Indium-111 Leukocyte Imaging in Patients with Rheumatoid Arthritis

Kimiichi Uno, Nobuo Matsui, Kunichi Nohira, Toru Suguro, Yusuke Kitakata, Guio Uchiyama, Takeyoshi Miyoshi, Sadao Uematsu, Shunichi Inoue, and Noboru Arimizu

Department of Radiology and Orthopedics, Chiba University School of Medicine; Chiba Rehabilitation Center; Kimitsu Chuoh Hospital; and Yamanashi Medical College, Inohana Chiba City, Chiba, Japan

This study evaluates the usefulness of labeled leukocyte imaging in patients with rheumatoid arthritis. In 33 patients, the incidence of pain and swelling in 66 wrist joints and 66 knee joints was compared with the accumulation of [^{111}In]leukocytes. No accumulation of [^{111}In]leukocytes was seen in any of the patients' wrists (0/12) or knee joints (0/14) when both pain and swelling were absent. In contrast, 93% (25/27) of wrist joints and 80% (24/30) of knee joints with both pain and swelling were positive by [^{111}In]leukocyte scintigraphy. There was little correlation between the stage of the disease, as determined by radiography, and [^{111}In]leukocyte accumulation. This study suggests that [^{111}In]leukocyte imaging may be a reliable procedure for monitoring the activity of rheumatoid arthritis, especially for confirming the lack of an ongoing inflammatory response.

J Nucl Med 27:339–344, 1986

Indium-111 (^{111}In) leukocyte scintigraphy has been recognized as a reliable modality for localization and evaluation of acute inflammatory processes (*1*,*2*). However, it has not been used commonly for imaging chronic inflammatory diseases. Though rheumatoid arthritis is regarded as a chronic disease, the active changes in synovial membrane can mimic the pattern of acute nonpyogenic inflammatory processes. This is demonstrated by the migration of large numbers of leukocytes (*3*). This study was undertaken to determine the usefulness of ^{111}In leukocytes for imaging inflammatory lesions of rheumatoid arthritis and whether the results of this procedure can be correlated with the absence or presence of ongoing inflammatory processes.

MATERIALS AND METHODS

Forty milliliters heparinized whole blood was obtained from each patient. The red blood cells were allowed to sediment for 30 min to 1 hr. This was facilitated by the addition of 6% hydroxyethyl starch in sterile polystyrene tubes. The resultant leukocyte-rich plasma was removed and centrifuged at 450 *g* for 5 min. The leukocyte pellet was washed twice in saline, resuspended and incubated with [^{111}In]oxine for 20 min at room temperature. Fifty to 300 million leukocytes labeled with 0.5-1 mCi of [^{111}In]oxine were administered to the patients. Imaging was performed at 24 hr and occasionally after 2 days. Whole-body images and spot views were obtained with a scintillation camera using a medium-energy collimator, and a 20% window centered at the 173 and 247 keV gamma photon peaks of ^{111}In. Thirty-three patients (age between 29 to 73 yr) were studied (Table 1). Female to male ratio was 10:1, and the average period of disease since onset was 15 yr. Radiographic stage of disease by acute rheumatoid arthritis criteria ranged between I to IV (*4*). All patients had drug treatments, 21 had steroids and 12 had nonsteroidal therapy. None of these patients had an infected joint as determined by their clinical course, laboratory data and/or synovial fluid culture.

RESULTS

The incidence of pain and swelling in 66 wrist joints and 66 knee joints was compared with the accumulation of ^{111}In leukocytes (Fig. 1). Most striking was the absence of ^{111}In imaging in any of the joints lacking both pain and swelling. Twenty-seven wrist joints and 30 knee joints had both pain and swelling. Twenty-five

Received Apr. 22, 1985; revision accepted Nov. 7, 1985.

For reprints contact: Kimiichi Uno, MD, Dept. of Radiology, Chiba University School of Medicine, 1-8-1 Inohana Chiba City, Chiba, Japan 280.

TABLE 1
Some Parameters of Cases Examined

Total	33 Cases
Classic RA	31 Cases
Definite RA	2 Cases
Age 29–73 yr	mean: 51 yr
Male	3
Female	30
Clinical course	10 mo–57 yr (mean: 15 yr)
Stage (ARA criteria)	
I	2
II	2
III	16
IV	13
Drug treatment	
Steroids	21 Cases
NSAID	2 Cases

wrist joints (93%) and 24 knee joints (80%) had positive images. The accumulation of ^{111}In leukocytes correlated very well with the activity of inflammed joints determined by the clinical signs of both pain and swelling. However, there seemed to be little correlation between the radiographic stage of disease and [^{111}In]leukocyte accumulation. This is because x-ray films do not reveal immediate acute inflammatory processes in the joints. Radiographs of joints affected by rheumatoid arthritis (RA) demonstrate the changes which had occurred over time, usually after many years. They are not particularly useful in showing soft-tissue inflammation or current disease activity. The negative scintigraphic examination of two wrist and six knee joints with both pain and swelling were considered to be in the late and "flare up" stages radiographically. Indeed, of three patients, one was a burnt out case of joint rheumatoid arthritis and the others had long standing RA. We felt clinically that their pain, with some small effusion, was due to secondary osteoarthritic disease rather than active RA.

A whole-body scan of a patient with malignant rheumatoid arthritis (Fig. 2) showed strong accumulation of ^{111}In leukocytes in multiple joints where pain and swelling were prominent. An x-ray examination of both wrist joints of this patient revealed osteolytic changes of the arthritis mutilans. A case of classic RA (stage IV, class 2) had marked accumulation of ^{111}In leukocytes in

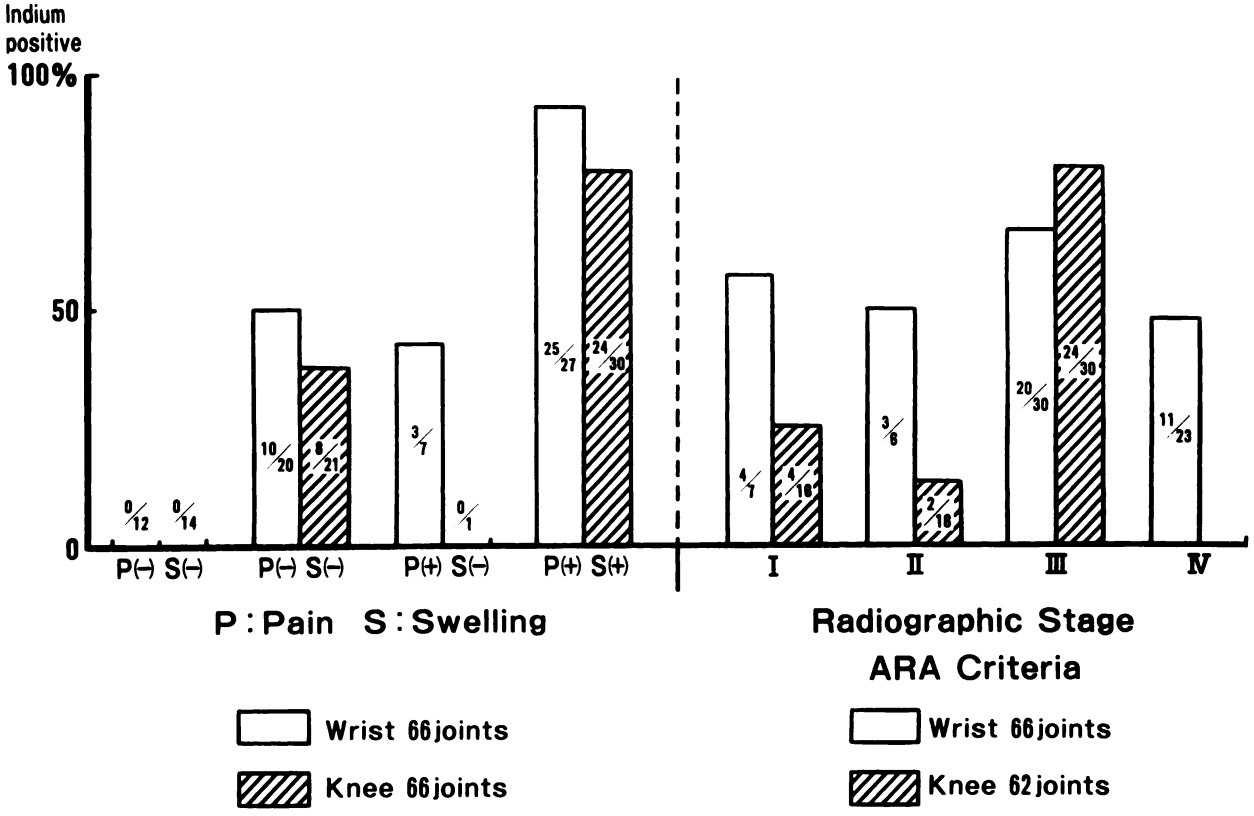
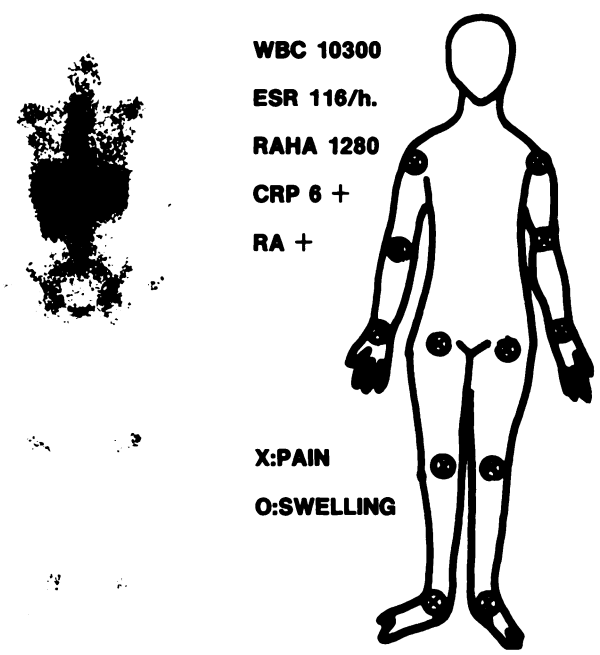


FIGURE 1
Clinical signs, bone changes and [^{111}In]white blood cell accumulation. Lack of ^{111}In accumulation correlated extremly well with absence of pain or swelling. Accumulation of ^{111}In leukocyte correlated very well with activity of inflammed joints with both pain and swelling. There was little correlation between stages, determined by radiography, and ^{111}In leukocyte accumulation



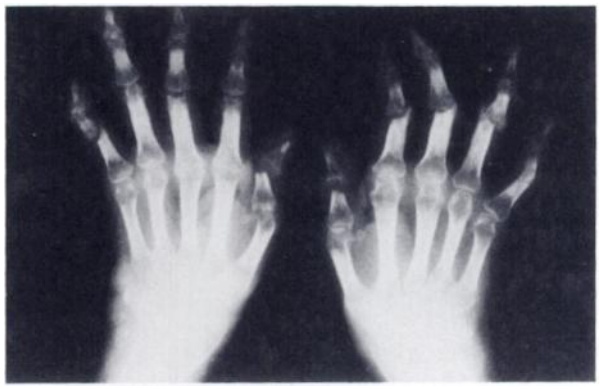


FIGURE 2
Case of malignant RA (stage III, class 3). Note accumulation of ^{111}In coincided with pain (x) and swelling (0) in every joint. X-ray examination of both hands and wrists revealed osteolytic changes of arthritis mutilans

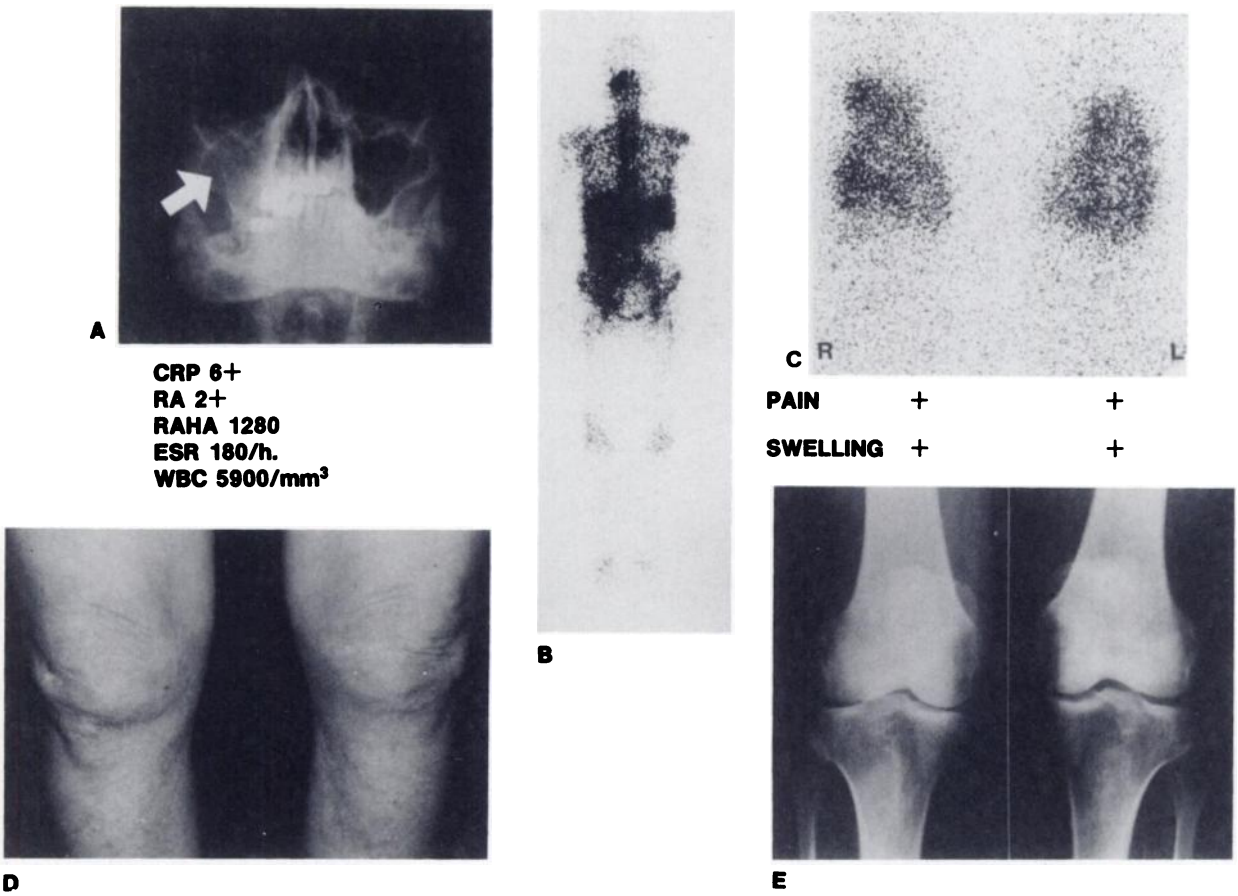


FIGURE 3
Classic RA (stage IV, class 2) with maxillary sinusitis (A, white arrow) had marked accumulation of [^{111}In]leukocytes in the right maxillary sinus, knee, (B) and foot joints (C). Both knees had marked swelling with pain (D) and showed narrowing of joint space radiographically (E)

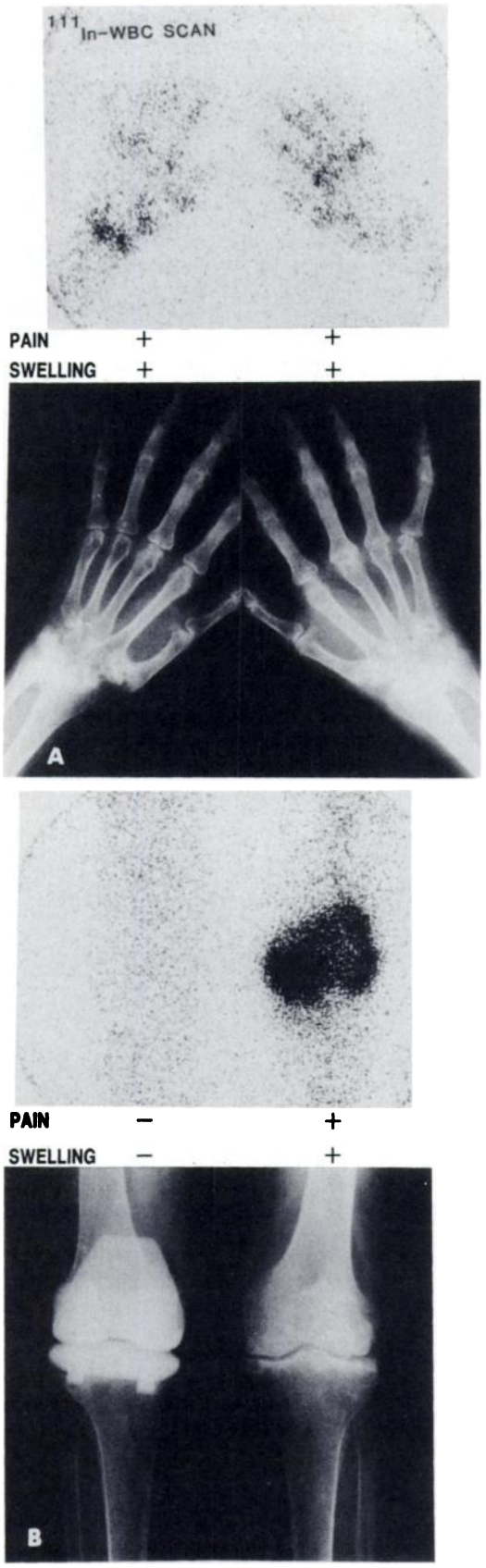


FIGURE 4
Classic RA (stage IV, class 2). A: [^{111}In]leukocyte images and radiographs of hands and wrists. B: Note absence of accumulation around right knee prosthesis and intense accumulation in left knee

the right maxillary sinus, knees, and joints of both feet (Fig. 3). A Water's view showed diffuse opacity in the right maxillary antrum. Indium-111 leukocyte accumulation was seen in the knee joints with pain and swelling. Narrowing of joint space was noted on radiographs. In another case of classic RA (Fig. 4), ^{111}In leukocytes accumulated in both symptomatic wrist joints. X-ray films revealed bone changes of stage IV in the corresponding areas. An additional example in which the left knee joint showed marked ^{111}In leukocyte accumulation, while the right knee (which was totally replaced 1 yr previously) showed no accumulation. Finally, a patient with osteoarthritis with joint space narrowing and osteoarthritic changes demonstrated by x-ray, did not have an abnormal accumulation of leukocytes even on spot views (Fig. 5).

DISCUSSION

Rheumatoid arthritis has been regarded as a chronic disease, yet leukocytes have been observed in the synovial fluid during active stages. The number of leukocytes in the synovial fluid parallels the severity of the inflammation of the synovial membrane (*5*). In one study of rheumatoid arthritis exudates (*6*), cellular counts indicated that up to 2×10^9 cells/day (or 3% of circulating neutrophils) could migrate into a single joint. Elevated leukocyte counts, > 2,000 cells per mm^3 were seen only in patients with rheumatoid arthritis (*7*). Counts over 12,000 cells/mm^3 all came from clinically active knees, and those below 6,000 cells/mm^3 were all from inactive knees (*8*). McCall et al. reported that gallium-67 (^{67}Ga) uptake in the joints increased steadily with increased synovial leukocyte concentration. Results from our laboratory indicate that ^{67}Ga also localizes in normal bone and joints (*9*). In a report by Rosenthall et al. (*10*), the accumulation of ^{67}Ga in a bone or joint did not always reflect infection. The usefulness of ^{111}In leukocyte labeling to detect inflammatory conditions has been demonstrated experimentally and clinically validated compared to [^{67}Ga]citrate (*3,11*). Indium-111 leukocyte imaging was reliable in patients with relatively acute inflammations (i.e., of less than 2 wk), but false-negative studies were observed in patients with prolonged illness (*12,13*). Indium-111 leukocyte images of normal knee joints showed accumulation of ^{111}In equivalent to that of other normal soft tissues. This makes it easier to distinguish the presence of inflammation than ^{67}Ga. Taken together, these studies have shown that it is difficult to determine acute inflammatory responses in rheumatoid arthritis joints without actual leukocyte counts. However, because ^{111}In has been used to successfully image other acute inflammatory processes we wished to examine its utility in rheumatoid arthritis.

Although technetium-99m methylene diphosphonate

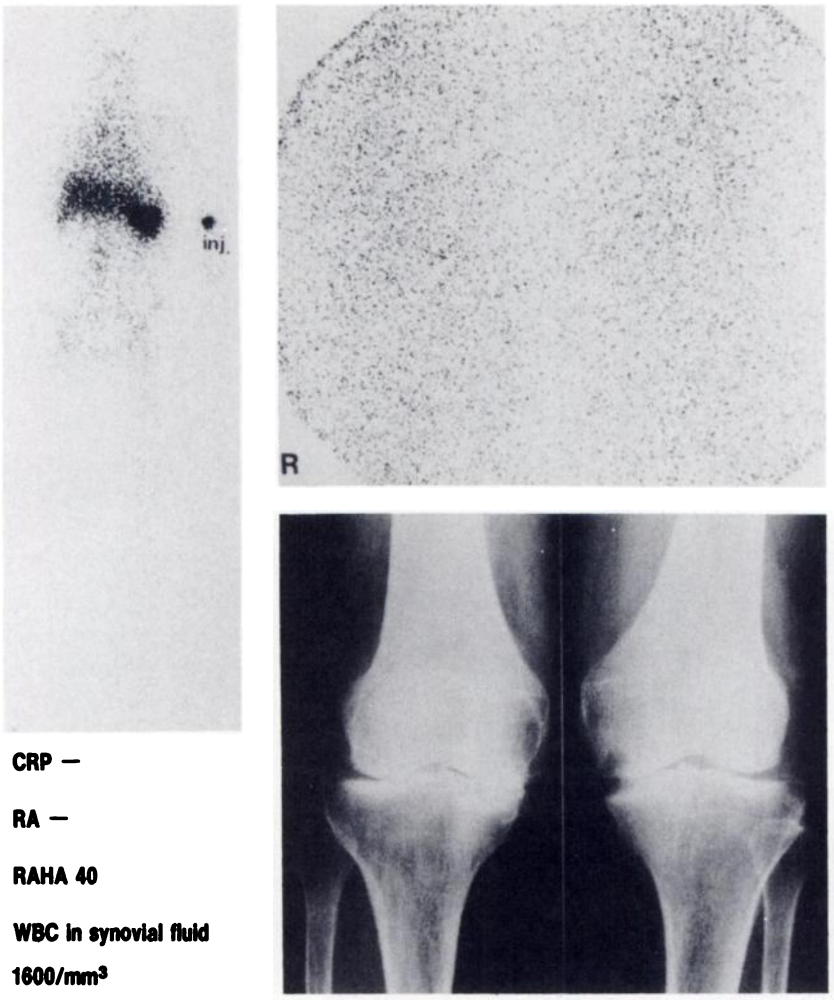


FIGURE 5
Patient with osteoarthritis showed no evidence of inflammation in hematological examination. (CRP: C-reactive protein, RA: rheumatoid arthritis test, RAHA: rheumatoid arthritis hemoagglutination test). Note absence of abnormal ^{111}In accumulation in joints

scans may show increased uptake in rheumatoid joints, these cases must already have advanced to a stage where there is involvement of the periarticular bone (*14*). In contrast to this, increased uptake by indium scanning does not need progression of disease to that extent.

The studies presented here clearly show that ^{111}In imaging can be used to demonstrate the absence of acute inflammatory responses in rheumatoid arthritis. When pain and swelling are present, a strong correlation exists between positive imaging and both of these symptoms. However, when only one of these symptoms is present, the value of ^{111}In appears questionable. While only one osteoarthritis patient was examined, the negative finding hopefully suggests false images will not occur in osteoarthritis.

It appears that ^{111}In has clinical usefulness in assessing the acute inflammatory processes in rheumatoid arthritis. Future studies determining synovial leukocyte counts will be required to determine if it is indeed as useful in patients with pain and swelling as it clearly is in patients who lack pain and swelling.

ACKNOWLEDGMENTS

The authors thank Dr. M. L. Thakur, Dr. M. Scott, and Dr. S. Esses for their suggestions, comments, and critical reading of the manuscript.

REFERENCES

1. Thakur ML, Lavender JP, Arnot RN, et al: Indium-111-labeled autologous leukocytes in man. *J Nucl Med* 18:1014–1021, 1977
2. Uno K: Basic and clinical study of In-111-oxine labeled leukocytes for detection of inflammatory foci. *Nippon Act Radiol* 42:565–575, 1982
3. Thakur ML, Coleman RE, Welch MJ: Indium-111-labeled leukocytes for the localization of abscesses: Preparation, analysis, tissue distribution, and comparison with gallium-67 citrate in dogs. *J Lab Clin Med* 89:217–227, 1977
4. Rodnan GP, ed. *Primer on the Rheumatic Diseases. Committee of the American Rheumatism Association,* 7th ed. New York, 1973
5. Ropes MV, Bauer W: *Synovial Fluid Changes in Joint Disease,* Cambridge, MA, Harvard University Press, 1953
6. Hollingsworth JW, Siegel ER, Creasey WA: Granulo-

cyte survival in synovial exudate of patients with rehumatoid arthritis. *Yale J Bio Med* 39:289, 1967
7. Pekin TJ, Zvaifler NJ: Hemolytic complement in synovial fluid. *J Clin Invest* 43:1372-1382, 1964
8. McCall IW, Sheppard H, Haddaway M, et al: Gallium-67 scanning in rheumatoid arthritis. *Br J Radiol* 56:241-243, 1983
9. Uno K, Arimizu N, Matsui N, et al: Evaluation of In-111-oxine labeled leukocyte images in bone and joint diseases. *Jpn J Nucl Med* 20:583, 1983
10. Rosenthall L, Lisbona R, Hernandez M, et al: Tc-99m-pp and Ga-67 imaging following insertion of orthopedic devices. *Radiology* 133:717-721, 1979
11. Uno K, Uchiyama G, Imazeki K, et al: Abscess imaging with In-111-oxine labeled leukocytes: A comparison with Ga-67 citrate in rabbits bearing abscesses. *Jpn J Nucl Med* 18:1413-1419, 1981
12. Sfakianakis GN, Ai-Sheikh W, Heal A, et al: Comparisons of scintigraphy with In-111 leukocytes and Ga-67 in the diagnosis of occult sepsis. *J Nucl Med* 23:618-626, 1982
13. Uno K, Arimizu N, Matsui N, et al: Comparisons of scintigraphy with Ga-67 and In-111 oxine labeled leukocytes in bone and joints diseases. *Nippon Act Radiol* 43:204, 1983
14. McCarty J, Hollander JL, eds: *Arthritis and Allied Conditions. A Textbook of Rheumatology*, Philadelphia, Lea & Febiger, 1985, pp 77-78