

PDF hosted at the Radboud Repository of the Radboud University Nijmegen

This full text is a publisher's version.

For additional information about this publication click this link.

<http://hdl.handle.net/2066/14868>

Please be advised that this information was generated on 2014-11-11 and may be subject to change.

Diagnosis of Bone, Joint, and Joint Prosthesis Infections with In-111-labeled Nonspecific Human Immunoglobulin G Scintigraphy¹

The diagnostic accuracy of scintigraphy performed after injection of indium-111-labeled nonspecific human immunoglobulin G (IgG) was studied in 113 patients with 120 foci of suspected infection in bone (52 chronic and eight acute infections), joints (15 localizations), joint prostheses (37 prostheses), and soft tissue of the locomotor system (eight localizations). All patients also underwent standard three-phase scintigraphy after injection of technetium-99m-labeled methylene diphosphonate. A scan obtained with In-111-labeled IgG was considered positive if focal increasing accumulation was noted over time. In 51 patients (45.1%), the results of scintigraphy were verified with intraoperative cultures, and in 21 patients (18.6%), with needle aspiration. The prevalence of infection was 59%; overall sensitivity, 97%; and specificity, 85%. Use of In-111-labeled IgG enabled correct identification of the presence, site, and extent of infection in 69 of 71 proved foci of infection; 41 of 48 negative studies were correct. Only two infections proved with culture were missed; in both patients, the cultures revealed growth of *Staphylococcus aureus* in low counts.

Index terms: Bones, infection, 40.201, 40.218 • Bones, radionuclide studies, 40.1299 • Gamma globulins • Joints, diseases, 40.21, 40.26 • Joints, infection, 40.26 • Joints, prostheses, 40.454, 48.70 • Joints, radionuclide studies, 40.1299 • Prostheses, 40.454

Radiology 1992; 182:195-199

ACCURATE noninvasive diagnosis of infection in bones, joints, and joint prostheses remains a vexing clinical problem. All widely used radiographic and scintigraphic techniques have limitations. Radiography has poor results in assessment of disease activity in osteomyelitis (1). Technetium-99m methylene diphosphonate (MDP) studies show excellent results in ruling out infection, but specificity is low (2,3). Reports on the use of gallium-67 scintigraphy are variable, but apparently it is less well suited for imaging infection because of its accumulation in areas of bone remodeling and physiologic excretion in the intestines (4). In chronic low-grade infections, decreased sensitivity of labeled white blood cell (WBC) scintigraphy has been reported (5). Initial results of a study on the usefulness of scintigraphy performed after administration of indium-111-labeled human nonspecific polyclonal immunoglobulin G (IgG) indicated the possibilities of a new, convenient technique for imaging infection (6). In our study we assessed the results of In-111-labeled IgG scintigraphy in patients with infections of bones, joints, joint prostheses, and soft tissues of the locomotor system.

MATERIALS AND METHODS

Radiopharmaceutical Doses

Human nonspecific polyclonal IgG, sterile and pyrogen-free monomeric IgG (Sandoglobulin; Sandoz, Nuremberg, Germany), was conjugated to diethylenetriaminepentaacetic acid (DTPA) bicyclic anhydride (bicyclic DTPA) according to the method described by Hnatowich et al (7) and labeled with In-111 (indium chloride; Amersham International, Bucking-

hamshire, England). The labeling efficiency was always higher than 95%. A dose of approximately 1 mg of IgG labeled with 75 MBq of In-111 was administered intravenously by means of bolus injection.

For therapeutic purposes, nonlabeled IgG has been used in gram doses for more than 20 years with an excellent safety record. In more than 800 patient studies, both in our department and at the Massachusetts General Hospital in Boston, no adverse reactions after injection of 1 mg of IgG radiolabeled with 75 MBq of In-111 were observed (6) (W.J.G.O., unpublished data, 1991).

Imaging Procedures

One hundred twenty foci of suspected infection were studied in 113 patients, who also underwent standard three-phase scintigraphy performed after injection of Tc-99m MDP. In-111-labeled IgG was injected either 2-7 days after Tc-99m MDP skeletal scintigraphy had been completed or after the second-phase Tc-99m-MDP scintigrams were obtained. Scintigrams were obtained with a gamma camera (Orbiter; Siemens Gammasonics, Hoffman Estates, Ill) connected to a commercially available image processor (Scintiview, Siemens Gammasonics).

At 4, 18-24, and 42-48 hours after injection of In-111-labeled IgG, gamma camera images were obtained for a preset time of 5, 7.5, and 10 minutes, respectively, with a medium-energy collimator. In most cases the gamma camera was set for both the 173- and the 247-keV photopeak with symmetric 15% windows. Typical count rates in the trunk region ranged from 1.0 million to 1.5 million counts; in the pelvic region, from 600,000 to 750,000 counts; and in the lower limb, from 80,000 to 150,000 counts.

When In-111-labeled IgG was injected shortly after the second phase of bone scanning, only the 247-keV peak was used to acquire In-111-labeled IgG images 4 and 18-24 hours after injection to avoid

¹ From the Departments of Nuclear Medicine (W.J.G.O., R.A.M.J.C., F.H.M.C.), Orthopaedics (J.R.v.H., T.J.J.H.S.), and Internal Medicine (J.W.M.v.d.M.), University Hospital Nijmegen, Geert Groote Plein Zuid 8, 6525 GA Nijmegen, The Netherlands. Received May 20, 1991; revision requested July 8; revision received July 25; accepted August 5. Address reprint requests to W.J.G.O.

© RSNA, 1992

Abbreviations: DTPA = diethylenetriaminepentaacetic acid, IgG = immunoglobulin G, MDP = methylene diphosphonate, WBC = white blood cell.

scatter of Tc-99m MDP on gamma camera images obtained with In-111-labeled IgG. No significant scatter of In-111 was observed in the Tc-99m-MDP scintigrams.

Image Interpretation

All images were interpreted by three observers (W.J.G.O., R.A.M.J.C., F.H.M.C.) blinded to the results of the verification procedures. The images obtained with In-111-labeled IgG were interpreted with the corresponding bone scintigram. The Tc-99m-MDP scintigrams were used to localize osseous structures, joint arthroplasties, or both. However, the presence or absence of infection was estimated with In-111-labeled IgG scintigraphy only. A scan obtained with In-111-labeled IgG was considered positive if focal increasing accumulation was noted over time. Nonvisualization of a suspected lesion or failure to show increasing accumulation on the scan was considered a negative finding.

Patient Categories and Verification Procedures

The patients were categorized on the basis of the nature of the suspected focus of infection: chronic osteomyelitis, infection of total hip prosthesis, infection of total knee prosthesis, acute osteomyelitis or spondylodiskitis, arthritis, or soft-tissue infection. For example, if a patient had chronic osteomyelitis with soft-tissue extension, this patient's case was categorized as chronic osteomyelitis. Whenever evidence of infection persisted for less than 2 weeks, we regarded an infection as being acute. Whenever clinical signs and radiographic and laboratory findings suggested persistence of infection for many weeks, months, or even years, the infection was regarded as chronic. Several patients had more than one joint prosthesis. Only the results of the In-111-labeled IgG scintigraphy of prostheses suspected of being infected are included in the Table.

In 51 patients (45.1%), the results of scintigraphy were verified by means of intraoperative cultures and in 21 patients (18.6%) by needle aspiration with subsequent Gram stains and cultures. In 26 patients (23.0%), 22 of whom had negative findings on scintigrams obtained with In-111-labeled IgG, verification was obtained with serial radiographic evaluation and long-term clinical follow-up of at least 6

months. In 15 patients (13.3%), a productive fistula was considered evidence of chronic osteomyelitis.

Initial results of scintigraphy performed after administration of In-111-labeled IgG in 32 patients, which were reported previously (8), are included in this study.

RESULTS

All patients had increased uptake of Tc-99m MDP on the bone scintigrams. All infections of joint prostheses were chronic. Nonsymptomatic prostheses with a normal appearance on radiographs never showed increased uptake of In-111-labeled IgG.

The Table shows the overall results of In-111-labeled IgG scintigraphy in the various categories, based on the results of the verification procedures.

Two uninfected total hip prostheses showing normal distribution of In-111-labeled IgG were uncemented; all other prostheses were cemented.

Most infectious lesions were caused by *Staphylococcus* organisms ($n = 30$ [60%], streptococci ($n = 8$ [16%]), *Pseudomonas aeruginosa* ($n = 5$ [10%]), or *Mycobacterium tuberculosis* ($n = 3$ [6%]). In four of the culture-proved infectious lesions (8%), other causative microorganisms or a mixed flora were cultured.

Seven studies showed accumulation of In-111-labeled IgG in lesions that proved to be noninfected (Table, "FP" column). In two of these patients, In-111-labeled IgG was accumulated near the neck of femoral component of a cemented total hip

Overall Results of In-111-labeled IgG Scintigraphy in Bone, Joint, and Soft-Tissue Infection

Condition	No. of Lesions	Findings			
		TP	TN	FP	FN
Chronic osteomyelitis	52	37	14	0	1
Infection of total hip prosthesis	31	7	21	2	1
Infection of total knee prosthesis	6	4	1	1	0
Acute osteomyelitis or spondylodiskitis	8	4	3	1	0
Infectious arthritis	15	11	2	2	0
Soft-tissue infection	8	7	0	1	0
Total	120	70	41	7	2

Note.—FN = false-negative for infection, FP = false-positive for infection, TN = true-negative for infection, TP = true-positive for infection.

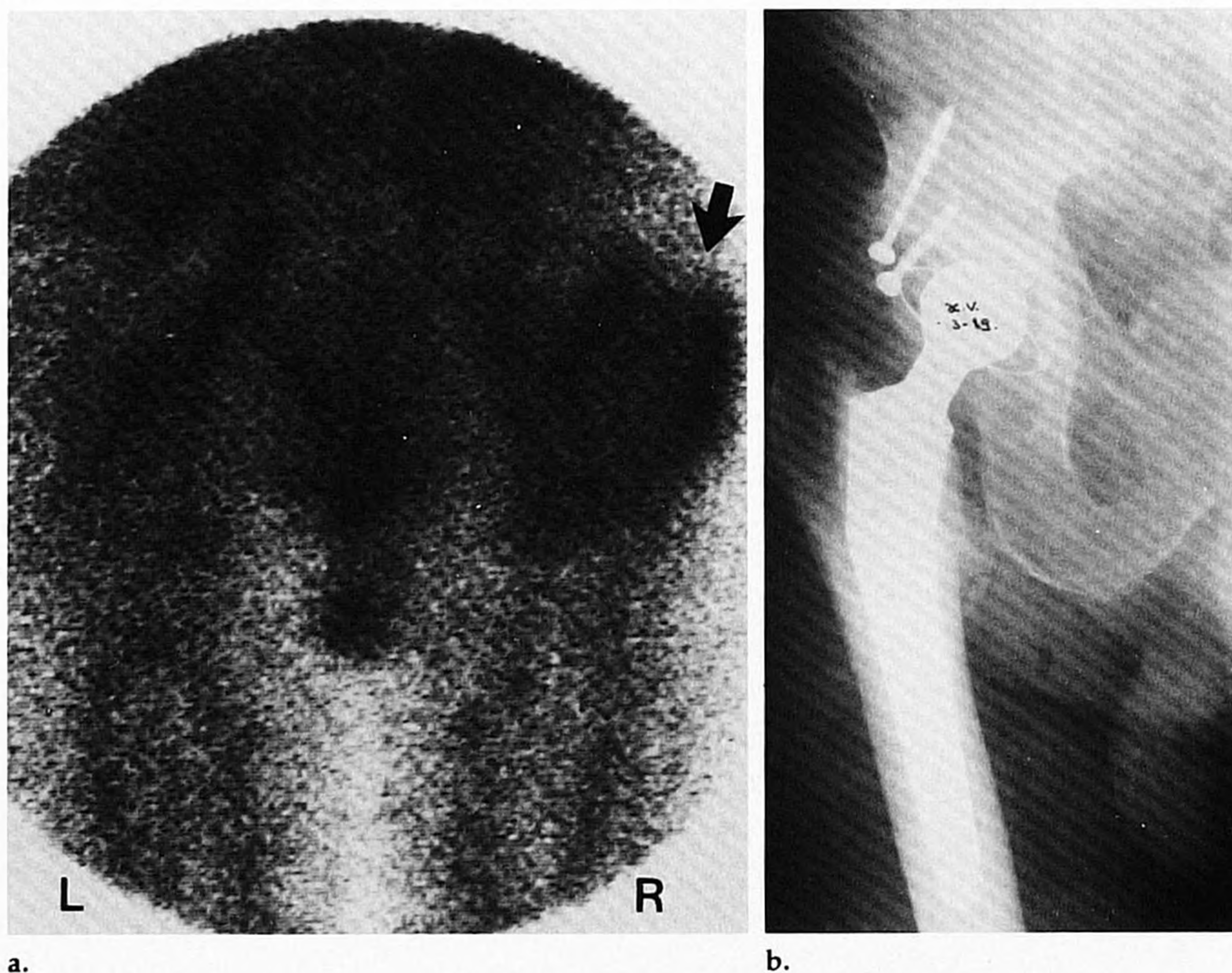
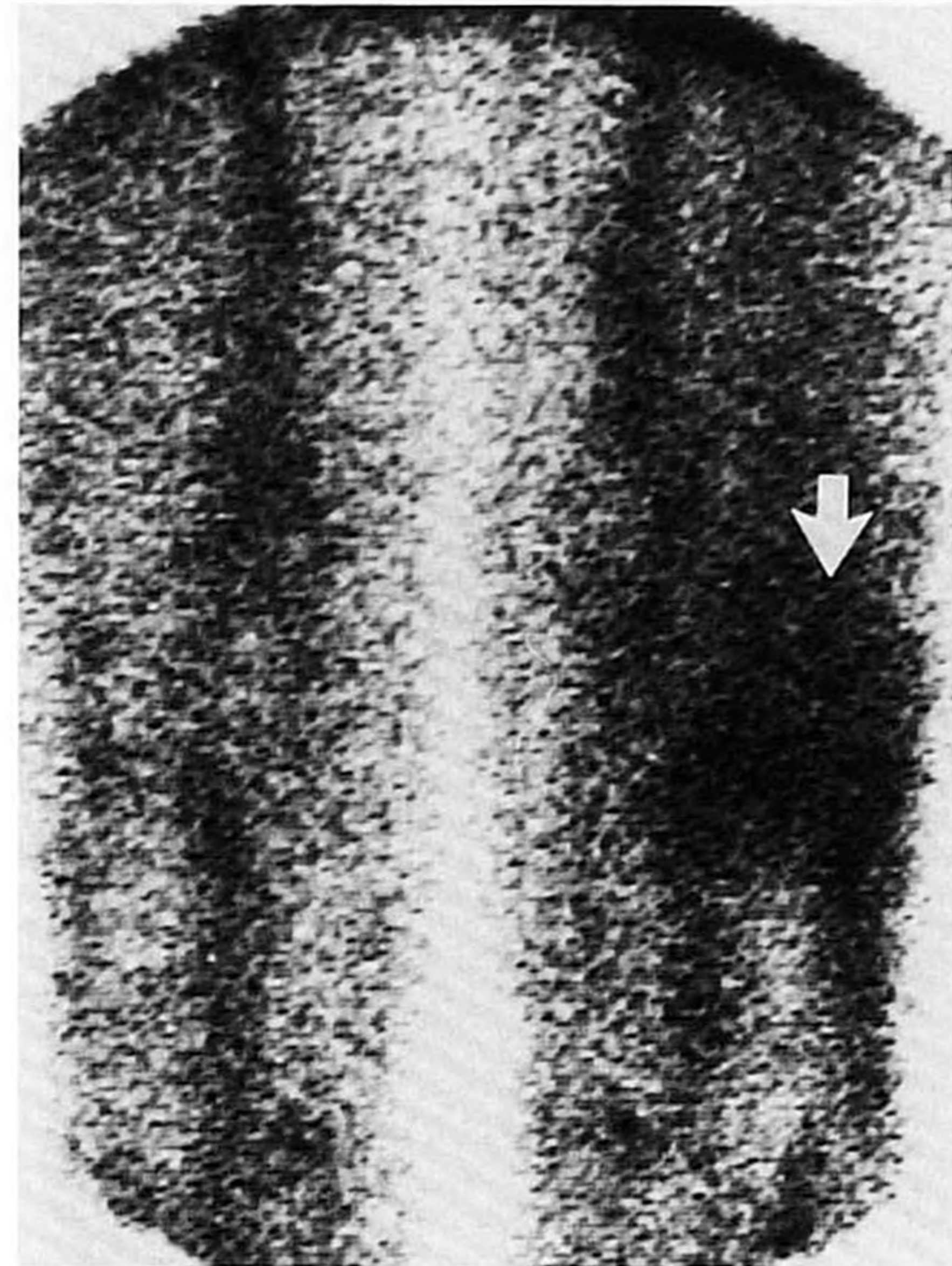


Figure 1. Right total hip prosthesis infected with *S aureus* in a man aged 81 years. (a) Scintigram obtained with In-111-labeled IgG (posterior view, obtained 48 hours after injection, with a preset time of 10 minutes and 600,000 counts) shows increased uptake of radionuclide around the prosthesis, with soft-tissue extension of infection (arrow). L = left, R = right. (b) Plain radiograph shows nonspecific osteolysis of a bone graft at the lateral margin of acetabular component but no evidence of infection such as femoral osteolysis.

prosthesis: In one patient, noninfected, necrotic, fibrinoid tissue was removed at surgery; in the other pa-



a.



b.

tient, active periarticular ossifications accounted for the false-positive findings at scintigraphy with In-111-labeled IgG. A hemorrhage in the total knee prosthesis of a patient with hemophilia and a hematoma after biopsy for chondrosarcoma in another patient caused uptake of In-111-labeled IgG. In two patients with suspected infectious arthritis of the knee, findings on scintigrams obtained with In-111-labeled IgG were positive, while an infectious origin could not be proved: One patient had severe, rapidly progressive degenerative osteoarthritis, and the other patient, sterile synovitis. The seventh patient with false-positive scintigrams obtained with In-111-labeled IgG showed increased uptake at the ventral side of a total knee prosthesis. At surgery, prepatellar bursitis was found. The bursa was removed. Subsequent cultures remained negative. The prosthesis itself appeared normal on the scintigrams. Results of this study were falsely positive for soft-tissue infection.

Only two infections proved with culture were missed: one case of low-grade hematogenous osteomyelitis in the intertrochanteric region and one infected cemented total hip prosthesis (Table, "FN" column). In both patients the intraoperative cultures revealed growth of *S aureus* in low counts.

In this group of 120 suspected infectious foci with a prevalence of infection of 59%, the sensitivity for the detection of infection was 97% and the specificity for infection, 85%, with a positive predictive value of 88% and a negative predictive value of 95%.

Figures 1-3 are typical examples of scintigrams obtained with In-111-labeled IgG. Figure 1 shows the scintigram and radiograph from a patient with an infected total hip prosthesis with extension of the infection in the soft tissue near the neck of the femoral component of the prosthesis. Figure 2 shows a scintigram and radiograph of a patient with chronic

◀ **Figure 2.** Chronic recurrent osteomyelitis of the left distal femur, caused by *S aureus*, in a man aged 58 years. (a) Scintigram obtained with In-111-labeled IgG (anterior view, obtained 48 hours after injection, with a preset time of 10 minutes and 150,000 counts) shows increased uptake of radionuclide in the left distal femur (arrow). (b) Plain radiograph shows 2-year-old beads containing gentamicin in the left distal femur. No definite radiographic evidence of active infection is seen.

osteomyelitis of the femur. Figure 3 shows the scintigrams of a large soft-tissue abscess of the upper leg.

Four patients with a suspected focus of infection and three other patients also had abnormalities of noninfectious origin (lesions not tabulated in the Table). Four recent noninfected fractures up to 4 weeks old without complications were positive on scintigrams obtained with In-111-labeled IgG. In contrast, two noninfected fractures 4-6 months old, without complications, that were clearly visible on the Tc-99m MDP images showed no accumulation of In-111-labeled IgG. A hemangioma showed some uptake of the radionuclide on the images obtained 4 hours after injection but was considered negative for inflammation, because In-111-labeled IgG did not further accumulate in the lesion on the subsequent images.

DISCUSSION

Our results indicate a high sensitivity of scintigraphy performed after injection of In-111-labeled IgG for the detection of infections in bones, joints, and joint prostheses. In our study only two low-grade *S aureus* infections were missed. The 85% specificity for infection was lower than the sensitivity. This is not surprising, because labeled IgG is a nonspecific radiopharmaceutical that accumulates not only in infection but also in various other types of inflammatory processes (6,8,9). In our study this is illustrated by the images categorized as false-positive. In all seven of these cases, an inflammatory component could be identified. In some patients with joint prostheses, wear of the prosthetic components may cause a foreign-body reaction that causes formation of granulation tissue (10). If this sterile inflammatory reaction is substantial, it could cause false-positive findings on scintigrams obtained with In-111-labeled IgG. In general, aseptic loosening of a prosthesis resulted in positive Tc-99m-MDP bone scans, but the images obtained with In-111-labeled IgG were unremarkable. Findings on scintigrams obtained with In-111-labeled IgG were positive in four recent noninfected fractures.

Accumulation in sterile inflammatory lesions has also been reported after administration of other radiopharmaceuticals such as Ga-67 and labeled WBC scintigraphy (11-13).

No consensus exists in the radiology literature on the utility of Ga-67 in infectious bone and joint disease.

Some authors presented rather poor results due to accumulation of Ga-67 in noninfected areas with increased bone turnover (14,15). Accuracy might improve with use of sequential Tc-99m-MDP and Ga-67 scintigraphy (16,17). The characteristics of Ga-67 have additional disadvantages: multi-peak, high-energy photon emission, which is less suited for imaging, and physiologic intestinal excretion (9). This excretion does not interfere with image quality in the limbs, of course, but it may obscure mild uptake in the lumbar and lower thoracic spine.

A relatively new radiopharmaceutical for evaluation of musculoskeletal infection is Tc-99m-nanocolloid. Although good results are obtained in acute infection, Tc-99m-labeled nanocolloid appears to be of limited value in the evaluation of the prosthetic joint (18).

The results of scintigraphy performed after administration of In-111-labeled WBCs in chronic infection are also variable. Some authors report excellent results (13,19,20). Others find relatively low sensitivity in low-grade infection (5,15). Initial results of Buscombe et al (9) indicate a similarity in performance between In-111-labeled WBCs and Tc-99m-labeled IgG in 16 patients with osseous infection. In a comparative study of In-111-labeled WBCs and In-111-labeled IgG, we found a significantly better performance of In-111-labeled IgG on scintigrams (21). Recently, Palestro et al (22) reported the efficacy of In-111-labeled WBCs and Tc-99m-labeled sulfur colloid in sequential imaging of bone marrow to detect infection of total hip prostheses. The usefulness of WBCs labeled with Tc-99m hexamethyl-propyleneamine oxime in scintigraphy of infectious bone and joint disease is not well established, but it is likely that the performance is similar to that of WBCs labeled with In-111. In a small group of patients, Roddie et al (23) reported good results with Tc-99m-labeled WBCs in scintigraphy. WBC scintigraphy shows high sensitivity and specificity in acute infection, especially when the patient's WBC count is elevated (5). Our study indicates that scintigraphy performed with In-111-labeled IgG also yields good results in low-grade infection when the 48-hour imaging protocol is used. In acute infection, accurate imaging is possible within 24 hours whenever images are obtained 4 and 24 hours after injection.

In addition to low sensitivity in low-grade infection, the need for cell labeling facilities is another drawback

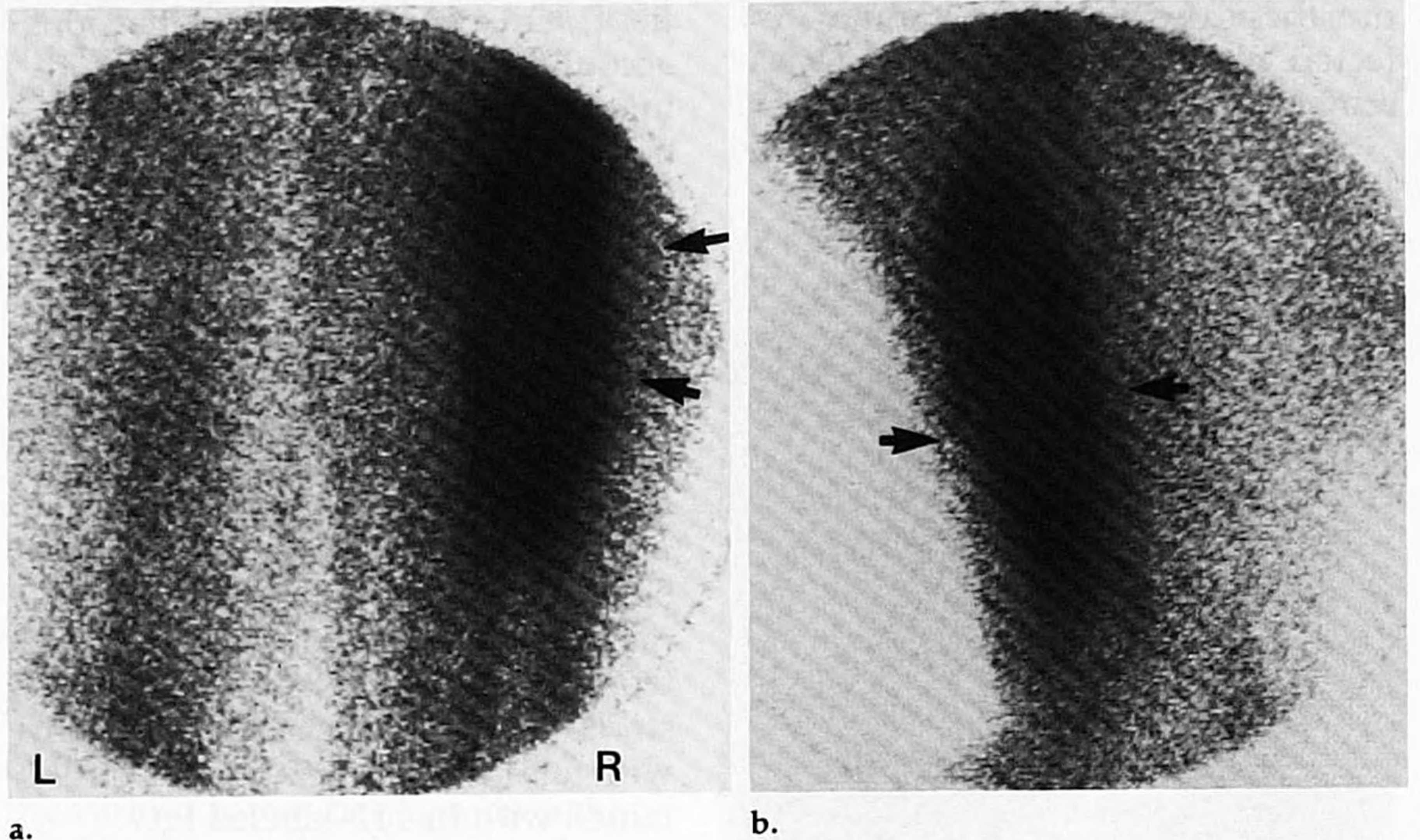


Figure 3. Soft-tissue abscess, caused by *S aureus*, in the flexor muscles of the right upper leg of a woman aged 60 years. (a) Scintigram obtained, like b, with In-111-labeled IgG (posterior view, obtained 48 hours after injection, with a preset time of 10 minutes and 300,000 counts) shows increased uptake of radionuclide in a large area in the upper right leg (arrows). L = left, R = right. (b) Scintigram (lateral view, obtained 48 hours after injection, with a preset time of 10 minutes and 250,000 counts) shows focus of infection (arrows).

for the widespread use of labeled-leukocyte scintigraphy. Moreover, isolation and labeling of WBCs is time-consuming and expensive and thus makes instantaneous preparation impossible. The IgG-DTPA conjugate is readily available as a sterile, pyrogen-free kit for rapid labeling without the need to handle blood of patients. This is especially valuable in acute infection, when results of scintigraphy should be available in the shortest possible time. In acute infection it is possible to make an accurate diagnosis with In-111-labeled IgG scintigraphy within 24 hours after referral to the nuclear medicine department.

Evaluation of chronic osteomyelitis with radiographs is difficult due to lack of accuracy (1,16). Magnetic resonance imaging could be an important modality for obtaining additional information in this group of patients (16).

Although the exact mechanism of accumulation of In-111-labeled IgG in foci of infection remains to be elucidated, we conclude that scintigraphy performed with In-111-labeled IgG is a valuable technique for the evaluation of infection in bones, joints, and joint prostheses. Because infection of the spine was studied in few patients, further studies are needed to fully elucidate the role of scintigraphy performed with In-111-labeled IgG in infections of the axial skeleton.

One has to remember that In-111-labeled IgG, like all other radiopharmaceuticals used for imaging infec-

tion, accumulates in any inflammatory focus, regardless of whether the focus is infectious or sterile. However, in chronic recurrent low-grade infection, which is one of the major indications for scintigraphy performed with In-111-labeled IgG, this distinction is of minor importance, because a sterile inflammation in these areas is less likely to occur. In our experience, uptake of In-111-labeled IgG due to sterile inflammation, such as repair after recent fracture and wound healing after surgical procedures, disappears after 4–6 months. Until then, prudent interpretation of scintigrams obtained with In-111-labeled IgG is necessary to avoid false-positive results. ■

References

1. Tumei SS, Aliabadi P, Weissman BN, McNeil BJ. Disease activity in osteomyelitis. *Radiology* 1987; 165:781–784.
2. Gupta NC, Prezio JA. Radionuclide imaging in osteomyelitis. *Semin Nucl Med* 1988; 18:287–299.
3. Delbeke D, Reza Habibian M. Noninflammatory entities and differential diagnosis of positive three phase bone imaging. *Clin Nucl Med* 1988; 13:844–851.
4. Propst-Proctor SL, Dillingham MF, McDougall IR, Goodwin D. The white blood cell scan in orthopedics. *Clin Orthop* 1982; 168:157–165.
5. Coleman RE. Radiolabeled leukocytes. In: Freeman LM, Weissmann HS, eds. *Nuclear medicine annual 1982*. New York: Raven, 1982; 119–141.
6. Rubin RH, Fischman AJ, Callahan RJ, et al. In-111 labeled nonspecific immunoglobulin scanning in the detection of focal infection. *N Engl J Med* 1989; 321:935–940.
7. Hnatowich DJ, Childs RL, Lantaigne D, Najafi A. The preparation of DTPA-coupled antibodies radiolabeled with metallic

- radionuclides: an improved method. *J Immunol Methods* 1983; 65:147-157.
8. Oyen WJG, Claessens RAMJ, van Horn JR, van der Meer JWM, Corstens FHM. Scintigraphic detection of bone and joint infections with indium-111 labeled nonspecific polyclonal human immunoglobulin G. *J Nucl Med* 1990; 31:403-412.
 9. Buscombe JR, Lui D, Ensing G, de Jong R, Ell PJ. Tc-99m-human immunoglobulin (HIG): first results of a new agent for the localization of infection and inflammation. *Eur J Nucl Med* 1990; 16:649-655.
 10. Schüller HM, Marti RK. Ten-year socket wear in 66 hip arthroplasties. *Acta Orthop Scand* 1990; 61:240-243.
 11. Staab EV, McCartney WH. Role of Gallium 67 in inflammatory disease. *Semin Nucl Med* 1978; 8:219-234.
 12. McAfee JG, Samin A. In-111-labeled leukocytes: a review of problems in image interpretation. *Radiology* 1985; 155:221-229.
 13. Wukich DK, Abreu SH, Callaghan JJ, et al. Diagnosis of infection by preoperative scintigraphy with Indium-labeled white blood cells. *J Bone Joint Surg [Am]* 1987; 69:1353-1360.
 14. Schauwecker DS, Park HM, Mock BH, et al. Evaluation of complicating osteomyelitis with Tc-99m MDP, In-111 granulocytes, and Ga-67 citrate. *J Nucl Med* 1984; 25:849-853.
 15. Wellman HN, Schauwecker DS, Capello WN. Evaluation of metallic osseous implants with nuclear medicine. *Semin Nucl Med* 1988; 18:126-136.
 16. Modic MT, Feiglin DH, Piraino DW, et al. Vertebral osteomyelitis: assessment using MR. *Radiology* 1985; 157:157-166.
 17. Tumei SS, Aliabadi P, Weissman BN, McNeil BJ. Chronic osteomyelitis: bone and gallium scan patterns associated with active disease. *Radiology* 1986; 158:685-688.
 18. Gericke M, Eckart L. Möglichkeiten und Grenzen der nanokolloid-szintigraphie in der Diagnostik von Infektionen am Bewegungsapparat. *Nucl Med* 1990; 13:93-105.
 19. Merkel KD, Brown ML, Dewanjee MK, Fitzgerald RH Jr. Comparison of indium-labeled leukocyte imaging with sequential technetium-gallium scanning in the diagnosis of low-grade musculoskeletal sepsis: a prospective study. *J Bone Joint Surg [Am]* 1985; 67:465-476.
 20. Esterhai JL, Goll SR, McCarthy KE, et al. Indium-111 leukocyte scintigraphic detection of subclinical osteomyelitis complicating delayed and nonunion long bone fractures: a prospective study. *J Orthop Res* 1987; 5:1-6.
 21. Oyen WJG, Claessens RAMJ, van der Meer JWM, Corstens FHM. Detection of subacute infectious foci with indium-111 labeled autologous leukocytes and with indium-111 labeled human nonspecific immunoglobulin G: a prospective comparative study. *J Nucl Med* 1991; 32:1854-1860.
 22. Palestro CJ, Kim CK, Swyer AJ, Capozzi JD, Solomon RW, Goldsmith SJ. Total-hip arthroplasty: periprosthetic indium-111-labeled leukocyte activity and complementary technetium-99m-sulfur colloid imaging in suspected infection. *J Nucl Med* 1990; 31:1950-1955.
 23. Roddie ME, Peters AM, Osman S, Danpure HJ, Lavender JP, Neirinckx RD. Osteomyelitis. *Nucl Med Commun* 1988; 9:713-717.