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Scintigraphic Evaluation of Experimental Colitis in Rabbits

Wim J.G. Oyen, Otto C. Boerman, Els T.M. Dams, Gert Storm, Louis van Bloois, Emile B. Koenders, Urbain J.G.M. van Haelst, Jos W.M. van der Meer and Frans H.M. Corstens

University Hospital Nijmegen, Departments of Nuclear Medicine, Internal Medicine and Pathology, Nijmegen; and Utrecht University, Institute for Pharmaceutical Science (UIPS), Department of Pharmaceutics, Utrecht, The Netherlands

Scintigraphic techniques are frequently used for evaluation of inflammatory bowel disease. The radiopharmaceutical of choice is labeled leukocytes. In this study, two new agents, ^{111}In-labeled polyethylene glycol-coated liposomes and ^{111}In-labeled human nonspecific gamma globulin (immunoglobulin G; IgG), were compared with ^{111}In-leukocytes in a rabbit model of colitis. **Methods:** In rabbits, acute colitis was induced by colonic instillation of trinitrobenzene sulfonic acid at 25 cm from the anal sphincter. After 24 hr, 15 MBq of the radiopharmaceuticals was injected intravenously in groups of four rabbits. Twenty-four hours after injection, the animals were killed and macroscopic abnormalities were scored in seven consecutive affected colonic segments of 5 cm each (0 = normal, 1 = inflammation, 2 = ulcers). The ex vivo uptake was measured in the normal ascending colon and the affected colonic segments. The colitis index (CI, affected-to-normal colon-uptake ratio) was calculated. **Results:** Histologically, an acute, patchy, transmural colitis was observed at the site of instillation and the distal colon. The CI of all agents in colitis lesions correlated with the severity of the abnormalities. With increasing severity, the CI for liposomes was 1.86 ± 0.24, 4.88 ± 0.42 and 7.42 ± 0.54 ($r^2 = 0.68$, $p < 0.001$); for leukocytes 1.77 ± 0.32, 3.10 ± 0.58 and 5.54 ± 0.83 ($r^2 = 0.31$, $p < 0.01$); for IgG 1.60 ± 0.29, 2.81 ± 0.21 and 2.65 ± 0.21 ($r^2 = 0.29$, $p < 0.02$). **Conclusion:** Indium-111-labeled-leukocytes, -IgG and -liposomes all show increased uptake in inflamed colonic tissue. Indium-111-liposomes showed the highest CI, which correlates best with the morphological abnormalities. Indium-111-leukocytes and ^{111}In-liposomes are superior to ^{111}In-IgG for this indication.

Key Words: radionuclide imaging; diagnostic imaging; gamma globulin; indium-111; scintigraphy; inflammatory bowel disease

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Inflammatory bowel disease is a condition with fluctuating episodes of relapses and remissions of acute colitis. In clinical practice, diagnostic procedures are most helpful for evaluating the status of the diseased colon. The major diagnostic tools are endoscopy (allowing direct inspection of the diseased mucosa), radiographic evaluation using barium enemas (providing images of the morphological abnormalities) and scintigraphic modalities (showing functional images of the degree of inflammatory activity in affected areas in the gut). For the latter technique, a variety of radiopharmaceuticals are available.

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For correspondence or reprints contact: Wim J.G. Oyen, MD, University Hospital Nijmegen, Department of Nuclear Medicine, P.O. Box 9101, 6500 HB Nijmegen, The Netherlands.

When scintigraphic evaluation of the abdomen is considered labeled leukocytes are currently the agent of choice, since high sensitivity and specificity is observed, especially in acute colitis (*1*). Unfortunately, the preparation of radiolabeled autologous leukocytes has several disadvantages that limit its application. In particular, the necessity to draw and handle possibly contaminated blood constitutes an inherent risk to other patients and staff (*2,3*). Moreover, isolation and labeling of leukocytes is a relatively complicated and time-consuming procedure that is not possible in every nuclear medicine facility (*4*). To overcome these difficulties, research has been directed toward developing agents that are as equally effective, but easier to produce from instant, ready-to-use radiolabeling kits.

In this study in a rabbit model of acute colitis, the targeting of ^{111}In-labeled-leukocytes is compared with the performance of two recently developed radiopharmaceuticals: ^{111}In-labeled human nonspecific polyclonal gamma globulin (immunoglobulin G; IgG) and ^{111}In-labeled sterically stabilized liposomes. Indium-111-IgG has already been applied in clinical practice for the diagnosis of a wide variety of infectious and inflammatory processes (*5*). Labeled liposomes have also been investigated in patients (*6,7*). However, these conventional liposomes, as used in the past, are rapidly cleared from the circulation by phagocytic cells of the mononuclear phagocyte system (*8*). The advantage of sterically stabilized liposomes is the prolonged residence time in circulation with consequently higher levels of uptake in inflammatory foci and low liver and spleen uptake (*9–11*).

MATERIALS AND METHODS

Animal Model

In female New Zealand white rabbits (weight 2.5–3 kg), acute colitis was induced as described previously with minor modifications (*12–14*). Experiments were performed in accordance with the local animal welfare committee guidelines. During the experiment, the rabbits were fasted, but had water ad libitum. Animals were anesthetized with an intravenous injection of a 0.7-ml mixture of fentanyl 0.315 mg/ml and fluanisone 10 mg/ml (Hypnorm). After retrograde insertion of a flexible silicone tube, 1 ml of 30 mg trinitrobenzene sulfonic acid in 30% ethanol, followed by 1 ml 50% ethanol flush, was instilled in the colon 25 cm from the anal sphincter. Thereafter, anesthesia was terminated by intravenous injection of 0.2 ml of naloxon hydrochloride 0.4 mg/ml (Narcan). Twenty-four hours after colitis induction, the respective radiopharmaceuticals were injected through the ear vein.

Radiopharmaceuticals

Indium-111-Leukocytes. One hundred milliliters of blood were drawn carefully from an anesthetized donor rabbit by carotid artery cannulation in 60 ml syringes, each containing 10 ml 0.33% methylcellulose in citric acid dextrose. The total leukocyte count of the donor rabbit was 10 × 10^9/liter, with approximately 50% granulocytes. Preparation of the labeled leukocytes was performed as described previously (*15,16*). In brief, after sedimentation of the erythrocytes, the supernatant was removed. The remaining cell suspension was centrifuged twice and the cell pellet was washed with phosphate buffered saline (PBS)/1% HSA. Indium-111-oxine (100 MBq) in 0.2 *M* tris(hydroxymethyl)aminomethane hydrochloride (pH = 8.0) was added to the cell suspension. After a 30-min incubation period, the cells were incubated at room temperature for 30 min, centrifuged and resuspended in PBS/1% human serum albumin. Morphological integrity of the leukocytes was checked by light microscopic examination. Labeling efficiency (cell associated activity/total activity × 100%) was higher than 95%. Indium-111-leukocytes (15 MBq) were administered intravenously.

Indium-111-Liposomes. Partially hydrogenated egg-phosphatidylcholine with an iodine value of 40 was derived (*17*). The polyethylene glycol 1900 derivative of distearoyl phosphatidylethanolamine was prepared as described previously (*18*). A chloroform/methanol mixture (10/1, v/v) containing polyethylene glycol-distearoyl phosphatidylethanolamine, partially hydrogenated egg-phosphatidylcholine and cholesterol was prepared in a molar ratio of 0.15:1.85:1. A lipid film was formed by rotary evaporation followed by high vacuum to remove residual organic solvent (*19*). The lipids were dispersed at room temperature in 6 m*M* Desferal in 0.9% HEPES buffer (10 m*M* HEPES/135 m*M* sodium chloride, pH 7.5) at an initial phospholipid concentration of 120 m*M*. The liposomes were sequentially extruded through polycarbonate filters of 0.2, 0.1, 0.08 and 0.05-μm pore size. Unentrapped Desferal was removed by gel filtration on an EconoPac 10 DG column. The particle size distribution was determined by dynamic light scattering with a Malvern 4700 system using a 25 mW Helium-Neon laser. The data were analyzed using the Automeasure 3.2 software. As a measure of particle size distribution of the dispersion, a polydispersity index was determined, ranging from 0.0 (entirely monodisperse dispersion) to 1.0 (completely polydisperse dispersion). The mean size of the liposome dispersions was 90 nm with a polydispersity index of approximately 0.1.

Preformed Desferal-containing liposomes were labeled with ^{111}In essentially as described previously (*10,20*). Indium-111 was transported over the lipid bilayer in the form of ^{111}In-oxine and trapped irreversibly in the internal aqueous phase by the encapsulated Desferal. Briefly, the liposomes (45 mmol phospholipid/ml) were incubated for 30 min at room temperature with 200 kBq ^{111}In-oxine per millimole of phospholipid. Removal of unencapsulated ^{111}In-oxine was achieved by gel filtration on a 10DG Econo Pak column. More than 95% of the radiolabel was associated with the liposomes. Indium-111-liposomes (15 MBq) were injected intravenously.

Indium-111-IgG. Human, nonspecific polyclonal IgG was conjugated to diethylenetriaminepentaacetic bicyclic anhydride (bicyclic DTPA) as described by Hnatowich et al. and labeled with ^{111}In-chloride (*21*). Labeling efficiency as determined by instant thin-layer chromatography was higher than 95%. Indium-111-IgG (15 MBq) was injected intravenously.

Histology

Two rabbits were killed with an overdose of sodium phenobarbital 24 hr after colitis induction. The colon was resected and tissues were fixed in 4% formaldehyde in PBS. Tissue samples were embedded in paraffin and 5-μm sections were stained with hematoxylin-eosin for light-microscopic examination.

Imaging Procedure and Biodistribution

Twenty-four hours after colitis induction, three groups of four rabbits were intravenously injected through the ear vein with either ^{111}In-leukocytes, ^{111}In-liposomes or ^{111}In-IgG. The rabbits were immobilized in a mold and placed prone on a gamma camera equipped with a parallel-hole medium-energy collimator. Each rabbit was imaged at 5 min, 1 hr, 4 hr, 10 hr and 20 hr after injection. Images (100,000 counts per rabbit) were obtained and stored in a 256 × 256 matrix.

After acquiring the final images, the rabbits were killed with an overdose of sodium phenobarbital and biodistribution of the radiopharmaceuticals was determined. Blood was obtained by cardiac puncture. Tissues [muscle, lung, liver, spleen, kidney, normal (ascending) colon and affected (transverse and descending) colon] were dissected. The affected colon was divided into seven consecutive affected colonic segments of 5 cm each. The colonic segments were scored macroscopically on an arbitrary scale (0 = normal, 1 = inflammation, 2 = ulcers). The samples were weighed and their radioactivity was measured in a shielded well scintillation

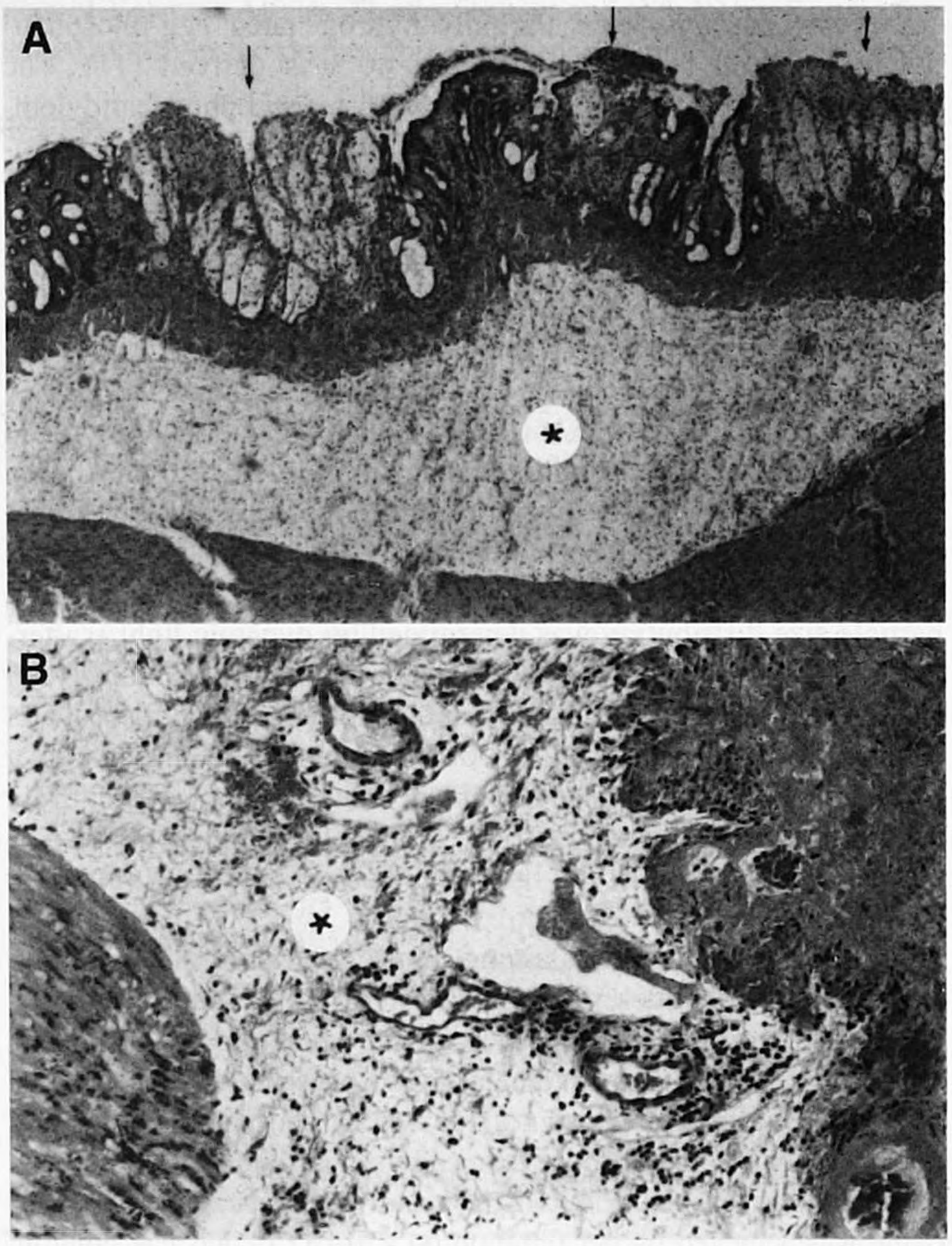

FIGURE 1. Histology of trinitrobenzene sulfonic acid-induced acute colitis. The mucosa shows beginning necrosis and ulceration (arrows). The submucosa is edematous (*). Areas of granulocyte infiltration can be identified throughout the colonic wall. Hematoxylin–eosin-stained transverse sections: (A) ×130, (B) ×330.

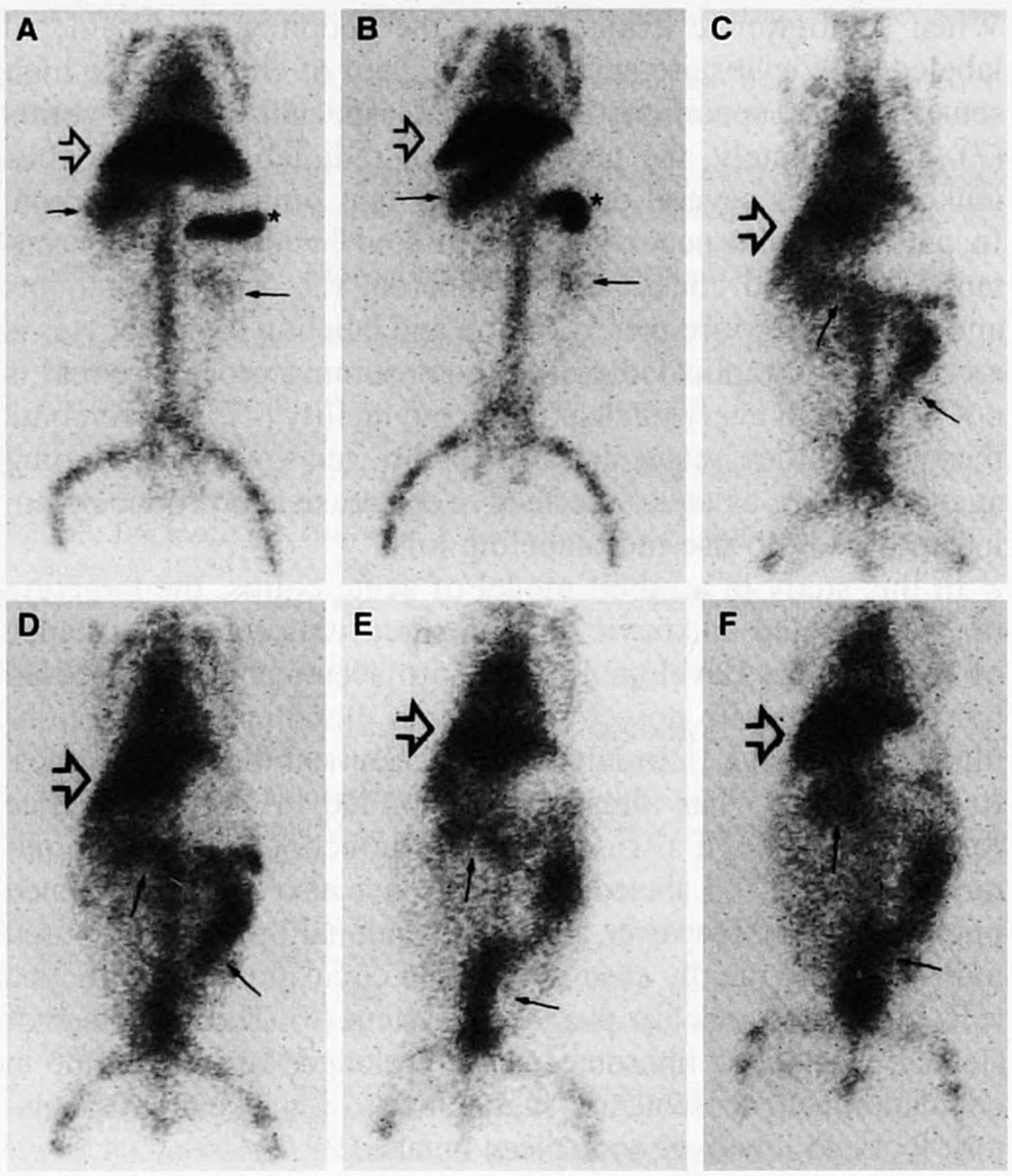

FIGURE 2. Scintigraphic images of rabbits with experimental colitis. (A) Indium-111 leukocytes, 10 hr postinjection. (B) Indium-111 leukocytes, 20 hr postinjection. (C) Indium-111 liposomes, 10 hr postinjection. (D) Indium-111 liposomes, 20 hr postinjection. (E) Indium-111 IgG, 10 hr postinjection. (F) Indium-111 IgG, 20 hr postinjection. Note the physiological uptake in liver, spleen and for ^{111}In-liposomes and ^{111}In-IgG also kidney and blood pool. ⇒S = liver; * = spleen; → = delineation of colitis.

gamma counter. To correct for physical decay and to permit calculation of the uptake of the radiopharmaceuticals in each organ as a fraction of the injected dose, aliquots of the injected dose were counted simultaneously. The results were expressed as percent injected dose per gram (%ID/g). From these results, the colitis index (CI, affected-to-normal colon ratio) for each of the radiopharmaceuticals was calculated in all segments.

Statistical Analysis

All mean values are given as %ID/g or ratios ± one s.e.m. Statistical analysis was performed using one way analysis of variance. Correlations were calculated by linear regression analysis. The level of significance was set at $p < 0.05$.

RESULTS

Histologically, multiple areas of mucosal necrosis were observed at the site of instillation and the part of the colon between instillation site and rectum. The submucosa was edematous and transmural granulocytic infiltration was seen (Fig. 1).

Over time, increasing accumulation of the radiopharmaceuticals in the diseased colon was observed on the scintigraphic images. Figure 2 shows images of rabbits recorded 10 and 20 hr after injection of the radiopharmaceuticals. Physiological uptake in kidneys (liposomes and IgG only), liver and spleen was seen. Furthermore, affected parts of the colon were delineated with all radiopharmaceuticals.

The biodistribution in tissue samples is given in Table 1. Indium-111-leukocyte blood levels were lower than those of ^{111}In-IgG and ^{111}In-liposomes. This faster clearance of ^{111}In-leukocytes was also reflected in significantly lower uptake in muscle, lung and uptake in nonaffected normal colon. The uptake in liver and spleen markedly differed between the various preparations. Indium-111-leukocytes had much higher splenic and—to a lesser extent—liver uptake than ^{111}In-liposomes and ^{111}In-IgG. Overall absolute uptake in the affected colon was significantly higher for ^{111}In-liposomes than for the two other agents. Absolute uptake of ^{111}In-leukocytes was relatively low. Still, as indicated below, abnormalities were also well delineated with ^{111}In-leukocytes, since uptake in nonaffected colon was extremely low and consequently CIs relatively high.

CIs (diseased-to-normal colon ratios) are given in Figure 3. When comparing the relative uptake in macroscopically normal colon (scored as Grade 0), the CIs for all three preparations were similar. In nonulcerative inflammation (scored as Grade 1) and ulceration (scored as Grade 2), the relative uptake of ^{111}In-liposomes in the diseased segments was higher than that of both ^{111}In-leukocytes and ^{111}In-IgG, reflected in significantly higher CIs of ^{111}In-liposomes ($p < 0.05$ and $p < 0.001$, respectively). The relative uptake of ^{111}In-IgG was significantly lower than that of ^{111}In-leukocytes in ulceration (Grade 2) ($p < 0.05$).

When evaluating the relative uptake in the affected segments for the individual radiopharmaceuticals, a positive correlation was observed between CIs and the severity of the macroscopic abnormalities. For ^{111}In-liposomes, correlation was strongest ($r^2 = 0.68$, $p < 0.001$). Similarly, for ^{111}In-leukocytes and ^{111}In-IgG, a correlation was observed but less striking ($r^2 = 0.31$, $p < 0.01$, and $r^2 = 0.29$, $p < 0.02$, respectively).

DISCUSSION

In this study, ^{111}In-labeled sterically stabilized liposomes were shown to be a superior imaging agent for evaluation of

TABLE 1
Tissue Distribution (%ID/g; mean ± s.e.m.) Obtained 48 hr after Colitis Induction and 24 hr after Injection of the Radiopharmaceuticals

Tissue	^{111}In-IgG	p*	^{111}In-leukocytes	p†	^{111}In-liposomes
Blood	0.22 ± 0.03	< 0.05	0.13 ± 0.008	< 0.05	0.22 ± 0.01
Muscle	0.01 ± 0.001	< 0.01	0.002 ± 0.0002	< 0.01	0.01 ± 0.001
Lung	0.09 ± 0.001	< 0.01	0.06 ± 0.002	< 0.01	0.10 ± 0.001
Liver	0.20 ± 0.02	< 0.01	0.53 ± 0.04	< 0.01	0.15 ± 0.03
Spleen	0.12 ± 0.008	< 0.01	8.08 ± 1.09	< 0.01	0.42 ± 0.04‡
Kidney	0.19 ± 0.02	< 0.01	0.05 ± 0.006	< 0.01	0.20 ± 0.02
Ascending colon (normal)	0.05 ± 0.002	< 0.01	0.01 ± 0.003	< 0.01	0.06 ± 0.007
Descending colon (affected, 35 cm)	0.13 ± 0.01	< 0.01	0.03 ± 0.006	< 0.01	0.37 ± 0.003‡

IgG = gamma globulin.
*^{111}In-IgG vs. ^{111}In-leukocytes.
†^{111}In-leukocytes vs. ^{111}In-liposomes.
‡^{111}In-liposomes vs. ^{111}In-IgG ($p < 0.01$).

acute trinitrobenzene sulfonic acid-induced colitis in rabbits. In clinical practice, leukocytes are considered the standard technique for scintigraphic evaluation of disease activity in inflammatory bowel disease (*1,22*). In this study, ^{111}In-liposomes showed higher absolute, as well as uptake, ratios in diseased colonic segments compared with the ^{111}In-leukocytes. Moreover, correlation of the macroscopic abnormalities observed in the affected colon and relative colonic uptake, of ^{111}In-liposomes was better compared with ^{111}In-leukocytes. In addition, hepatosplenic uptake of ^{111}In-liposomes was considerably lower than that of ^{111}In-leukocytes, which is not only important for adequate scintigraphic evaluation of the alimentary tract in the upper abdomen, but also for reduction of the radiation burden to the spleen and to long-living T-lymphocytes, which are also labeled in mixed leukocyte preparations (*23*). Despite the lower absolute uptake of ^{111}In-leukocytes in colitis lesions, diseased colon segments could be delineated well since uptake in the background tissues (i.e., normal colon and muscle) was extremely low, providing sufficient contrast. Abnormalities were depicted early on the ^{111}In-leukocyte images due to the relatively fast blood clearance. A major advantage of ^{111}In-liposomes is the ease of preparation of a high-quality radiopharmaceutical without the need to isolate and handle blood.

The superiority of ^{111}In-leukocytes over labeled gamma globulin confirms clinical results with labeled gamma globulin (*5,24*). The abnormalities depicted by the labeled leukocytes scintigraphy were shown to correlate better with disease activity than those observed on labeled gamma globulin images, indicating relatively low sensitivity and specificity of the latter agent (*24,25*). In this study, this was exemplified by the lower relative uptake of ^{111}In-IgG in affected colon as compared with ^{111}In-leukocytes (and ^{111}In-liposomes). This lower ratio will obviously make it more difficult to differentiate accumulation in inflamed from normal tissue uptake. Moreover, even the limited physiological excretion of labeled gamma globulin in the gut may interfere with adequate evaluation of diseased colon (*5*).

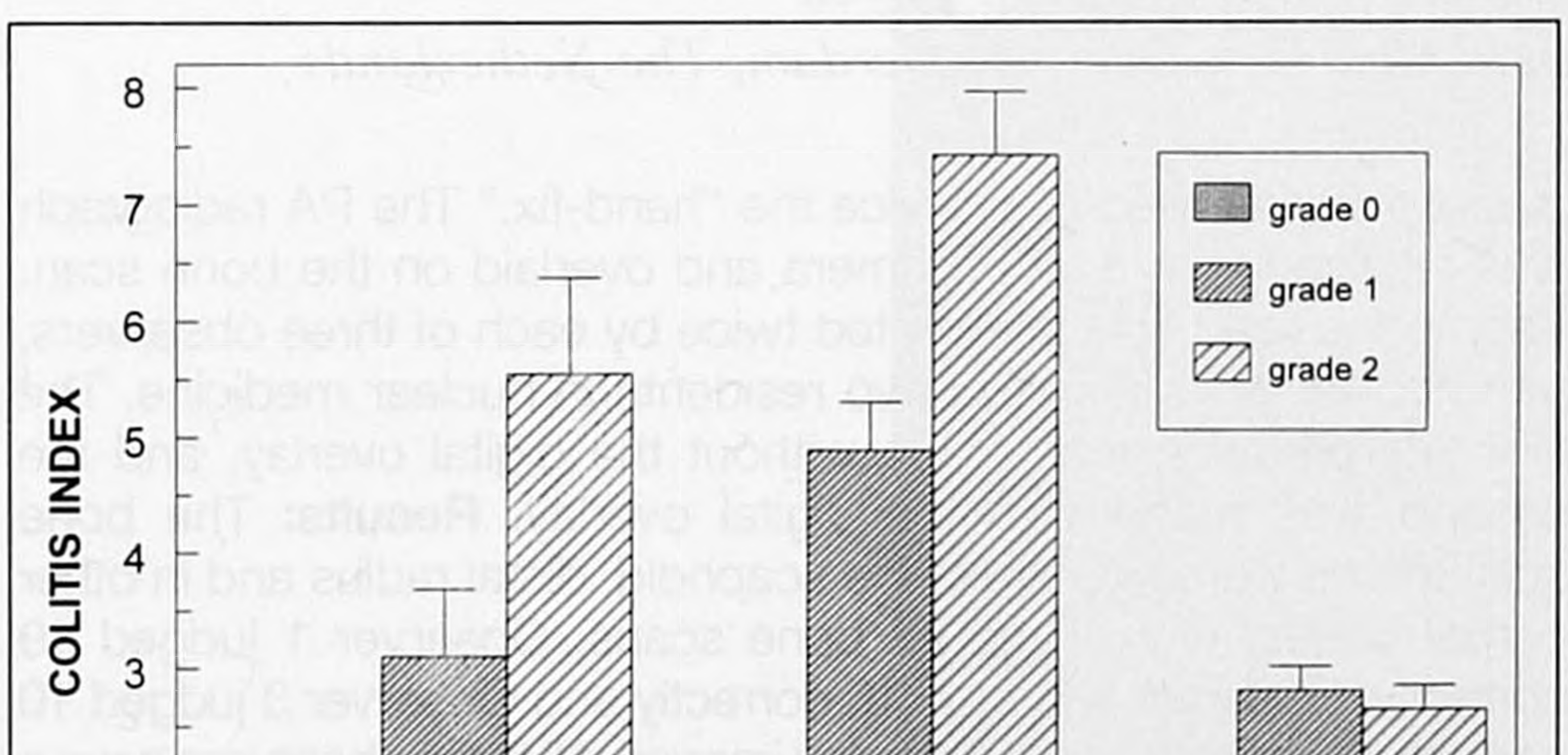

FIGURE 3. CI (mean ± s.e.m.) of the radiopharmaceuticals as compared with the macroscopic severity of abnormalities in the affected colon. (Grade 0 = normal; Grade 1 = inflammation; Grade 2 = ulcers.)

The mechanism of accumulation in the target area of ^{111}In-leukocytes and the two new radiopharmaceuticals is entirely different (*26*). Adequate ^{111}In-leukocytes scintigraphy requires viability of the cells with intact chemotactic capacities, since the labeled cells must actively migrate to an inflammatory target similar to unlabeled leukocytes. When damaged, the labeled cells show prolonged margination in the lungs, followed by enhanced clearance by the mononuclear phagocytic system (*27*). This further emphasizes the need for careful preparation of leukocytes during labeling. Indium-111-liposomes and ^{111}In-IgG both accumulate in inflamed tissue by virtue of increased vascular permeability (*26*). Thus, prolonged intravascular activity will be beneficial for the degree of uptake in inflammation. This also explains why agents like labeled colloids (also a particulate radiopharmaceutical) do not provide adequate delineation of colitis (*28,29*). Colloids have a short circulation time and distribute rapidly to liver, spleen and bone marrow without sufficient focal uptake in disease. Similar characteristics can be observed with non-PEGylated larger liposomes (*6,7*). Whether any specific uptake of labeled liposomes in inflammatory cells plays a role in accumulation of the radiopharmaceutical in inflammatory foci remains to be established.

CONCLUSION

Indium-111-liposomes were superior to ^{111}In-leukocytes for scintigraphic evaluation of acute colitis due to high focal uptake and relatively low accumulation in many organs. In addition, in view of the ease of preparation, this new formulation is particularly attractive for progression to clinical studies. Indium-111In-IgG was not very well suited for imaging colitis, because the uptake in diseased segments was relatively low and