of fecal excretion were abnormal in three of six patients with (+) scans, in eight of eight with (++) scans and in all three patients with (+++) scans.

Analysis of the individual data for Group A (12 Crohn's disease patients) revealed a poor correlation ($r = 0.21$, $p = 0.3$) between fecal excretion and CDAI in 22 studies (Fig. 4).

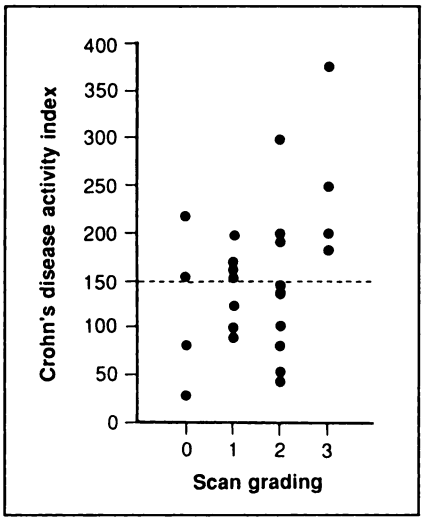

FIGURE 3. Comparison between Crohn's disease activity index (CDAI) and scan grading in 24 studies performed on 2 occasions for 12 IBD patients in Group A.

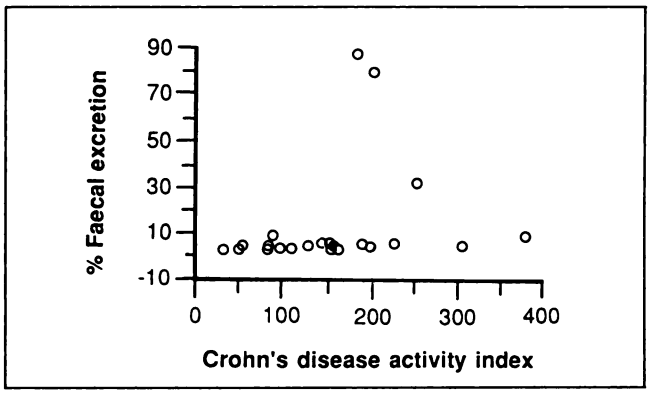

FIGURE 4. Relationship between fecal ^{111}In-leukocyte excretion (direct measurement) and Crohn's disease activity index (CDAI) in 22 studies performed on 2 separate occasions for 12 patients with inflammatory bowel disease in Group A.

Whole-Body Retention

Comparison was made between whole-body retention calculated from the injected dose corrected for physical decay and whole-body retention calculated with reference to a simultaneously measured standard. The mean ratio of the two values was 0.99 ± 0.079. Background costs in patients with nonactive disease were about 5% of total counts at 1–3 hr, and ranged from 10% to 25% of total counts at 4–6 days. Nevertheless, counts at 1–3 hr were about 100K and at 4–6 days 25K. Whole-body retention (indirect measurement of percent fecal excretion) was also related to image grading (Fig. 5).

In Group A, abnormal whole-body retention of <90% (the lower 95% confidence limit from a previous study in normal individuals) was found in two of four patients with negative scans, six of eleven with (+) scans, ten of twelve with (++) scans and all five patients with (+++) scans. In Group B, abnormal whole-body retention was found in three of six patients with (+) scans, all eight patients with (++) scans and the three patients with (+++) scans. In the 12 Group A patients for whom CDAI was calculated, there was a significant correlation ($r = 0.54$, $p = 0.008$) between CDAI and whole-body retention (indirect measurement of fecal excretion) (Fig. 6). Correlation between whole-body retention and erythrocyte sedimentation rate was also significant ($r = 0.56$, $p < 0.01$); however, correlation between whole-body retention and C-reactive protein was poor ($r = 0.1$, $p = 0.6$).

Correlation Between Fecal Excretion (Direct Measurement of Radioactivity in Feces) and Whole-Body Retention (Indirect Measurement)

The correlations between whole-body retention and fecal excretion in Groups A and B are shown in Figures 7 and 8. In Group A, whole-body retention = 14.8 ± 0.56 fecal excretion ($r = 0.7$, $n = 32$, $p < 0.001$); and in Group B, whole-body retention = 8.1 ± 0.8 fecal excretion ($r = 0.95$, $n = 18$, $p < 0.001$). In both groups, the zero line intercept was significantly different from zero (Group A, $p < 0.001$; Group B, $p < 0.01$).

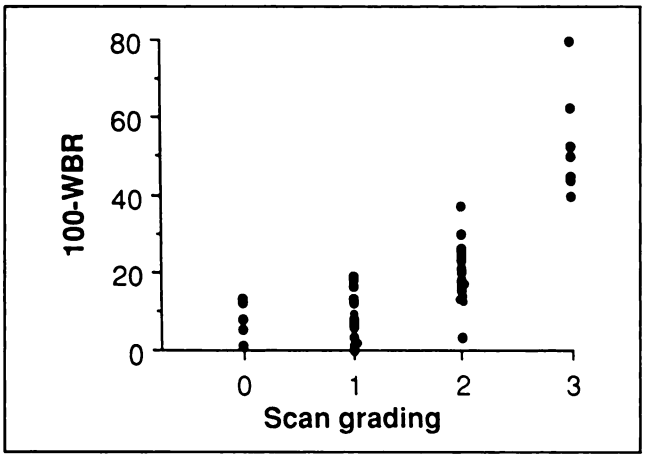

FIGURE 5. Comparison between 100-whole-body retention (indirect measurement of radioactivity loss in feces) and scan grading in patients with inflammatory bowel disease.

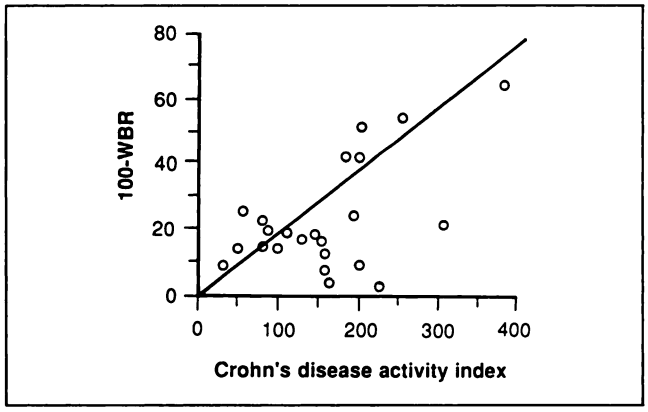

FIGURE 6. Relationship between 100 whole-body retention (indirect measurement of fecal loss) and Crohn's disease activity index (CDAI) in 24 studies done on 2 separate occasions for 12 patients with inflammatory bowel disease.

Relationship Between Leukocyte Excretion Measurements (Fecal Excretion and Whole-Body Retention) and Scan Grading of Activity

In Group A, 17 fecal excretion studies were normal. Of these, 14 had positive images, 5 of which were graded as (++) and 8 as (+). Whole-body retention studies were normal in nine cases. Of these six had positive images, five of which were graded as (+) and one as (++). Of seven studies in which whole-body retention and fecal excretion were both normal, six had positive images, one of which was graded as (++) and five as (+). There were no studies showing negative images in which fecal excretion and whole-body retention were both abnormal. However, of the four studies with negative images, whole-body retention was abnormal in two and fecal excretion abnormal in one. Among all 32 studies from Group A, fecal excretion was inconsistent with both imaging and whole-body retention in 9, while whole-body retention was inconsistent with fecal excretion and imaging in only 2. In Group B, of four studies in which fecal excretion was normal, three had positive images graded as (+). Of the four studies in

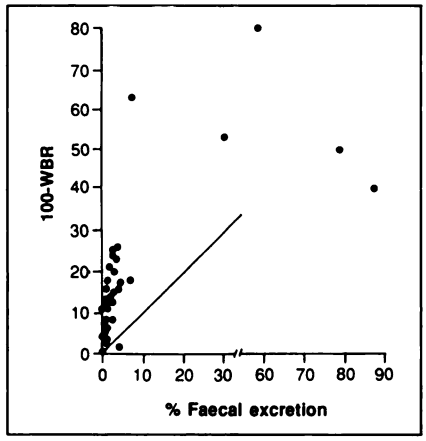

FIGURE 7. Comparison between fecal ^{111}In-leukocyte excretion (direct estimation) and 100-whole-body retention (indirect estimation of fecal loss) in Group A patients with inflammatory bowel disease.

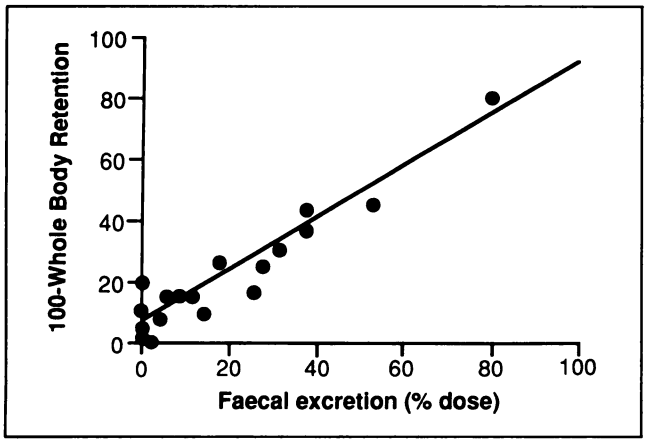

FIGURE 8. Comparison between fecal ^{111}In-leukocyte excretion (direct estimation) and 100-whole-body retention (indirect estimation) in Group B patients with IBD.

which whole-body retention was normal, three had positive images graded as (+). There were no studies with positive images and normal fecal excretion and whole-body retention. Moreover, there were no negative images with both abnormal fecal excretion and whole-body retention. Among the 18 studies in Group B, fecal excretion results were inconsistent with those of imaging and whole-body retention in two, whereas whole-body retention results were inconsistent with those of fecal excretion and imaging in two.

DISCUSSION

We studied the ability of fecal excretion (direct estimation of radioactivity in stools) and whole-body retention (indirect measurement) to quantify disease activity in patients with IBD and also assessed the relative sensitivity of these methods by comparing the incidence of abnormal results and the degree of concordance between them. Our results indicate a good correlation between fecal and whole-body retention, provided there is accurate fecal collection.

Fecal Excretion

For both groups of patients, fecal excretion was abnormal in a high proportion of individuals with active disease who had abnormal scan imaging. However, a better correlation between disease activity and fecal excretion was found in Group B, which included patients who collected their feces following careful instructions and were closely monitored, than in Group A patients whose stool collection was less accurate.

Our results are in agreement with those of other authors who found that in patients with IBD the fecal excretion of ^{111}In-granulocytes correlates well with the severity of the disease. Segal et al. (*8*) found that approximately 20% of the administered radioactivity appeared in the stools of patients with IBD. Buxton-Thomas et al. (*9*) and Saverymuttu et al. (*10*) also found a good correlation between disease activity and recovery of labeled leukocytes in feces. Furthermore, in patients with IBD, ^{111}In excretion has been compared with conventional methods, such as endoscopy, histology and determination of CDAI (*11,12*), and was found to be an accurate noninvasive means of assessing disease extent and severity. Fecal excretion also showed a good correlation with clinical parameters, such as the CDAI, which was calculated in the 12 patients with Crohn's disease. The CDAI is the best known of the clinical indices and its use has facilitated management decisions in patients with Crohn's disease and also enabled the prediction of the patient's outcome. However, this index only provides an indirect assessment of disease activity and depends on subjective values.

Although measurement of fecal excretion is a useful tool to quantitate disease activity in patients with IBD, this technique relies heavily on an adequate stool collection, which is often difficult, particularly in non-hospitalized patients. It is also rather unpleasant to both patients and technical staff, with the consequent reluctance to use it for the routine assessment of disease activity. We therefore sought to evaluate a simpler, alternative method of measuring ^{111}In retention that should theoretically provide similar or better information than the fecal excretion technique.

Whole-Body Retention

Our results indicate that a good correlation exists between whole-body retention, fecal excretion, imaging and clinical indices. Correlation between whole-body retention and scan grading was good, although within each grading category there was a wide range of whole-body retention values.

When fecal excretion (direct measurement) and whole-body retention (indirect measurement) were compared with each other and the imaging data, it was observed that in Group A, fecal excretion was "out of step" on nine occasions compared to two for whole-body retention, whereas in Group B, both fecal excretion and whole-body retention were inconsistent in just two separate instances each. These results, along with the evidence that fecal collections are frequently incomplete, suggest that whole-body retention is a reliable method for quantification of activity, particularly when complete fecal collection cannot be guaranteed, and can safely replace the measurement of fecal excretion.

Whole-body retention was calculated between 4 and 6 days after injection. Using any time between 4 and 6 days offers considerable advantages for scheduling examinations and does not, perhaps surprisingly, introduce significant inaccuracies. In the absence of inflammation, the rate of loss ^{111}In-granulocyte is only 1% per day. In IBD, serial collection of feces of patients in the hospital demonstrated that most of the radioactivity excreted via the gut is eliminated early on. For example, on a 4-day collection, Day 1 yielded 6% of the excreted radioactivity, Day 2 an additional 3%, Day 3 an additional 7% and Day 4

an additional 3% or less. Thus, exponential fall in radioactivity excretion indicates that the precise loss of counts between 4 and 6 days will introduce an inaccuracy of >3% at most (*2*). Since normal routes of ^{111}In loss include saliva and urine (*13*), 100-whole-body retention would be expected to exceed fecal excretion, but by no more than a few percent of the dose. This is based on a statistically significant control population which consisted of subjects without inflammation (*5*), and indeed in the current status, a significant positive intercept was recorded in the regression between ^{111}In retention and fecal excretion in Group B. It is conceivable, however, that the rate of ^{111}In loss may differ in these individuals, compared to those patients with enclosed sepsis (who, although not losing granulocytes via external communication of their septic foci, nonetheless have inflammatory disease).

As discussed above, it seems highly probable from our results that counting ^{111}In in the feces may in some cases underestimate the true ^{111}In loss. This is not surprising in view of the difficulty of achieving a complete fecal collection over 4 days, especially for patients in whom bowel actions are usually frequent. Results obtained in our two groups of patients showed a clear difference according to the accuracy of fecal collection. In Group A, 20 of 32 (63%) 100-whole-body retention measurements exceeded fecal excretion by more than 10% of the dose, an amount clearly greater than what could be expected from additional routes of ^{111}In loss.

Fecal Excretion, Whole-Body Retention and Scan Imaging

In a number of studies, whole-body retention and fecal excretion were normal, yet there was clear evidence of disease on the gamma camera images. However, such disease was usually minimally graded as [+], (although in five studies from group A in which fecal excretion was normal it was [++]). Imaging is probably the most sensitive means for detecting disease activity. However, its ability to quantify disease activity is quite low. This is consistent with our previous experience in patients with bronchiectasis in whom migrating granulocytes are mobilized (as in IBD) and ultimately excreted (*5*) i.e., imaging was more sensitive in disease detection than ^{111}In retention.

Although there were no instances in which whole-body retention and fecal excretion were both abnormal in the presence of a normal scan, there were two studies in Group A in which whole-body retention alone was abnormal and one in which fecal excretion alone was abnormal. It is therefore quite likely that imaging will occasionally miss mildly active disease, which is nonetheless detectable by whole-body counting or fecal excretion. This is more likely to occur if disease is confined to the small bowel, since the relative mobility of this organ results in lesser sensitivity of the imaging technique. This was, after all, one of the reasons for developing the fecal excretion technique in the first place. On the other hand, a possible cause for an increased ^{111}In excretion not related to IBD is co-existing inflammatory lung disease with mobilization and excretion of labeled neutrophils. By inducing granulocyte migration into airways, cigarette smoking may add to the whole-body losses resulting from active IBD. The extent to which smoking may also add to the 4-day fecal excretion measurement would depend on how much purulent sputum was swallowed or expectorated by the patient. Smoking could therefore adversely influence the correlation between whole-body retention and fecal excretion, although none of the patients studied had evidence of significant purulent chest disease.

Earlier studies of whole-body retention in bronchiectasis were based on anterior whole-body count only. By also performing a posterior count and taking the geometric mean of both, we could correct any errors resulting from a varying distribution of ^{111}In throughout the body in turn resulting from varying spleen size, varying distribution of activity between liver and spleen and a redistribution of activity between 3 hr and 4 days. Although some redistribution does take place over this interval, resulting predominantly from an increasing bone marrow signal and, to a lesser extent, hepatic signal, it is not marked, with activity in the spleen, for instance, remaining essentially constant since ^{111}In on pooled cells gradually becomes replaced by ^{111}In from destroyed cells (*13*). Statistical accuracy has also been improved by increasing the counting time from 1 to 2 min, thereby giving a four-fold increase in total counts collected.

The use of a standard is not essential but was employed here as an additional means of quality control. We took the average of values based on "direct" correction for physical decay and on the standard since errors are associated with both. The main error associated with decay correction is exactly regaining the same energy window. The rather low activity in the standard, on the other hand, limits the accuracy of this approach; thus, statistical errors from a low count rate from the standard at 6 days negates any benefits of longer whole-body counting times and high whole-body activities. Furthermore it has already been reported in control subjects without evidence of inflammation that there was a slow decrease in whole-body ^{111}In on the order of 1% per day, so that by 136 hr (5.6 days) it was 95% of the initial level (*5*).

We feel that a pure population studied with labeled granulocytes is needed to fully exploit this technique. Otherwise, whole-body losses, effectively expressed as a percentage of injected dose, become somewhat meaningless. Theoretically, using a "mixed" leukocyte preparation, which is technically easier, may be satisfactory if a density gradient separation is made on an aliquot of the injectate to determine the percentage of the injected dose present on granulocytes.

CONCLUSIONS

The results of this study suggest that measurement of fecal ^{111}In excretion is a reliable method, provided a com-

plete and accurate stool collection is made for quantification of disease activity in IBD. However, both the difficulty in achieving such a complete collection and the aesthetic nonacceptability of it render the method impractical. Therefore, the measurement of ^{111}In whole-body retention is an accurate alternative method. For detecting disease, however, gamma camera imaging is more sensitive than measuring ^{111}In losses, either with whole-body counting or fecal excretion.

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