

PRELIMINARY NOTE

Comparisons of Scintigraphy with In-111 Leukocytes and Ga-67 in the Diagnosis of Occult Sepsis

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In a prospective study involving 32 patients with clinical suspicion of focal infection, the sensitivity and specificity of In-111-labeled leukocyte (In-WBC) scintigraphy were compared with those of Ga-67 scintigraphy performed 24–48 hr later. Of a total of 192 body sites studied, 26 foci of infection were diagnosed by aspiration, cultures, or chest radiographs. Indium-WBC indicated 19 (73%) true-positive (TP) and four (2.5%) false-positive (FP) foci of abnormal accretion; Ga-67 had 21 (81%) TP and 15 (9%) FP. The 7/26 (27%) false-negative (FN) In-WBC scintigrams involved infection foci of more than 2-wk duration; the 5/26 (19%) FN Ga-67 studies were in patients with infections manifested for <1 wk. The results of this study are useful in considering the indications of the two tracers.

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Scintigraphy with In-111-labeled leukocytes (In-WBC) is reportedly a reliable method for the diagnosis and location of sepsis (1–12). This method utilizes leukocytes obtained from 50 ml blood, and their separation and labeling is cumbersome, requiring expertise, precision, and time (13). False-negative results have been reported in a small percentage of studies (3,6,9) and “pitfalls” have already been recognized (5,14). Clinical experience, however, is still not very extensive, considering that infections are a frequent clinical entity and may present a wide clinicopathological spectrum. Several factors may affect the course of an infection, including the type of pathogen, the diversity of site of localization, the host response, and therapy. The relative migration of intravascular leukocytes toward the site of infection depends upon such factors, and it is related to the duration of infection (15). Although it has been demonstrated that separation and labeling does not affect leukocyte function (13,16), a limiting factor that has to be considered with this method is its dependence upon the relative migration of the circulating leukocytes toward the focus of infection.

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On the other hand, Ga-67 scintigraphy, a currently applied procedure to locate sepsis, is easy to perform, has been widely used, and critical reviews of its clinical usefulness in diagnosing occult sepsis have been widely published (17). Despite the well-recognized lack of specificity, Ga-67 scintigraphy has been a sensitive method for infection location, particularly in combination with ultrasound or transmission tomography (18).

Our preliminary work in six rabbits with *E. coli* induced subcutaneous abscesses showed, as expected, that In-WBC scintigraphy was successful in demonstrating the abscesses early after inoculation; but in four animals studied between 3 and 6 wk later, In-WBC scintigrams barely showed the abscesses, whereas Ga-67 scintigraphy performed a few days later clearly delineated them (Fig. 1). This observation, although of limited statistical significance because of the small number of animals studied, prompted a clinical study to compare the two scintigraphic approaches in locating focal infection. This is a preliminary report of a prospective clinical study, which compared the sensitivity and specificity of In-WBC and Ga-67 scintigraphy performed in the same population sequentially within a short period of 1–2 days. The findings indicated a greater usefulness of leukocyte imaging in the acute infection, but a higher sensitivity

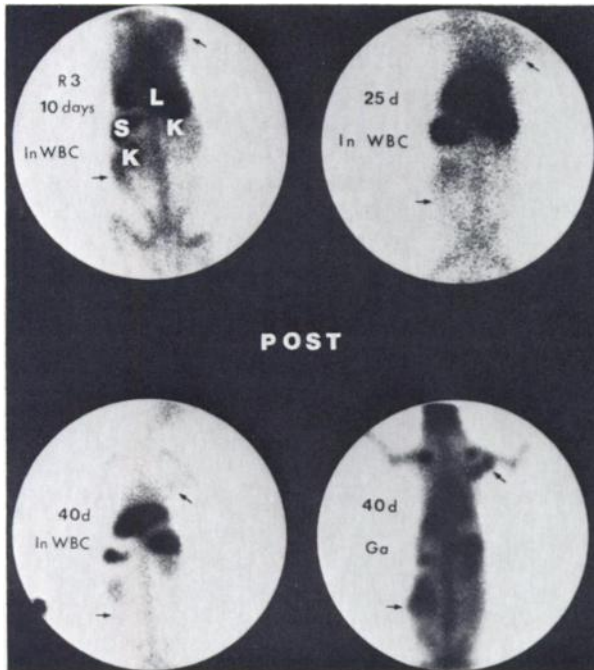


FIG. 1. Scintigrams in rabbit with two subcutaneous abscesses due to inoculation with *E. coli* and fecal material. Arrows indicate location of the abscesses. In-WBC shows declining intensity of accumulation from tenth to fortieth day, but Ga-67 accumulated vigorously on fortieth day. L = liver, S = spleen, K = kidney. In-WBC on Days 10, 25, and 40 after inoculation, Ga-67 on Day 40.

of the Ga-67 scintigraphy in the subacute or chronic infection. When both studies were performed, no focal infection was missed.

METHODS

Patient population. Thirty-two patients (male and female, 20-66 yrs old) suspected of having a focal inflammatory process were imaged using both In-111-labeled leukocytes and Ga-67 citrate (Table 1). All patients had been evaluated with several imaging modalities including conventional radiography, ultrasound, computed tomography, and scintigraphy according to indications. All were inconclusive at the time of presentation, and as such the patients were admitted to the study.

A total of 192 body sites were evaluated and 26 foci of infection were proven by (a) aspiration or surgical or spontaneous drainage, (b) culture of aspirates or wipes from identified sites, or (c) chest radiographs showing infiltrates compatible with infection (Table 2). In ten patients no focus of infection was proven and they became afebrile on conservative treatment. Some patients had more than one focus (Table 2).

The time of onset and the duration of infection were estimated by history (onset of symptoms or fever) or clinical findings at or during hospitalization (fever, elevated white cell count, positive cultures, abnormal radiographs, etc.) (Fig. 2).

Protocol of study, and data analysis. The protocol followed the signing of an informed consent, following which autologous leukocytes were prepared, labeled, and reinjected (Day 0). After completion of In-WBC scintigraphy, Ga-67 was injected (Day 1). Gallium-67 imaging was performed on Days 2 or 3, and occasionally later. Results of In-WBC scintigrams were not reported and therapy was not influenced until the gallium results were obtained and reported together with the findings on the In-WBC scintigrams. Interpretation of the two scintigrams of each patient was performed independently by different physicians without knowledge of results of the other study but with other clinical and laboratory information from previous examinations available. Evaluation of the scintigrams was by consensus and no interobserver or intraobserver variation was evaluated. The patient records were reviewed 1-6 mo after the scintigrams, and results were correlated with the final diagnosis.

Indium-111-leukocyte imaging. Autologous white blood cells were labeled utilizing a slight modification of the method published by Thakur et al. (1,2,13,19). The procedure was performed in closed sterile tubes with rubber caps, at room temperature and with pyrogen-free and sterile reagents. Cells or supernatant were removed with syringes having long sterile needles, inserted through the rubber caps after alcohol cleaning and drying. Fifty milliliters of blood was drawn in a 50-ml syringe containing 5 ml ACD. Five milliliters of solution of the polysaccharide Volex was added aseptically and mixed in. The syringe was allowed to stand on the plunger end for separation of the supernatant, rich in leukocytes and platelets, after erythrocyte sedimentation. The leukocytes were separated from platelets by centrifugation (350 g for 5 min), then washed in normal saline. If the erythrocyte count was higher than half the leukocyte count, hypotonic hemolysis was applied (1 ml water for 60 sec) followed by removal of the hemoglobin

TABLE 1. PATIENT POPULATION

Status after abdominal operation*		20
septic wounds	12	
infections	5	
hemorrhage	1	
blunt trauma	2	
Fever of unknown origin		7
Acute abdomen		2
Bone infection		2
Heart/lung infection		1
	Total	32

* These patients had a laparotomy and afterward they developed or continued having fever; for this reason they were admitted to this protocol.

TABLE 2. CORRELATION BETWEEN FINAL DIAGNOSIS AND RESULTS OF SCINTIGRAMS

Body sites studied	Foci of infection documented*		Results of In-WBC scintigrams				Results of Ga-67 scintigrams			
			TP	TN	FP	FN	TP	TN	FP†	FN
Lungs	32	14	11	16	2	3	10	17	1	4
Liver	32	3	3	29	—	—	2	26	3	1
Abdomen	32	6	3	26	—	3	6	16	10‡	—
Pelvis	32	—	—	30	2	—	—	31	1	—
Kidneys	32	1	—	31	—	1	1	31	—	—
Skeleton	32	2	2	30	—	—	2	30	—	—
Total	192	26 [§]	19	162	4	7	21	151	15	5
Sensitivity TP/(TP+TN)			19/(19+7) = 73%				21/(21+5) = 81%			
Specificity TN/(TN+FP)			162/(162+4) = 98%				151/(151+15) = 91%			
Accuracy TP+TN/(TP+TN+FN+FP)			19+162/(19+162+7+4) = 94%				21+151/(21+151+5+15) = 90%			

TP = true positive, TN = true negative, FP = false positive, FN = false negative.

* See text for method of documentation.

† Ga-67 accumulation within tumor sites was considered false positive.

‡ In 18 patients there was recognizable physiologic bowel activity, which was not considered false positive. The 10 FP scintigrams were either healing wound activity (7) or of unknown origin (3).

§ Eighteen patients had one focus of infection each, and four patients had two foci each. In ten patients no focus of infection was found; they became afebrile on antibiotics and were eventually discharged.

and the ghosts. Labeling of the leukocytes was performed by incubation for 30 min at room temperature in 5 ml normal saline after adding 600 μ Ci In-111 bound to 50 μ g oxine (8-hydroxyquinoline) in 0.05 ml ethanol.*

After washing, the labeled leukocytes were resuspended in platelet-poor plasma prepared from the patient's original supernatant. After testing for labeling

efficiency and viability, the In-WBC were slowly injected intravenously (over 2-3 min).

Labeling efficiency was usually in the 80-90% range. Viability was tested by three techniques: (a) the trypan blue rejection technique (applied in all patients and showed more than 90% intact cells), (b) the unstimulated nitroblue tetrazolium (NBT) (applied selectively and

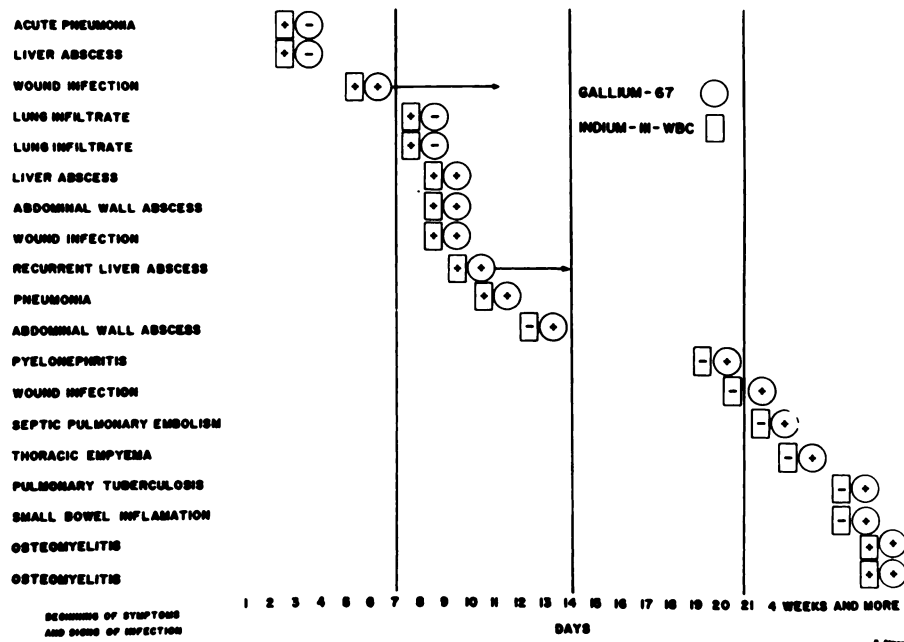


FIG. 2. Results of In-WBC and Ga-67 scintigraphy as related to duration of infection in 19 patients in whom time of onset could be estimated (four of them had two foci of infection). In three patients, duration of infection could not be established. Statistical analysis (chi-square test for independence) revealed that duration of infection significantly affected results of In-WBC ($P < 0.005$) and Ga-67 ($P < 0.005$).

showed 15–20% positive cells), and (c) the stimulated NBT technique with bacterial extract (applied selectively and showed an increase in the number of the positive cells) (20).

The patients were injected with more than 10^8 WBC carrying 150–600 μCi of In-111. Imaging was performed at 24 hr with a LFOV gamma camera using two 30% windows (172 and 247 keV). Two intensities were used for the radiographic film: one lower, to visualize the liver, and a higher one to visualize bone marrow clearly elsewhere in the body. Triple-exposure Polaroid photography was found especially well suited to cover the needed range of intensities. Technetium-99m sulfur colloid liver imaging was performed concurrently if an upper abdominal lesion was suspected (8,21).

Gallium-67 imaging. The citrate was given in a dose of 6 mCi, and scintigraphy was performed at 24 and 48 hr and occasionally later. The same camera was used with three effective windows (93, 184, and 296 keV). Because of the difference in dosage, duration of each image, intensity settings, and elapsed time, In-111 photon detection on Ga-67 images was insignificant, except for the spleen, barely visible.

RESULTS

In the 32 patients of this study, 192 body sites were evaluated, 26 foci of infection were proven and 166 body sites were found free of infection. Table 2 indicates the distribution of the 26 sites in which the diagnosis of infection could be confirmed as described above. Indium-WBC studies were positive in 19 (73%) whereas Ga-67 was positive in 21 (81%) of those sites. The sensitivity, specificity, and accuracy of the two scintigraphic methods were included in Table 2. Despite the high general score, there were a significant number of false studies, both positive and negative. On In-WBC studies 7/26 (27%) of sites were falsely negative (FN) and 4/166 (2.5%) falsely positive (FP), compared with 5/26

(19%) FN and 15/166 (9%) FP for the Ga-67. Interestingly, FN and FP were different for the two tracers, and an effort was made to identify technical or clinical correlations.

No correlation was found with dose of In-111, erythrocyte lysis, labeling efficiency, or number of reinjected WBC. The correlation with fever and blood WBC counts on the day of injection of the In-WBC is indicated in Table 3. A statistically significant correlation was found between the duration of infection and results of the scintigrams (Fig. 2): in all patients whose infections had been clinically manifested for a period of up to 2 wk, the In-WBC scintigrams were positive, but they were mostly negative or questionable in infections of longer duration. Gallium-67 scintigrams were negative or at least questionable in some infections with a very short duration but they were consistently positive thereafter. Infections of shorter duration had generally higher fevers and blood WBC counts. Characteristic examples were included in Figs. 3–12, with explanatory legends.

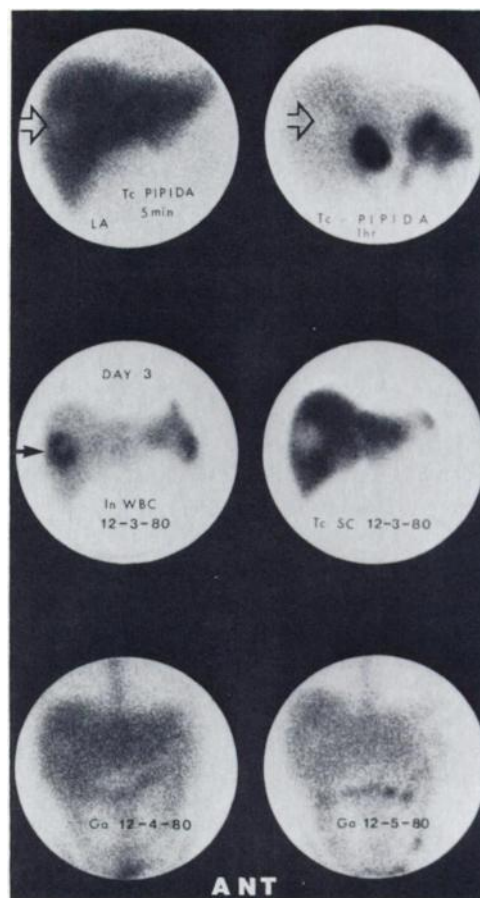


FIG. 3. Scintigrams from 34-yr-old man admitted with a 24-hr history of symptoms and signs suggesting acute cholecystitis until Tc-99m PIPIDA study showed focal defect (open arrow) within right lobe of liver. Indium-WBC scintigram, performed on Day 3 after onset of clinical manifestations of disease, was strongly positive (arrow), but Ga-67 studies were negative at 24 and 48 hr. Pus was aspirated but did not grow microorganisms, because patient was already on antibiotic therapy that cured abscess.

TABLE 3. CORRELATION OF TEMPERATURE AND PERIPHERAL BLOOD WBC COUNTS WITH RESULTS OF In-WBC SCINTIGRAPHY

Results of In-WBC scintigrams	Temperature mean (s.d.)	Peripheral-blood WBC counts mean (s.d.)
True positives	102.1 (1.18)*	16.88 (6.53)†
True negatives	100.6 (1.4)*	12.6 (3.1)
False negatives	100.6 (0.4)	9.1 (5.3)

*The difference between means was statistically significant ($P < 0.025$) between the temperatures of the true positives and the true negatives (t-test). The differences between means of all other pairs were not statistically significant ($p > 0.05$).

† In thousands per mm^3 .

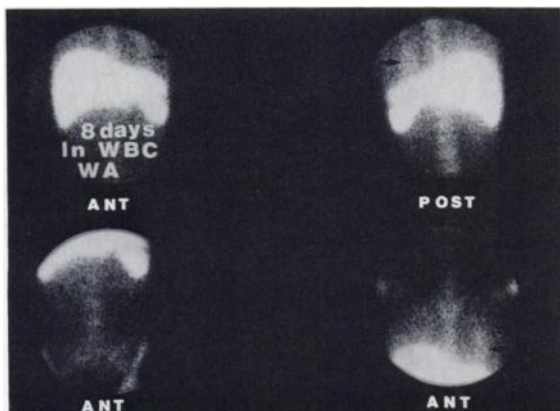


FIG. 4. Indium-WBC scintigram of patient with 8-day picture of postoperative sepsis, showing pulmonary paracardiac focus of accumulation (arrow) (continue in Fig. 5).

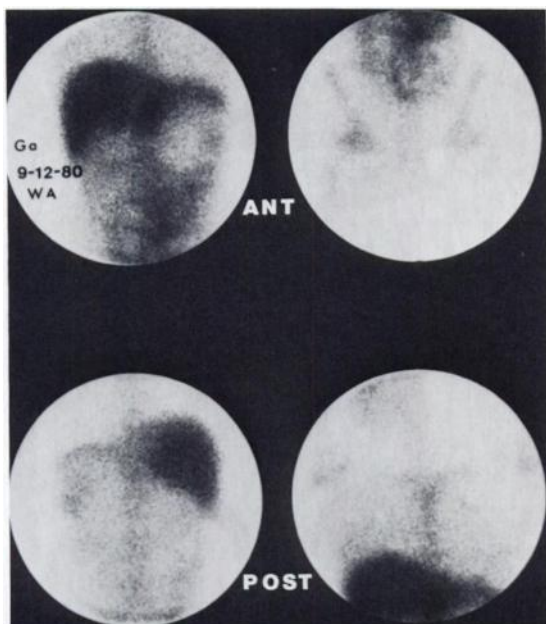


FIG. 5. Gallium-67 scintigram (48 hr) of patient in Fig. 4 showing confusing abdominal activity but no pulmonary accumulation. Diagnosis of bronchopneumonia was made from chest radiograph. Treatment was conservative and picture of sepsis resolved concurrent with radiographic findings.

DISCUSSION

An inverse correlation was found between the duration of the manifestations of infection and the sensitivity of the In-WBC scintigraphy (Fig. 2). We found positive

In-WBC scintigrams in short-duration infections, and most false negatives were in those cases with an infection more than 2 wk old. Gallium-67 scintigrams appeared to have the opposite tendency, with a few false-negative or questionable studies in short-duration infections and TP studies subsequently (Fig. 2). The results presented in this report are preliminary and from a small sample of a selected population. They were, however, obvious and in agreement with the theoretical consideration that acute focal infections associated with vigorous leukocyte migration should have a rapid, clear and intense visualization with In-WBC scintigraphy (Fig. 3); those with an insufficient WBC migration—such as chronic encapsulated abscesses, chronic or subacute infections, or foci with very low rates of accumulation of circulating leukocytes—could not be optimally visible (Fig. 10), if at all detectable, with In-WBC.

Previous reports (1,2,6,7) showed a higher sensitivity for this method, but no temporal correlation was mentioned and the population might have been different. Experience with osteomyelitis by other authors, however, has indicated that In-WBC scintigrams were positive in acute, and negative in chronic, osteomyelitis (6,22). Some authors have mentioned that false-negative scans are more likely in old lesions (3,9). We know of no systematic comparative In-WBC and Ga-67 studies in humans, and those in animals were only in acute abscesses (16,23). We found only one case report showing greater effectiveness of In-WBC relative to Ga-67 in an acute liver abscess (24).

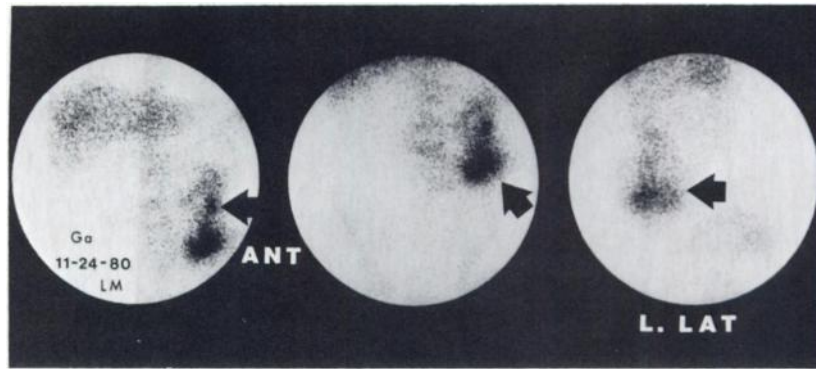
Technical factors were first considered but could not explain findings. The viability of the reinjected leukocytes, as tested, was normal. The tests we performed could not establish the migrating integrity of the cells, but the method we consistently followed was confirmed to render functioning leukocytes (13,16) and we were not able to identify any problems with our procedure that could explain failures (false negatives) and at the same time good results (true positives). Therapy certainly played no role, since all the patients were on antibiotics at the time of the study. It is known, however, that in subacute or chronic infections the population of the migrating cells is different and the rate of migration is low, and most probably this is the cause of the FN In-WBC studies.

We agreed with previous investigators (1-12) that the



FIG. 6. A 22-yr-old patient with gunshot wound of abdomen had evidence of post-operative sepsis of 9 days' duration. Indium-WBC study showed left abdominal accumulation (arrow) (continue in Fig. 7).

FIG. 7. Gallium-67 scintigram of patient in Fig. 6, performed at 48 hr and immediately after the In-WBC study, showed identical abnormality (arrow). An abdominal-wall abscess was subsequently evacuated.



specificity of In-WBC scintigraphy is excellent. Bladder activity (2 cases) and pulmonary activity from embolized cells (2 cases) were the cause of our four false-positive In-WBC scintigrams. They created problems of inter-

pretation when they happened at the beginning of this study. We have since prevented this by washing the WBC after labeling and by vortexing them just before injection.

Gallium scintigraphy to locate infection is known to be sensitive but not specific (17,25). The few false-negative results with the short-duration infections need

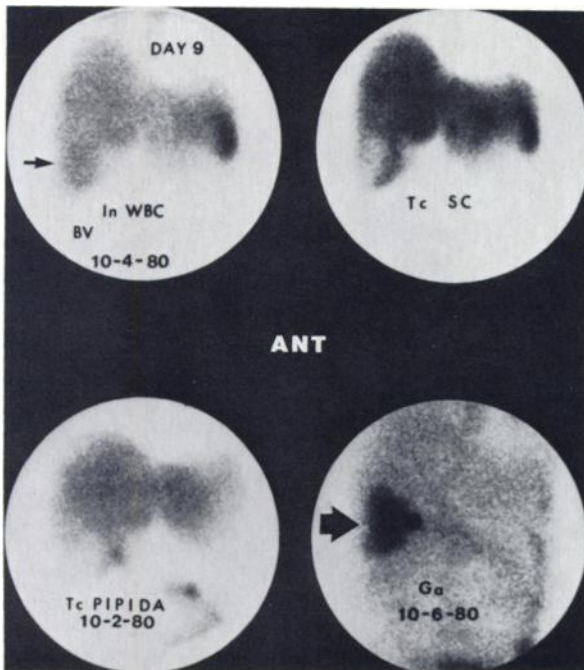


FIG. 8. A 46-yr-old female with pyogenic liver abscess. On ninth day after onset of symptoms she gave this In-WBC scintigram, which was faintly positive (arrow). Gallium-67 image, however, was strongly positive at 48 hr (arrow).

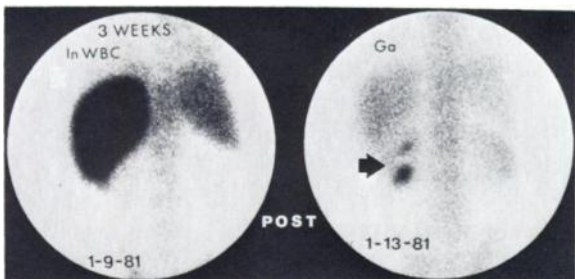


FIG. 9. Woman with 3-wk history of pyelonephritis under no effective treatment gave this negative In-WBC image and a positive Ga-67 scintigram (4 days after injection).

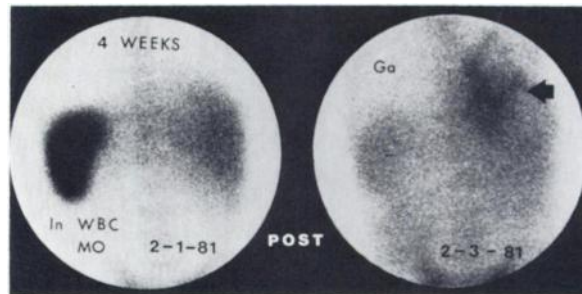


FIG. 10. Man with 4-wk-old dated empyema, aspirated later, gave this negative In-WBC image and positive 48-hr Ga-67 scintigram (arrow).

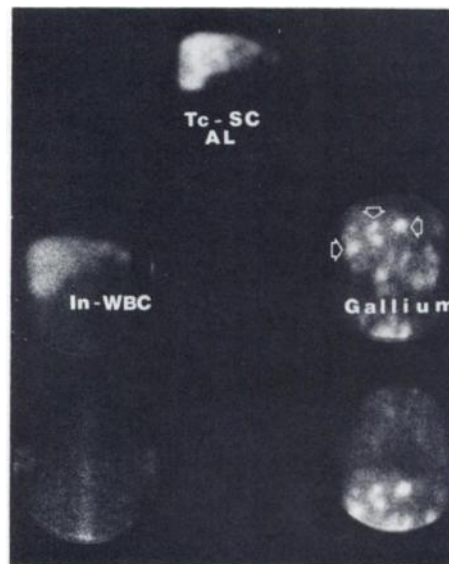


FIG. 11. Elderly woman with lung carcinoma metastatic to liver presented with continuous fever. In-WBC study was true negative. Positive, 48-hr Ga-67 study (arrows) could not differentiate between tumor and infection (48 hr).

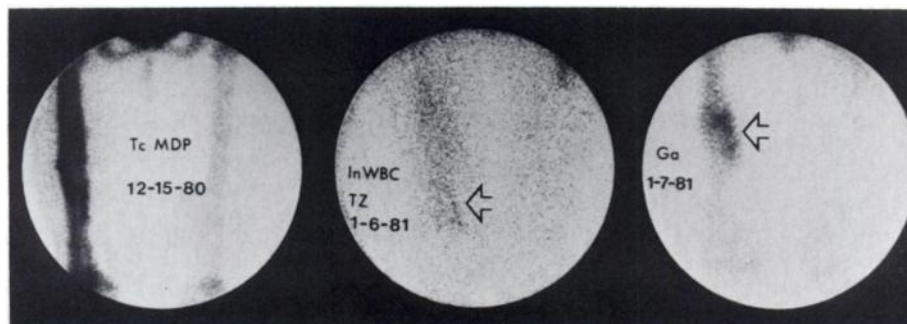


FIG. 12. Scintigrams from man with intramedullary rod for fracture of right femoral shaft. Pus was drained later upon removal of rod. Faint accumulation (arrow) of In-WBC (exposure time 28 min) was present. Ga-67 (24 hr) showed intense activity (arrow) but with different distribution. This subacute or chronic infection, obviously associated with low rate of leukocyte migration, could easily be missed on less conclusive In-WBC scintigrams. Gallium-67 activity could have been attributed to site of fracture. Example indicates limitations of both studies in subacute infections associated with bone repair.

further confirmation to constitute a reliable argument about the quality of the test.

Indium-WBC scintigraphy with autologous cells is usually performed at 24 hr, although positive scintigrams have been obtained at 4–6 hr (1,2). Results with homologous WBC in granulocytopenic patients have reported successful scintigrams as early as 30 min (12). All the In-WBC in this series were performed at 24 hr. Gallium-67 scintigraphy has been successful in granulocytopenic patients (26–30), and, in general, positive images can be obtained as early as 6 hr (25). In this series, however, Ga-67 scintigraphy was performed at 24 hr and, unless clearly positive, it was repeated at 48 hr, since higher accuracy is expected by this approach (17,25–30).

The correlation between positive In-WBC and high fever or high blood WBC counts (Table 3) could not serve as a prediction of the outcome of scintigraphy because they are present in nonfocal infections and they do not operate in immunosuppressed or granulocytopenic patients. They may, however, be considered as an adjunctive factor in determining the indications for In-WBC or Ga-67 scintigraphy, should further work confirm our findings.

There are indications that the ability of homologous granulocytes to localize at infected sites correlates with antibody status (12). We do not know whether autoantibodies play any role in the false-negative studies from our patients, or whether the postulated decreased migration rate of the leukocytes is an intrinsic chemotactic result of the subacute or chronic infection.

Although other methods have been used for leukocyte labeling (31–33), it has been shown that the In-111-oxine approach renders more stable and more efficient labeling (34,35). With the doses used, no radiation damage to the granulocytes was expected (13,36) and any damage to lymphocytes would not be manifested earlier than 24–48 hr (36). We do not expect that the use of a different labeling method would provide better re-

sults in subacute or chronic infection; the higher photon flux of a technetium-99m preparation (33) would probably be compromised by the absolute high background activity from physiologic accretion sites.

CONCLUSION

In the 32 patients studied, comparative In-WBC and Ga-67 studies show that leukocyte scintigraphy is a reliable method of sepsis location in patients with an infection of short duration (2 weeks in this group). For more prolonged infections, leukocyte scintigraphy may be falsely negative, and in such instances should probably be followed by a gallium study. This becomes particularly important if disharmony occurs between clinical impression and In-WBC results. Alternatively and despite the lack of specificity, Ga-67 imaging may be preferable if the clinical conditions suggest a low-grade chronic infection, and if the gallium study is positive, tumor or other causes of false positive should be excluded clinically and by ultrasonography or transmission computed tomography (18). In the future, single-photon emission tomography may play a role in improving the sensitivity and specificity of Ga-67 studies; if so, gallium scintigraphy could emerge as a much stronger method with low-grade subacute or chronic infections. For infectious endocarditis, In-111-labeled platelet scintigraphy appears to be the method of choice, whereas In-WBC was not successful (37); Ga-67 also did not accumulate consistently in vegetations (38). Finally, the high sensitivity and specificity of In-WBC scintigraphy for the detection and location of the acute focal infection, the availability of homologous In-WBC imaging, and the possibility of earlier imaging (12) make leukocyte scintigraphy a very promising method for the quick and correct diagnosis of the acute focal sepsis. To differentiate between phlegmon and abscess, ultrasonography and transmission computerized tomography would be useful if the clinical correlation is not sufficient (9).

FOOTNOTE

* In-111 oxine, Medi-Physics, Inc., Emeryville, CA 94608.

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