Continuing Education

Preparation and Clinical Utility of In-111 Labeled Leukocytes

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This is the third of a series of continuing education articles on radiopharmaceuticals. After reading and studying this article, the Nuclear Medicine Technologist will be able to: (1) discuss technical considerations of labeling leukocytes with In-III, and for imaging In-III such as activity administered, imaging times, the collimator of choice, window settings; and (2) discuss the clinical utility of In-III leukocyte imaging.

The diagnosis of an abscess is often difficult. Since an abscess is an accumulation of leukocytes, labeling the patient's own leukocytes with gamma-emitting radionuclides is an appealing way to detect these focal infections. And, indeed, clinical trials have confirmed that leukocyte scanning is a sensitive means of detecting sites of infection.

The first survey of radioactive tracers that could be incorporated into leukocytes was done by McAfee and Thakur (*1,2*), who looked at a variety of radioactive-soluble agents and radioactive particles. Of the various agents and labeling techniques evaluated, indium-111 chelated with 8 hydroxyquinoline (oxine) gave the best results.

Methods for Labeling Leukocytes

Indium-111 Oxine: Over the last 7 years we have performed In-111 leukocyte labeling on over 2,500 patients. During that time we have tried several modifications of the original technique reported by Thakur et al. (*3*).

The first method involved the in-house preparation of In-111 oxine (*4*) by chloroform extraction. Major drawbacks to this technique were: meticulous glassware preparation; radiation exposure to the radiopharmacist; the large amount of time required for preparation; and, poor labeling efficiency (30 to 75%). The availability of commercially prepared In-111 oxine, although expensive, has saved time and decreased radiation exposure. The product supplied by MediPhysics contains 1 mCi of In-111 in 0.05 ml of 95% ethanol; indium oxine supplied by Amersham is in an aqueous solution, 1 mCi of In-111 per ml of solution.

With the availability of oxine in aqueous solution, our labeling procedure was modified to include a prelabeling wash with saline to remove plasma from the leukocytes (Table 1). Since In-111 has an affinity for transferrin contained in plasma, removing the plasma increases the concentration of indium for labeling leukocytes, thereby increasing the labeling efficiency. Our labeling efficiency using this procedure routinely exceeds 90% (*5*). A drawback to the removal of the plasma is that the white cells are not protected by a protein coat and may therefore have decreased viability.

TABLE 1

METHOD FOR LABELING AUTOLOGOUS WBC'S WITH In-111 OXINE

The following procedures are used in the labeling of autologous leukocytes:

1. Collect 40 cc of whole blood in a 50 cc syringe containing 5 cc of ACD solution, mix well. Add 1 part Hespan (6% Hetastarch, a settling agent) to 10 parts whole blood in syringe. (This replaces the heparin previously utilized as an anticoagulant.)
2. Remove any blood from the tip of the syringe, then place the syringe in a clamp at an 80° angle, with the needle up, and allow the red blood cells to settle.
3. Remove the needle from the syringe and replace with a butterfly catheter.
4. Take a 50 ml sterile propylene centrifuge tube with a screw top and express the supernatant containing the leukocyte rich plasma from the syringe into the centrifuge tube, taking care not to collect any red blood cells.
5. To obtain the WBC button, centrifuge the supernatant collected in Step 4 and 450 G for 5 minutes. The WBC button will contain some red blood cells. This is normal and will not affect the preparation.
6. Pour off the leukocyte poor plasma (LPP) and supernatant into an identical sterile centrifuge tube and save.
7. Resuspend the WC button by gently adding 5 ml of sterile saline. Agitate very gently to resuspend the WBC button. Spin down and discard wash.

TABLE 1 *continued on next page*

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TABLE 1 *continued*

8. Resuspend with 5 ml of saline and add 650 μCi of indium-111 oxine to the concentrated cell suspension and incubate for 30 minutes. Gently agitate the mixture 3 or 4 times during incubation to insure adequate mixing.
9. After the incubation is completed, using a 10 ml disposable syringe, withdraw 5 ml of LPP from tube of step 6 and gently add this to the labeled WBC saline mixutre, agitate gently to resuspend the labeled cells. Centrifuge the mixture for 5 minutes at 450 G. Pour the supernatant into a separate container and count each fraction for labeling efficiency.
10. Assay the wash and cells in the dose calibrator. The labeling efficiency is calculated by the formula:

$$E = \frac{C}{C + W} \times 100\%$$

where "C" is the activity associated with the cells, "W" is the activity associated with the wash, and "E" is the labeling efficiency.
11. Using a 10 ml syringe, withdraw 6 ml of LPP saved from step 6 and add this to the labeled WBC button, agitate gently to resuspend the labeled cells.
12. The indium-111 labeled leukocytes are now ready for injection back into the patient. Save the small amount of labeled cells remaining in the tube for a WBC count and microscopic examination. The amount of activity in the final product should be limited to 500μCi.

Indium-111 Tropolone: With the increased use of In-111 labeled leukocytes, various other methods of labeling have appeared in the literature (*6–12*).

An article by Peters et al. (*8*) indicated earlier visualization of inflammatory processes with In-111 tropolonate. We are currently evaluating tropolonate-labeled leukocytes in our laboratory.

The tropolone technique we used is a slight modification of Peters' (*8*) (Table 2). Our labeling efficiency is usually 80% or greater as compared to the 50–80% reported by Peters et al. The major difference between our procedure and Peters' is that we incubate for 10 min rather than 5 min. Unlike the oxine method, In-111 tropolonate uses acid citrate dextrose (ACD) as an anticoagulant (rather than heparin) and a settling agent, hydroxyl ethyl starch (Hetastarch).

The microscopic examination of the WBCs labeled by the tropolonate method contrasts that seen with indium oxine. The suspension of the indium tropolonate labeled white cells is consistently smooth and homogeneous without the clumping associated with the oxine method.

TABLE 2

PREPARATION OF TROPOLONE SOLUTION

1. Dissolve 238.3 mg of HEPES buffer (M.W. 238.3 Aldrich Chemical, Milwaukee, WI 53201) in 40 ml of normal saline.
2. Add 10 mg of Tropolone (M.W. 122.12 Aldrich Chemical Milwaukee, WI 53201) and dissolve completely in HEPES solution.
3. Adjust to pH 7.6 with 0.1 N NaOH.
4. Add normal saline up to a volume of 50 ml.
5. Filter 20 ml into a 20 ml sterile evacuated vial with 0.22 μ millipore filter.
6. Solution is stable for at least 3 months. 0.1 ml of this solution yields 20 μg of Tropolone in a 20 ml solution of HEPES buffer.

TABLE 2 *continued on next column*

TABLE 2 *continued*

METHOD FOR LABELEING LEUKOCYTES WITH In-111 TROPOLONE

1. Collect 40 cc of whole blood in a 50 cc syringe containing 5 cc of ACD solution, mix well.
2. Add 1 part Hespan (6% Hetastarch) to 10 parts whole blood in syringe.
3. Invert and place syringe in incubator (37°) with needle up and allow to settle for 30 minutes.
4. Express leukocyte rich plasma (LRP) through 19 gauge butterfly into a 50 ml centrifuge tube.
5. Centrifuge the LRP for 5 minutes at 450 G.
6. Pour off the supernatant into another 50 ml centrifuge tube labeled PPP for platelet poor plasma.
7. Centrifuge the tube labeled PPP for 5 minutes at 1600 G.
8. Add 0.1 ml of tropolone solution (26 μg/0.1 ml in HEPES buffer) to the cell button left over from step 4 above.
9. Add 700 μCi of $^{111}InCl_3$ to the button and tropolone solution and resuspend.
10. Incubate the cells in the incubator at 37° for 10 minutes.
11. "Wash" the cells with 6 ml of the supernatant in the centrifuge tube labeled PPP. This will "scavenge" any free Indium Chloride left in solution.
12. Centrifuge the cells and PPP for 5 minutes at 450 G.
13. Pour off the supernatant into a tube labeled "WASH" and assay it for activity.
14. Resuspend the cell button in 6 ml of PPP.
15. Assay the cells for activity.
16. Determine tagging efficiency.
17. Dispense 500 μCi of activity associated with the leukocytes.
18. Count the number of WBC's in a hemocytometer and examine microscopically.

Quality Control

Various methods reported for labeling leukocytes (*4,10–12*) list a number of quality control procedures that can be performed prior to reinjection of the labeled leukocytes. These include the Ficoll-Paque distribution analysis, trypan blue exclusion test (*13*) (Table 3), and others. We have used the Ficoll-Paque distribution analysis and other procedures and have not found them to be good predictors of clinical utility. We routinely perform a white cell count, a microscopic examination, and determine labeling efficiences.

A separate log should be maintained for leukocyte studies which includes: date, physician, hospital, patient, labeling method used, labeling efficiency, and volume and activity injected. This log is invaluable for assessing changes in labeling efficiencies, number and identity of studies performed, and trends of use.

IMAGING CONSIDERATIONS

Clinical Use

Abscesses usually occur as complications of surgery, injuries, or inflammatory diseases of the gastrointestinal tract, and occur less commonly from complications involving the genito-urinary system. Because untreated intra-abdominal abscesses carry a mortality of 35%, the importance of prompt, accurate detection is obvious.

Radiographs of the abdomen are helpful if classical signs

TABLE 3

DETERMINATION OF VIABILITY BY TRYPAN BLUE EXCLUSION

The number or percentage of viable white blood cells can be determined by staining cell populations with trypan blue. Viable cells exclude the dye, while non-viable cells take it up. After being stained with trypan blue, the cells must be counted within 3 minutes; after that time viable cells will begin to take up the dye. Also, since trypan blue has a great affinity for proteins, elimination of serum from the cell diluent allows a more accurate determination of viability.

MATERIALS AND REAGENTS

Cell suspension at 2-5 × 10^6 cells/ml
Trypan blue, 0.2% (w/v) in water
4.25% NaCl (w/v)

PROCEDURE

1. On the day of use, mix 4 parts of 0.2% trypan blue with 1 part 4.25% NaCl.
2. To 1 part of the trypan blue saline solution, add 1 part of the cell suspension (1:2 dilution).
3. Load cells into a hemocytometer and count the number of unstained (viable) white blood cells and stained (dead) cells separately. For greater accuracy, count more than a combined total of 200 cells:

$$\text{viable cells/ml} = (\text{average number of viable cells in a large square}) \times 10^4 \text{ ml} \times \frac{1}{\text{dilution}};$$

$$\%\ \text{viable cells} = \frac{\text{number of viable cells}}{\text{number of viable cells} + \text{number of dead cells}} \times 100$$

such as extraluminal gas are present. However, in many instances, X-ray films are inconclusive or show no evidence of an abscess. In these cases, further studies are necessary to confirm or exclude the presence of an abscess. Radionuclide studies, abdominal computed tomography (CT), and ultrasound (US) have all been shown to be accurate methods for detecting abscesses. It is between these three modalities that the clinician must choose.

Knochel, et al. studied 170 patients to determine the best imaging modality to use for patients with suspected intra-abdominal abscesses (*14*). Eighty-two patients were studied with 1 modality, 66 with 2 modalities, and 22 had all 3 modalities performed. Diagnoses were confirmed by needle aspiration, surgery, autopsy, and a review of their chart. A diagnostic accuracy of 96% was achieved by CT, 93% with In-111 labeled leukocytes, and 90% with US. Using more than one modality in difficult patients allowed all the abscesses to be detected. The major advantage of radionuclide imaging was that it allowed the entire body to be examined rather than being limited to just one area.

Based on this study, the following criteria are now used at our institution to decide which examination to perform first (Fig. 1). In those patients whose condition is not critical and for whom there is a low clinical suspicion of abscess, a leukocyte scan is performed. If the scan is negative, no further work-up is done. If there is a high clinical suspicion but no localizing signs, again, a leukocyte scan is performed. If the radionuclide study is negative, a second modality (CT or US) is used to be sure that an abscess is not missed. If both are negative, no further examinations are performed. When a disagreement exists between the In-111 labeled leukocyte study and CT or US, a third modality is used to resolve the question. In acutely ill patients when immediate intervention is necessary and in patients with specific localizing signs, US or CT is used first.

Imaging Technique

A large field camera with a medium energy collimator is recommended using both photopeaks (173 and 247 keV) with 20% windows. The first image is taken over the liver and spleen with an ID of 500–700 over the liver or a minimum of 200,000 counts. Anterior and posterior images over the abdomen, pelvis, and chest are then done for the same time as the liver/spleen image. Images of the extremities require increased time to obtain an adequate film density.

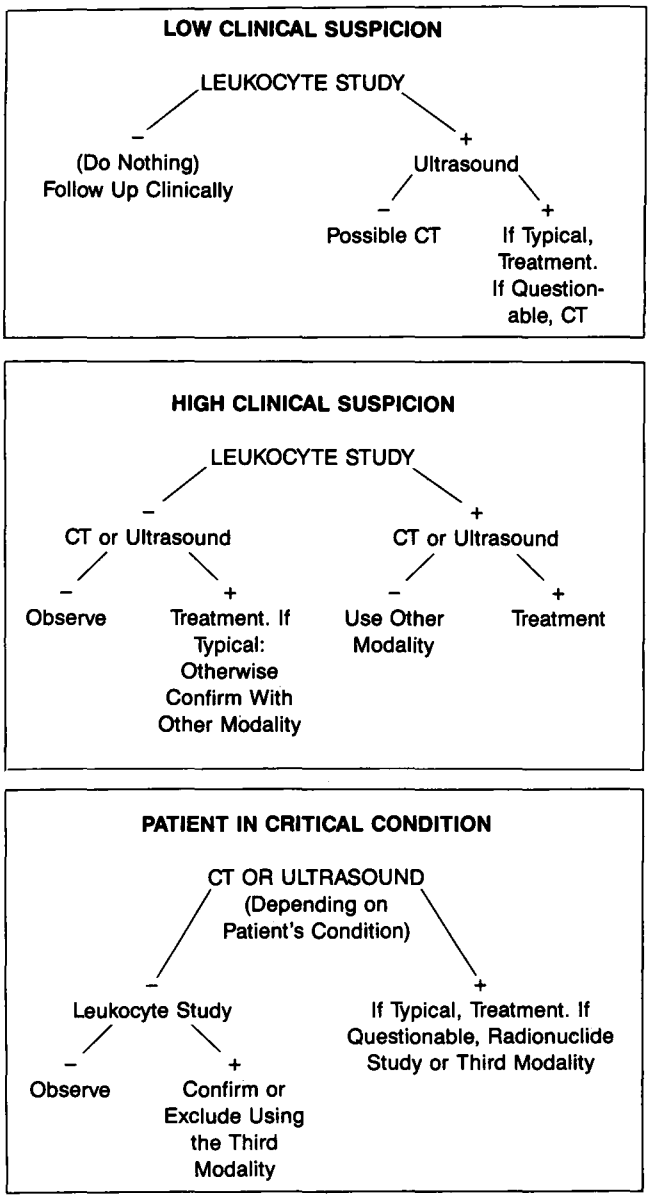

FIG. 1. Criteria used at the University of Utah to determine whether to use US, CT, or a leukocyte scan on patients with possible abscesses.

Normal Distribution

A normal leukocyte scan shows early pulmonary uptake in the first 30 minutes. This rapidly decreases. The cause of early lung uptake is unknown, but may be secondary to minimal damage to the leukocytes which is repaired in the lung. A second possibility is that the leukocytes "marginate" in the lungs' blood vessels (*15*).

After the initial lung uptake, increasing liver, spleen, and bone marrow activity is seen. On a normal scan, the spleen shows the most activity, the liver less, and the bone marrow the least activity (Fig. 2). The normal uptake in these organs likely reflects both the normal distribution of leukocytes and the uptake of damaged cells by the reticuloendothelial system. In addition, any labeled red cells will increase splenic activity. Any areas of uptake outside these normal areas indicate areas of inflammation (Fig. 3).

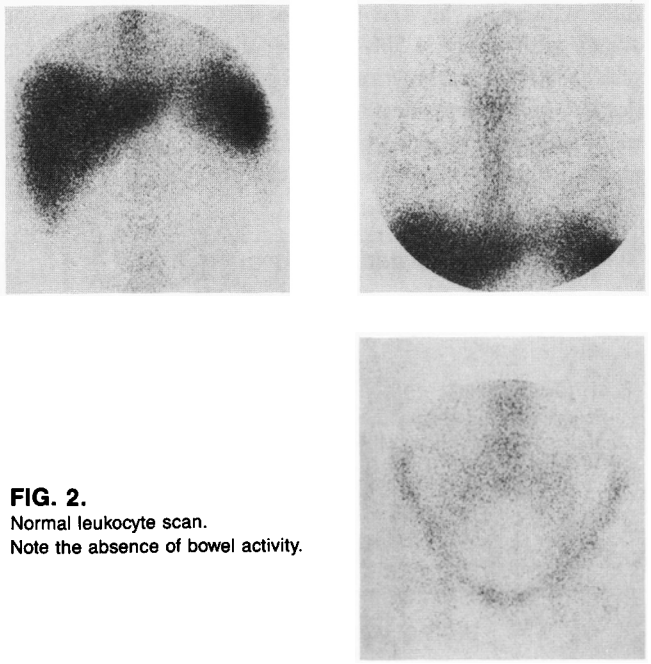

FIG. 2.
Normal leukocyte scan.
Note the absence of bowel activity.

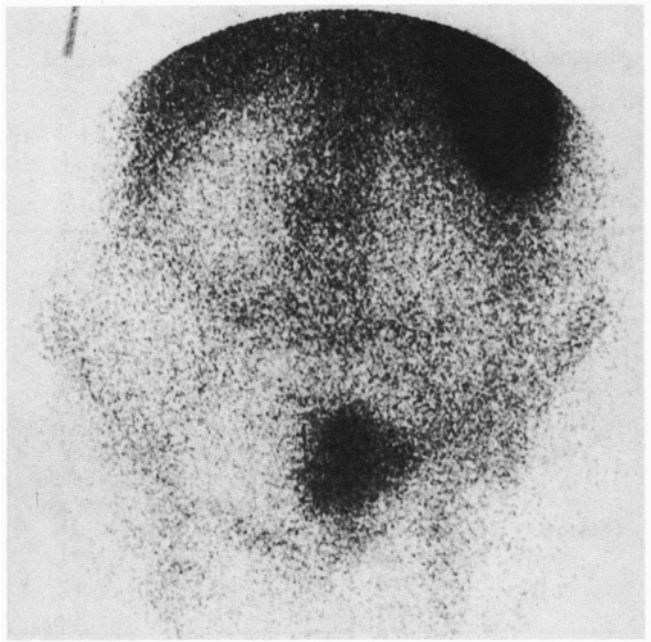

FIG. 3. Abdominal abscess located in the pelvis.

Early Imaging

Indium-111 leucocytes are usually imaged 24 hours after injection. Recently, there have been two reports (*8,16*) indicating that abdominal abscesses and other inflammatory sites could be detected as early as one-half hour following injection.

Dutcher et al. (*16*) gave indium oxine labeled donor leukocytes to 14 patients with known sites of infection; 13 of these were positive after only 30 minutes. Subsequent computer-enhanced scans at both 4 and 24 hours were still positive, with the delayed scans showing more intense uptake than the early ones. Peters et al., using In-111 tropolonate (*8*) detected 75% (27/36 studies) of inflammatory sites within 40 minutes following injection with an additional 9 picked up at 3 hours. Peters related their success to the enhanced viability of leukocytes labeled with tropolone. They feel that removing leukocytes from plasma, as is required with oxine, may significantly decrease leukocyte viability.

Our attempts at performing early imaging have not been as successful as these authors' (*5*). In a prospective study of 40 patients with possible occult infection, early images done 1–4 hours following injection with oxine labeled leukocytes had a sensitivity of only 33%. This is compared to a 95% sensitivity at 24 hours (Fig. 4). Of the 7 studies that were positive on both early and delayed images, two-thirds had more intense uptake at 24 hours. In no cases did the early image pick up an abscess that was missed on delayed views.

We are not certain why our results with early imaging differ from the other investigators'. Dutcher imaged activity at 30 minutes which may represent blood pool activity, as has been suggested by Dougherty and Goodwin (*17*). Differences in the design of the studies may also have contributed. Dutcher knew her patients were infected and where the infection was located, while our study reflected the usual clinical situation in which the film reader does not know if the patient is septic or not. Finally, it is possible that differences in leukocyte kinetics be-

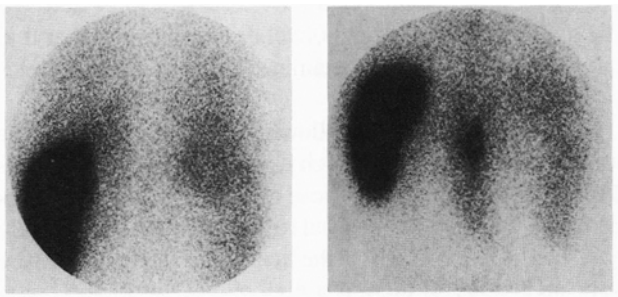

FIG. 4. Early image on left at 4 hours is negative. Delayed view (right) shows a para-spinal abscess.

tween granulocytopenia and "normal" patients allows earlier visualization.

The difference between our oxine studies and Peters' tropolonate exams is also not clear. Although it is possible that tropolonate does improve viability of labeled cells, other authors have found decreased viability with tropolonate at concentrations required for optimal labeling (*18*). Another factor to consider is the difference in the patient population. We studied only infected patients, whereas Peters' patients had a variety of causes of inflammation (half had inflammatory bowel disease) in addition to infection.

Since there have been no false positives at this time, we feel that early scans should be done when a rapid diagnosis is needed. However, if a negative scan is obtained, we suggest delayed imaging.

Tropolone

As mentioned above, there is an ongoing debate whether oxine or tropolone is the best labeling agent for indium leukocytes. We have done a prospective study to see which material gives the best clinical results 24 hours following injection (*19*). Sixty-six patients (35 labeled with oxine and 31 with tropolone) were imaged 24 hours post-injection. The final diagnosis was confirmed by clinical course, x-ray study, surgery, and necropsy.

In our study, there was no difference in the sensitivity of oxine versus tropolone. Oxine had an overall sensitivity of 95% compared to 93% for tropolone. We feel that, at least at 24 hours, tropolone has no advantage over oxine. We are currently investigating the sensitivity of tropolone imaged at earlier times. In the small number of patients done thus far, we have not seen any significant improvement over oxine (*20*).

Combining Technetium-99m Sulfur Colloid Scans with Leukocyte Scans

Diagnosing upper abdominal abscesses is often difficult because the normal accumulation of activity in the liver and spleen can mask an adjacent inflammatory focus. To overcome this problem, we routinely do a technetium sulfur colloid scan immediately following the leukocyte scan.

In a study we did of 44 patients with suspected abdominal abscesses, the liver/spleen scan was considered necessary to diagnose an upper abdominal abscess in almost half of patients with upper abdominal abscesses (*21*) (Fig. 5). The liver/spleen scan was also helpful in defining the extent of the abscess and in planning the surgical approach. In a number of other patients, we were able to pick up abnormalities such as hepatocellular disease, transplant rejection, and avascular necrosis.

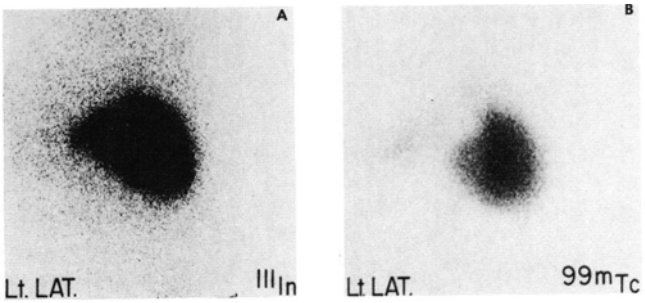

FIG. 5. (A) Leukocyte scan; left lateral view of spleen. A definite abscess cannot be seen. (B) Sulfur colloid image in the same projection shows that activity at arrow is not spleen. At surgery, an abscess was found adjacent to the spleen.

TABLE 4

CAUSES OF LEUKOCYTE UPTAKE IN THE ABDOMEN OTHER THAN AN ABSCESS

Indwelling enteric tubes (GI activity)
Ostomies
Swallowed leukocytes (e.g., sinusitis, rhinitis, endotracheal tube, nasogastric tube)
Bowel infarction
Crohn's disease
Cystic fibrosis
Herpes esophagitis
Idiopathic pseudo-obstruction
Infected necrotic tumor
Ischemic colitis (e.g., rheumatoid vasculitis, polyarteritis nodosa)
Multiple enemas
Ulcerative colitis
Phlegmon
Accessory spleen
Acute cholecystitis
Acute pyelonephritis
Graft infection
Pancreatitis
Transplant rejection
Wound—non-infected

Low White Counts

Because abscesses frequently occur in patients with bone marrow depression, we are often asked to do leukocyte scans on granulocytopenic patients. The question is, how good is the leukocyte scan in these types of patients? Anstall and Coleman (*22*) have reported using donor leukocytes in 8 severely leukopenic patients (less that 300 granulocytes per mm^3). They found that the donor leukocytes worked as well as autologously labeled cells. Our experience since that report has supported the use of labeled donor cells in these patients.

PITFALLS IN INTERPRETATION

Other Causes of Uptake

Like gallium, leukocytes can be taken up by causes other than acute abdominal abscess (*23*) (Table 4). For example, gastrointestinal activity can be seen due to indwelling enteric tubes, ostomies, or swallowed leukocytes from sinusitis. Even when an abdominal infection is present, it may be due to a phlegmon rather than a drainable abscess. For these reasons, an US or CT should be considered to confirm the presence of a drainable abscess before advising surgery in patients showing positive uptake.

Lung Uptake

The leukocyte scan will show increased uptake in the lungs on about one-sixth of all scans. Although one might imagine

that uptake in the lungs would indicate an infection, unfortunately, this often is not the case (Fig. 6). In reviewing 48 cases showing pulmonary uptake, we found that 52% of patients with focal uptake and only 10% of patients with diffuse uptake were infected (*24*). The uptake was due to a variety of non-infectious causes including atelectasis, congestive heart failure, ARDS, pulmonary embolism, and aspiration pneumonia. Although lung uptake of indium leukocytes is a poor predictor of pulmonary infection, the focal pattern is more likely to be associated with an infection than diffuse.

Summary

Leukocyte imaging is an extremely useful tool in the diagnosis of intra-abdominal abscesses. The labeling technique is not technically difficult, although it requires strict attention to detail.

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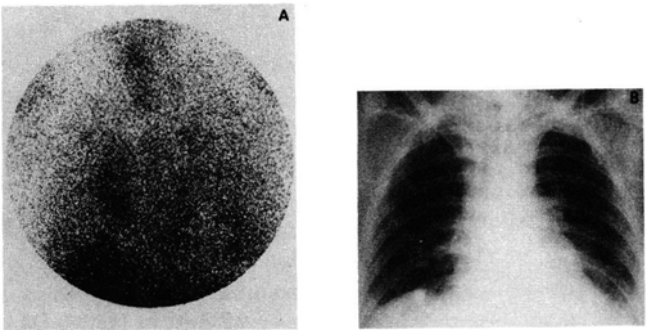

FIG. 6. (A) Diffuse uptake of leukocytes in a patient with ARDS. There was no clinical evidence of an infection. (B) Chest radiograph showing ARDS.

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