
Detection of Occult Infection Following Total Joint Arthroplasty Using Sequential Technetium-99m HDP Bone Scintigraphy and Indium-111 WBC Imaging

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Preoperative exclusion or confirmation of periprosthetic infection is essential for correct surgical management of patients with suspected infected joint prostheses. The sensitivity and specificity of [^{111}In]WBC imaging in the diagnosis of infected total joint prostheses was examined in 28 patients and compared with sequential [$^{99\text{m}}\text{Tc}$]HDP/[^{111}In]WBC scintigraphy and aspiration arthrography. The sensitivity of preoperative aspiration cultures was 12%, with a specificity of 81% and an accuracy of 58%. The sensitivity of [^{111}In]WBC imaging alone was 100%, with a specificity of 50% and an accuracy of 65%. When correlated with the bone scintigraphy and read as sequential [$^{99\text{m}}\text{Tc}$]HDP/[^{111}In]WBC imaging, the sensitivity was 88%, specificity 95%, and accuracy 93%. This study demonstrates that [^{111}In]WBC imaging is an extremely sensitive imaging modality for the detection of occult infection of joint prostheses. It also demonstrates the necessity of correlating [^{111}In]WBC images with [$^{99\text{m}}\text{Tc}$]HDP skeletal scintigraphy in the detection of occult periprosthetic infection.

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Painful prosthetic loosening following total joint arthroplasty may result from either mechanical failure or infection (1). While loosening secondary to overt sepsis is frequently diagnosed on clinical grounds, detection of loosening as a result of occult sepsis remains a significant diagnostic challenge (2,3). The identification of occult sepsis as the cause of prosthetic loosening is critical for the proper management of the failed total joint prosthesis. The preoperative exclusion or confirmation of periprosthetic infection allows improved preoperative planning and treatment of the infection prior to the implantation of a new prosthesis. As the use of structural allogenic bone grafts becomes more widespread in revision arthroplasty, the increased risk of infection makes the preoperative exclusion of infection even more critical.

Various diagnostic modalities have been examined to determine their accuracy in differentiating mechan-

ical loosening from that caused by occult sepsis. Methods studied have included laboratory tests (2,4,5), radiography (3), aspiration arthrogram (6,7), and radionuclide studies (8-12). Evaluation of the erythrocyte sedimentation rate (ESR), white blood cell (WBC) count and differential, and febrile response to infection has demonstrated that these tests lack both sensitivity and specificity in determining the presence of occult infection in the prosthetic joint (2,4). Aspiration arthrography has historically been utilized to confirm the diagnosis of infection, but has lacked the necessary sensitivity to rule out infection as a cause of prosthetic joint loosening (11,13,14). Nuclear medicine studies including skeletal scintigraphy, gallium imaging, and, more recently, indium-111 white blood cell ([^{111}In]WBC) scintigraphy have been employed in the evaluation of painful prosthetic joints (8,15). Skeletal scintigraphy is a highly sensitive method to detect bone infection (8,11,12,16,17), but lacks the specificity to differentiate between infection, fracture, heterotopic ossification, neoplasms, and arthritis. Initial reports on sequential technetium-99m hydroxymethylene diphosphonate [$^{99\text{m}}\text{Tc}$]HDP/gallium-67 (^{67}Ga)citrate scan-

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ning indicate that this technique can detect infected hip prostheses with an accuracy of 70% to 75% (9,10,11,18,19).

The use of [^{111}In]WBC scintigraphy has gained considerable attention in the evaluation of the painful, loose total joint prosthesis, offering a test with high sensitivity and specificity in detecting occult infections (11,13,20–24).

This study reports the results of a prospective study performed to determine the specificity and sensitivity of sequential [$^{99\text{m}}\text{Tc}$]HDP/[^{111}In]WBC scans in the preoperative determination of periprosthetic infection in patients with painful loose total joint arthroplasties.

MATERIALS AND METHODS

Twenty-eight patients with 29 joint arthroplasties were evaluated to determine the possibility of occult infection as the cause of a painful total joint prosthesis. The patient population included 15 females and 13 males with a mean age of 60 yr (range 30–76 yr). There were 21 total hip arthroplasties, three hip hemiarthroplasties, two total knee arthroplasties, one cup arthroplasty, one total shoulder arthroplasty, and one knee unicompartamental arthroplasty. The mean time from the initial arthroplasty was 6 yr (range 2 to 10 yr).

All patients presented with clinical and radiographic findings consistent with loosening of their prosthesis. Excluded from this study were patients with gross evidence of an infected total joint (i.e., draining sinus tracts or pus on joint aspiration). All patients were scheduled for revision of their failed arthroplasties and underwent a preoperative evaluation which included ESR, white blood cell count with differential, plain radiographs, aspiration/arthrogram with joint fluid culture, and sequential [$^{99\text{m}}\text{Tc}$]HDP/[^{111}In]WBC scintigraphic imaging. None of the patients studied were receiving antibiotic therapy during the period of preoperative evaluation.

Joint aspiration arthrograms were performed using aseptic technique under fluoroscopic control. An anterolateral approach was utilized for all hip aspirations. A 22-gauge, 3½-in. spinal needle was used for the aspiration. If free fluid could be aspirated from the joint, it was sent for aerobic and anaerobic cultures. If no fluid was aspirated, 8 to 12 cc of nonbacteriostatic saline was injected into the joint, then reaspirated and sent for culture. At the conclusion of each aspiration procedure, a small amount of water soluble contrast material was injected to confirm the intraarticular location of the needle, followed by a formal arthrogram using 10 to 12 cc of contrast material.

Skeletal scintigraphy was performed 3 hr following the i.v. administration of 20 mCi of [$^{99\text{m}}\text{Tc}$]HDP. Images were obtained using a large field-of-view gamma camera (Siemens Medical Systems, Iselin, NJ) fitted with a low-energy, all purpose collimator. A 15% window centered at the 140 keV photopeak was used. The extremities were imaged for the time required to obtain 700,000 counts over the chest.

Indium-111 oxine labeling of white blood cells was carried out using a modified Thakur technique (17,25). Images were obtained 48 hr after the bone scan and 24 hr postintravenous administration of 500 μCi of [^{111}In]WBC allowing for sufficient decay of [$^{99\text{m}}\text{Tc}$]HDP before [^{111}In]WBC imaging. A

large field-of-view gamma camera (Siemens) fitted with a medium-energy, parallel hole collimator was used. A 20% window for the 172 keV photopeak and a 25% window for the 247 keV photopeak were utilized. The periprosthetic region was imaged for 10 min or the time required to obtain 200,000 counts.

The [^{111}In]WBC images were interpreted in two ways. In the first method, the [^{111}In]WBC scan was read independent of the [$^{99\text{m}}\text{Tc}$]HDP scan. Images were interpreted as positive if they demonstrated hyperactivity in any distribution (Fig. 1). In the second method, referred to as sequential [$^{99\text{m}}\text{Tc}$]HDP/[^{111}In]WBC imaging, the [^{111}In]WBC images were interpreted as positive if they demonstrated focal hyperactivity in either an incongruent distribution or increased activity relative to the [$^{99\text{m}}\text{Tc}$]HDP images (Fig. 2). Hyperactivity on [^{111}In]WBC scanning describes an area of locally increased [^{111}In]WBC activity compared with the normal adjacent marrow around the prosthesis and/or contralateral bone marrow. Incongruent distribution of sequential [$^{99\text{m}}\text{Tc}$]HDP/[^{111}In]WBC imaging describes the localization of [^{111}In]WBC activity in a different distribution when compared with that of the bone scintiscan. Increased [^{111}In]WBC activity relative to the [$^{99\text{m}}\text{Tc}$]HDP image refers to an area of congruently elevated sequential [$^{99\text{m}}\text{Tc}$]HDP/[^{111}In]WBC activity where the relative increase in [^{111}In]WBC activity is greater than that exhibited by the bone scan. All scans were interpreted independently by two nuclear medicine physicians without prior knowledge of the clinical data or results of other preoperative testing. There were two cases of interobserver disagreement in the interpretation of the sequential [$^{99\text{m}}\text{Tc}$]HDP/[^{111}In]WBC images. The two cases were later reviewed together by the two observers and a final diagnosis made without prior knowledge of the intraoperative bone cultures.

Patients with positive sequential [$^{99\text{m}}\text{Tc}$]HDP/[^{111}In]WBC scans or a positive joint culture underwent resection arthroplasty. Those patients with negative scintigraphy underwent revision of their prosthesis. At the time of surgery, appropriate tissue was examined by frozen section, permanent sections, and gram stain. Aerobic and anaerobic cultures were taken of the joint fluid, pseudocapsule, and the fibrous membrane at the bone-cement interface and delivered directly to the microbiology laboratory.

If the previously mentioned intraoperative examinations were suggestive of periprosthetic infection, the patient was begun on the appropriate broad spectrum antibiotic while still in the operating suite. If final culture reports confirmed periprosthetic infection, the patient was continued on the appropriate antibiotic regimen for 6 wk. Those patients without intraoperative or postoperative evidence of infection were not treated with antibiotics.

RESULTS

The diagnosis of periprosthetic infection was made purely on the basis of the intraoperative cultures. Nine of the 28 patients had positive intraoperative cultures.

Preoperative Laboratory Studies

The mean ESR of the 28 patients was 28.4 (range 1–74 mm/hr Westergren method) at 1 hr. The mean ESR in those patients with positive intraoperative cultures

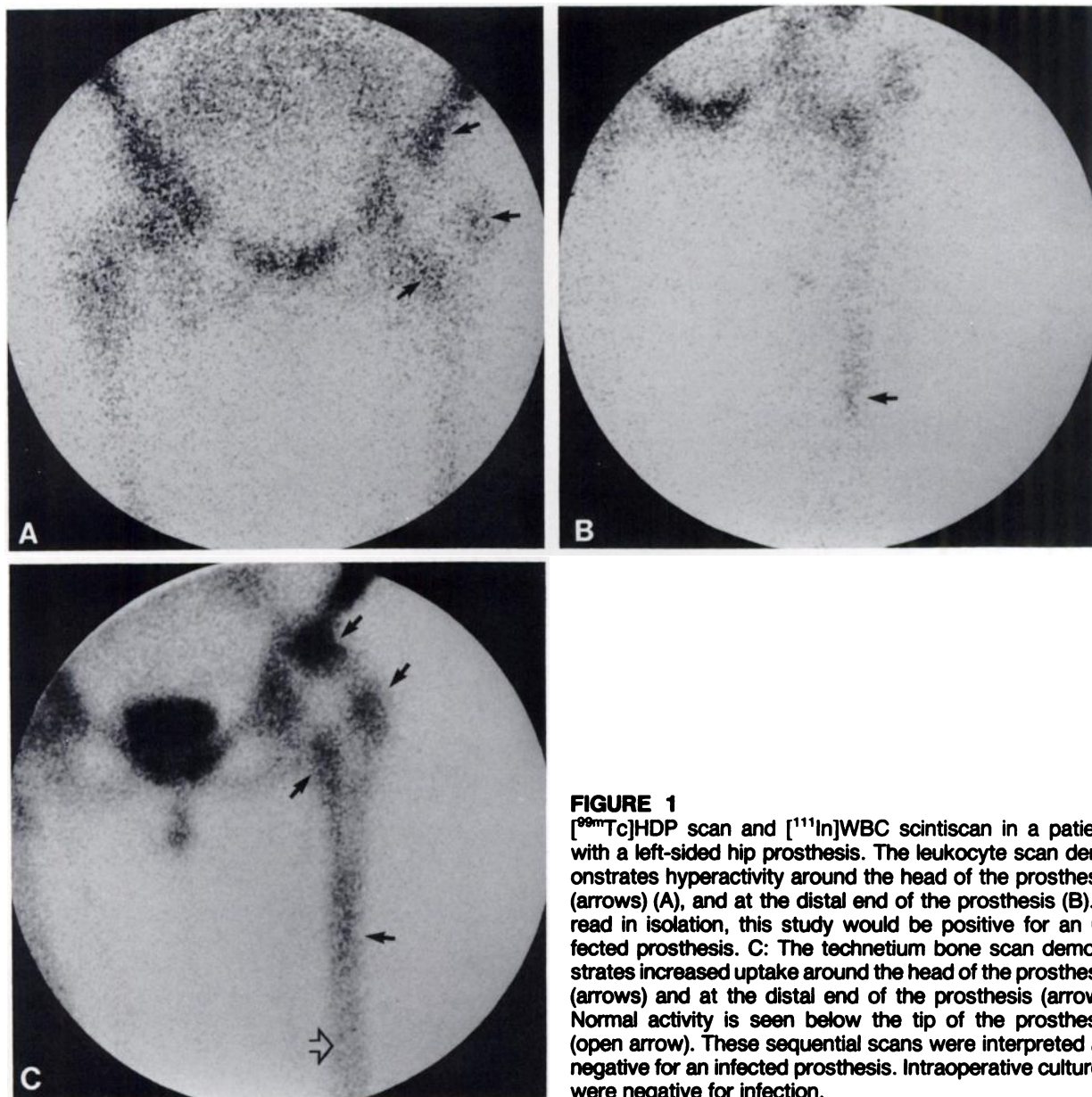


FIGURE 1
 ^{99m}Tc HDP scan and ^{111}In WBC scintiscan in a patient with a left-sided hip prosthesis. The leukocyte scan demonstrates hyperactivity around the head of the prosthesis (arrows) (A), and at the distal end of the prosthesis (B). If read in isolation, this study would be positive for an infected prosthesis. C: The technetium bone scan demonstrates increased uptake around the head of the prosthesis (arrows) and at the distal end of the prosthesis (arrow). Normal activity is seen below the tip of the prosthesis (open arrow). These sequential scans were interpreted as negative for an infected prosthesis. Intraoperative cultures were negative for infection.

was 32 (range 14–74 mm/hr). There were six patients with an ESR rate >40 mm/hr; of these, two patients had infection confirmed at surgery. The mean leukocyte count was 7.8 thousand/mm³ (range 3.9–21.7). The mean leukocyte count of those patients with positive intraoperative cultures was 9.7 thousand/mm³. The mean leukocyte count of those patients with negative intraoperative cultures was 6.8 thousand/mm³.

Preoperative and Intraoperative Cultures

Preoperative joint aspirations identified only one of the nine patients with positive intraoperative cultures (Table 1). In five patients, neither free joint fluid nor joint fluid wash could be obtained. There were nine positive intraoperative cultures among the 29 replacement arthroplasties (Table 2).

Scintigraphic Results

A positive ^{99m}Tc HDP/ ^{111}In WBC scan with a positive intraoperative culture was considered a true positive. Similarly, a negative ^{99m}Tc HDP/ ^{111}In WBC with a negative intraoperative culture was considered a true negative. A false-positive test was a positive sequential scan with a negative intraoperative culture. A false-negative test was a negative sequential scan with a positive intraoperative culture. The result of the preoperative aspiration culture was not taken into account in this evaluation.

Eight of the nine patients with positive intraoperative cultures had a positive ^{99m}Tc HDP/ ^{111}In WBC scan preoperatively. One patient with positive intraoperative cultures had a negative ^{99m}Tc HDP/ ^{111}In WBC scan preoperatively and represents the false-negative scan in

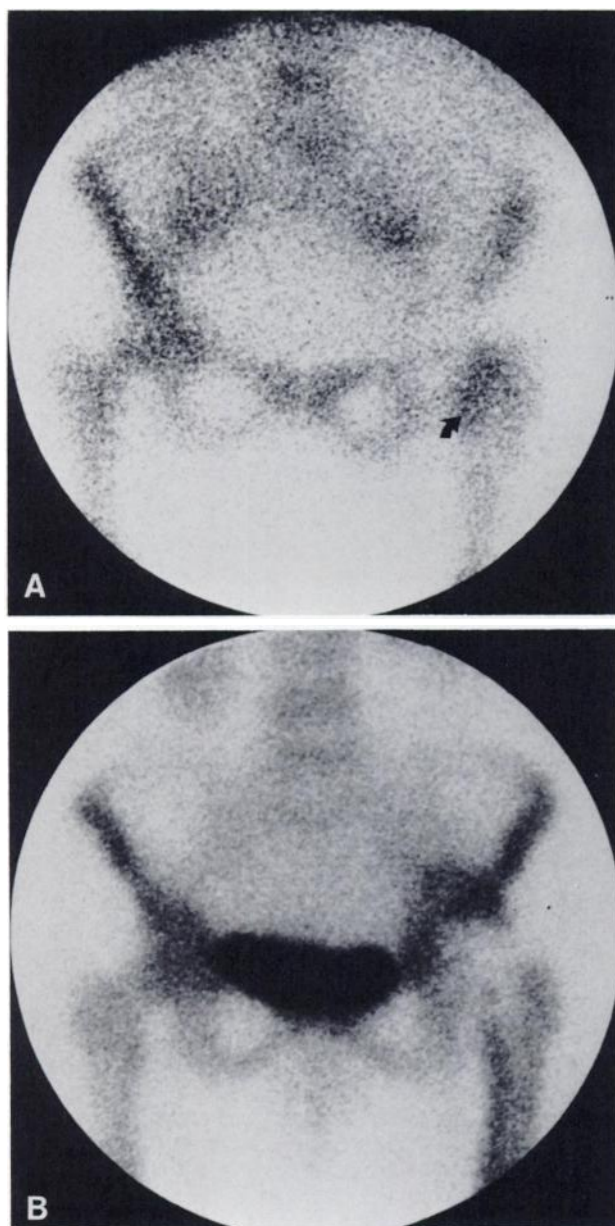


FIGURE 2
[^{99m}Tc]HDP scan and [¹¹¹In]WBC scan in a patient with a left-sided hip prosthesis. A: The leukocyte scan demonstrates increased uptake (arrow). If read in isolation, this study would be considered as positive for an infected prosthesis. B: The technetium bone scan demonstrates increased uptake in the acetabular region, but shows no congruent area of hyperactivity compared to the [¹¹¹In]WBC scan. The sequential scans were interpreted as positive for an infected prosthesis. Intraoperative cultures were positive for infection.

this series. Nineteen of 20 patients with negative intraoperative cultures had a negative [^{99m}Tc]HDP/[¹¹¹In]WBC scan preoperatively. One patient with negative intraoperative cultures had a positive [^{99m}Tc]HDP/[¹¹¹In]WBC scan preoperatively and represents the false-positive scan in this series.

TABLE 1
Comparison of [¹¹¹In]WBC Scans, [^{99m}Tc]HDP/[¹¹¹In]WBC Scans and Joint Aspiration Cultures with Intraoperative Cultures in Patients with Replacement Arthroplasties

	Positive intra-op cultures	Negative intra-op cultures
Positive [¹¹¹ In]WBC	9	10
Negative [¹¹¹ In]WBC	0	10
Positive [^{99m} Tc]HDP/[¹¹¹ In]WBC	8	1
Negative [^{99m} Tc]HDP/[¹¹¹ In]WBC	1	19
Positive joint aspiration	1	3
Negative joint aspiration	7	13
Failed joint aspiration	1	4

The data were computed for sensitivity (number of true-positive tests/number of patients with infection), specificity (number of true-negative tests/number of patients without infection), and accuracy (number of true-positive tests plus number of true-negative tests/all patients). The data were also computed for a predictive value of a positive test (number of patients with a positive test and infection/number of patients with a positive test) and a predictive value of a negative test (number of patients with a negative test and without infection/number of patients with a negative test).

Preoperative joint aspirations identified only one of the nine patients with positive intraoperative cultures. The sensitivity of joint aspiration in the diagnosis of periprosthetic infection was 12%, with a specificity of 81% and an accuracy of 58%. The predictive value of a positive test was 25%. The predictive value of a negative test was 65%. Three additional patients had positive joint aspiration/culture but negative intraoperative cultures (Table 3). For the purposes of these calculations, these were not considered to have infected prostheses.

The sensitivity of sequential [^{99m}Tc]HDP/[¹¹¹In]WBC scanning in the diagnosis of periprosthetic infection was 88%, with a specificity of 95% and an accuracy of 93%. The predictive value of a positive test was 88%, and the predictive value of a negative test was 95%. Similarly, data obtained from [¹¹¹In]WBC scans were interpreted (Table 3).

TABLE 2
Identified Organisms Obtained Intraoperatively in Nine Patients with Infected Replacement Arthroplasties

Isolated organism	No. of cases
<i>Staphylococcus aureus</i>	6
<i>Escherichia coli</i>	1
<i>Staphylococcus epidermis</i>	1
<i>Enterococcus</i>	1

TABLE 3
Comparison of [^{111}In]WBC, [$^{99\text{m}}\text{Tc}$]HDP/[^{111}In]WBC and Aspiration/Culture

	Preoperative asp./culture	[^{111}In]WBC	[$^{99\text{m}}\text{Tc}$]HDP/ [^{111}In]WBC
True positive	1	9	8
False positive	3	10	1
True negative	13	10	19
False negative	7	0	1
Sensitivity (%)	12	100	88
Specificity (%)	81	50	95
Accuracy (%)	58	65	93
Predictive value of positive test (%)	25	47	88
Predictive value of negative test (%)	65	100	95

DISCUSSION

Occult infection associated with joint replacement surgery has become a diagnostic problem of increasing significance. The preoperative diagnosis of periprosthetic infection is of great concern in light of the increasing numbers of complex revision arthroplasties utilizing structural allografts and custom prostheses. The ability to diagnose and treat insidious infections prior to the revision avoids compromise of complex reconstruction procedures. If there is evidence of periprosthetic infection preoperatively, then an active treatment choice can be made. A two-stage revision with a first-stage resection arthroplasty followed by i.v. antibiotics and a delayed revision can be selected. Other options include an exchange arthroplasty with or without antibiotic-impregnated cement and i.v. antibiotics or a permanent resection arthroplasty. The key factor that remains is that with accurate preoperative information regarding periprosthetic infection, the surgeon and patient are allowed active choices between alternative therapeutic plans.

Great effort has been expended to explore different methods to reliably and reproducibly diagnose periprosthetic infection in the painful total joint replacement. As in previous studies (2,4), laboratory data including ESR, white cell count, and differential could not reliably differentiate infected from noninfected prosthesis. Standard roentgenographs have been useful in detecting various complications of total joint arthroplasty including fracture, dislocation, heterotopic new bone formation and loosening (26,27). In our study, all patients presented with radiographic findings consistent with a loosened prosthesis, i.e., radiolucent lines at the prosthetic-cement interface, shift of component positions, cement fracture, or a bone-cement interface radiolucency which was complete and >2 mm. However, radiographs have been of limited value in differentiating septic from aseptic loosening. Progressive bone resorption, or osteolysis, is a mechanism for loos-

ening of a prosthesis which is radiographically similar to the image of loosening secondary to infection. This process further decreases the specificity of plain radiographs in evaluating periprosthetic infection.

Aspiration/arthrograms have yielded relatively poor results in detecting occult infections of painful total joint replacements. A study of 12 patients with preoperative hip aspirations noted a sensitivity of 66.7% with four false negatives (13). In another study in which aspiration arthrograms were used to evaluate 25 painful total hip arthroplasties, three of the 25 hips had negative aspirations with subsequent positive intraoperative cultures (14). A recent study from the Mayo Clinic reported only two of six aspiration arthrograms diagnostic for infection with two false negatives (11). This study continues to support the limited value of aspiration arthrograms in detecting occult infections in total joint replacements.

Previous scintigraphic evaluation of painful total joint replacements for possible occult infection relied predominantly on the use of bone and [^{67}Ga]citrate scintigraphy either alone or as sequential scans.

Technetium-99m HDP accumulates in areas of high metabolic activity, producing positive scans in acute and chronic osteomyelitis, primary and metastatic bone tumors, fractures, heterotopic ossification, and inflammation secondary to arthritis (9,12,15,28). Bone scintigraphy, including both triple phase and static imaging techniques, is sensitive but lacks the specificity to distinguish mechanical loosening from infection (28,29).

Gallium-67 shows increased uptake in areas of infection, primary and metastatic bone tumors, and soft-tissue tumors (28). Some studies have shown increased ^{67}Ga uptake in areas of periosteal new bone formation and in the normal physis (11). This physiologic uptake of ^{67}Ga in periosteal new bone formation adjacent to a noninfected loose prosthesis is indistinguishable from the increased localization seen in a loose hip prosthesis with low grade infection. Since gallium is taken up by both infection and neoplasm, it provides high sensitivity but lacks specificity as a diagnostic modality (18,19,23,28).

The sequential use of [$^{99\text{m}}\text{Tc}$]HDP/ ^{67}Ga scintigraphy has been examined, focusing on congruency or incongruency of the scans in detecting occult prosthetic infections. Accuracy of sequential scans has been reported to be 70% to 75% (11). However, a recent prospective study of 30 patients with intraoperative cultures reported by Merkel et al. yielded a sensitivity of 48%, specificity of 86%, and a diagnostic accuracy of only 57% (11). In that same study, [^{111}In]WBC scintigraphy had a diagnostic accuracy of 94% in patients presenting with a painful prosthesis (11).

Indium-111 WBC scans may show increased uptake in areas of acute osteomyelitis (23,28), acute exacerbation of chronic osteomyelitis, septic arthritis, soft-tissue

abscesses (28), fractures (9), recent surgical wounds (23), and in the area of recent surgical procedures such as bone marrow aspirations and bone graft donor sites (28). Indium-111 WBC scans do not show increased uptake in the area of inactive chronic osteomyelitis (23,28), degenerative arthritis, or avascular necrosis.

In multiple studies evaluating the efficacy of [¹¹¹In]WBC scintigraphy in detecting occult musculoskeletal infection, sensitivity has ranged from 83% to 98% (11,18,21,28) with diagnostic accuracies in the range of 83% to 93% (18,21,24,28). All of these studies, however, looked at a mixed population of musculoskeletal infections, i.e., osteomyelitis, septic arthritis, abscess, and painful arthroplasties.

Several studies have specifically looked at the results of [¹¹¹In]WBC scans to differentiate aseptic from septic prosthetic loosening. Merkel et al. reported an accuracy of 94% in patients with a prosthesis (11). Mulumba et al. reported on 30 patients who had [¹¹¹In]WBC scans and surgical exploration (13). In the latter review, the sensitivity of [¹¹¹In]WBC was 92%, with a specificity of 100%, and an accuracy of 97%. The study performed by Mulumba et al. used sequential [^{99m}Tc]SC/[¹¹¹In]WBC scintigraphy for diagnosis of an infected arthroplasty (13). The leukocyte scan was considered positive only when there was [¹¹¹In]WBC activity in addition to that of the [^{99m}Tc]SC scan. Pring et al. used [¹¹¹In]WBC to scan 74 prosthetic joints. They reported a sensitivity of 100% and a specificity of 92% (30). The high specificity reported by Pring et al. (30) using [¹¹¹In]WBC scintigraphy alone is more difficult to explain, since a positive indium granulocyte scan merely reflects migration of granulocytes into the region and is not specific for infection. McKillop et al., in a comparison of gallium and indium scanning, reported a sensitivity of 50% and a specificity of 100% for indium, and a sensitivity of 83% and a specificity of 79% for gallium (10). The poor results obtained by McKillop et al. (10) with [¹¹¹In]WBC scanning may be accounted for by their labelling technique and the use of crude rather than pure granulocytes. To test McKillop's hypothesis, we performed a chi-squared analysis of their data, which showed the difference in sensitivity and specificity between ⁶⁷Ga and [¹¹¹In]WBC scintigraphy to be only marginally significant ($p>0.05$) due to the small number of patients studied.

Although several studies have reported a high sensitivity and specificity using [¹¹¹In]WBC scintigraphy in the detection of occult infected joint prosthesis, our data demonstrated a relatively low specificity when using this technique alone. This low specificity was accounted for by the fact that [¹¹¹In]WBC scintigraphy may be positive even in the absence of culture-proven infection in patients with painful loose hip prostheses. In contrast, we found that sequential [^{99m}Tc]HDP/[¹¹¹In]WBC provides an imaging technique with high

sensitivity and specificity to detect occult-infected hip joint prostheses.

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