INVITED COMMENTARY

Nuclear Medicine, the Painful Prosthetic Joint, and Orthopedic Infection

Although the notion of replacing the failed human joint originated centuries ago, modern joint replacement surgery is less than 50 y old. Today's prosthesis, a combination of metal (cobalt-chromium or titanium) and plastic (ultrahigh-molecular-weight polyethylene), can be attached to native bone in numerous ways. Cemented prostheses are anchored with polymethylmethacrylate. The cementless prosthesis is fixated through bony ingrowth into a porous coating applied to the surface. Bonding can also be accomplished through the application of a hydroxyapatite compound to the surface of the components, stimulating new bone formation and serving as an attachment for newly formed osseous tissue. Acetabular components can be forced, or press-fit, into the acetabulum and secured with orthopedic screws, as needed (*1*).

Although many complications of prosthetic joint surgery are readily diagnosed and treated, differentiating aseptic loosening from infection can be difficult because the clinical presentation of, and the histopathologic findings in, both entities are often similar (*2*,*3*).

Aseptic loosening, radiographically evident in up to 50% of prostheses within 10 y, is usually due to an immune reaction between patient and prosthesis. Particulate debris, produced by component fragmentation, activates tissue phagocytes normally present around the prosthesis. This debris, resistant to enzymatic destruction, thwarts the inflammatory cells, resulting in repeated, failed, attempts at phagocytosis. The continuing attempts at phagocytosis stimulate proinflammatory cytokine and proteolytic enzyme secretion, damaging bone and cartilage and leading to osteolysis, loss of supporting osseous tissues, and loosening of the prosthesis. Histopathologically, a pseudomembranous structure develops at the cement/bone interface. The cellular composition of the pseudomembrane is varied: histiocytes and giant cells are present in most cases, with lymphocytes and plasma cells found about one fourth of the time. Neutrophils, in contrast, are present in less than 10% of the cases (*4*–*8*).

The rate of infection after primary implantation is about 1%−2% for primary, and about 3%–5% for revision, implants. Approximately one third of these infections develop within 3 mo, another third within 1 y, and the remainder more than 1 y after surgery. The inflammatory reaction accompanying the infected prosthesis is nearly identical to that present in aseptic loosening, with an important difference: neutrophils, usually absent in aseptic loosening, are invariably present in infection (*9*–*11*).

Because their treatments are very different, the importance of accurate preoperative differentiation of aseptic loosening from infection cannot be overemphasized. Aseptic loosening can be treated with a single-stage revision arthroplasty requiring only 1 hospital admission. The treatment of infected hardware is more complex. An excisional arthroplasty is performed, followed by several weeks of intravenous antibiotic therapy. Eventually, several months or more later, the patient undergoes a revision arthroplasty (*1*).

To be useful, therefore, any preoperative diagnostic test used must be both sensitive and specific. The sensitive but nonspecific test can lead to multiple costly, unnecessary operations on patients in whom a single intervention may have sufficed. Similarly, the specific but insensitive test will also result in additional surgical interventions, because any revision arthroplasty implanted in the setting of infection will fail.

Given the similarities between aseptic loosening and infection, it is not surprising that nonspecific markers of inflammation are not useful for distinguishing between these 2 entities. The results of joint aspiration have also been disappointing. Plain radiographs are neither sensitive nor specific, and cross-sectional imaging modalities, such as CT and MRI, are hampered by hardware-induced artifacts (*1*).

Over the years, a plethora of radionuclide imaging studies has been investigated. Bone scintigraphy is ubiquitously available, easily performed, and exquisitely sensitive. For hip prostheses, diffusely increased periprosthetic uptake is often equated with infection. This appearance is probably due to generalized osteolysis, which is present in aseptic loosening secondary to inflammation as well as infection. Scintigraphically, then, these 2 entities may be indistinguishable. The diffuse pattern associated with infection was described in patients with cemented prostheses. The introduction of cementless and hybrid prostheses, among others, further complicates matters because the evolution of periprosthetic uptake patterns around these devices has not been well established (*12*,*13*).

Periprosthetic uptake patterns around knee prostheses are extremely variable, with asymptomatic patients often dem-

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For correspondence or reprints contact: Christopher J. Palestro, MD, Division of Nuclear Medicine, Long Island Jewish Medical Center, 270-05 76th Ave., New Hyde Park, NY 11040.

E-mail: palestro@lij.edu

onstrating persistent periprosthetic activity for several years after implantation (*14*,*15*).

Adding to the difficulty is the fact that about two thirds of all joint replacement infections occur during the first year after implantation, when, regardless of the type or location of the prosthesis, periprosthetic uptake is so variable that only a bone scan with normal findings contributes useful information. The overall accuracy of radionuclide bone imaging in the evaluation of the prosthetic joint is about 50%–70% (*13*).

Gallium imaging is often performed to enhance the specificity of bone scintigraphy. Uptake of gallium is related to inflammation in general and not to infection specifically. With an overall accuracy of about 70%–80%, the combined technique, which offers only a modest improvement over bone imaging alone, is still less than satisfactory for distinguishing the inflamed, aseptically loosened prosthesis from the infected one (*13*).

Labeled leukocyte imaging is most useful for detecting neutrophil-mediated inflammatory processes. Theoretically, then, this procedure should be able to differentiate the inflamed aseptically loosened prosthesis, in which neutrophils are generally absent, from the infected prosthesis, in which neutrophils are present. The results reported, however, have varied widely on the accuracy of this technique. Poor sensitivity has been attributed to "chronicity" of the process, and poor specificity to "inflammation" (*1*).

The paucity of neutrophils in the aseptically loosened prosthesis, and the invariable presence of these cells in the setting of infected hardware, however, point to another explanation for the inconsistent results. Labeled leukocytes accumulate not only in infection but in the bone marrow as well. The distribution of hematopoietically active marrow is extremely variable, making it difficult, when the images are interpreted in isolation, to distinguish uptake of labeled leukocytes in infection from uptake in aberrantly located but otherwise normal marrow.

This problem has been overcome by the addition of complementary bone marrow imaging performed with ^{99m}Tc-sulfur colloid. Both labeled leukocytes and sulfur colloid accumulate in the bone marrow, but only labeled leukocytes accumulate in infection. Thus, on combined labeled leukocyte/marrow imaging, when there is activity on the labeled leukocyte images without corresponding activity on the sulfur colloid images, the labeled leukocyte uptake is due to infection. In contrast to the results reported for labeled leukocyte imaging alone, the results of combined leukocyte/marrow imaging in suspected prosthetic joint infection have been uniformly excellent, with an accuracy of 95% or greater, making this study the current radionuclide gold standard for diagnosing prosthetic joint infection (*16*–*19*).

There are, however, significant limitations to leukocyte/marrow scintigraphy. The in vitro labeling process is labor intensive, is not always available, and requires direct contact with blood products. The need to perform marrow imaging adds to the complexity and cost of the study and is an additional inconvenience to patients, who are often elderly and debilitated. Thus, the quest continues for an agent as efficacious as, but without the limitations of, the in vitro labeled leukocyte study. Methods of in vivo leukocyte labeling using peptides and antigranulocyte antibodies have been investigated, but none are approved for routine use in the United States.

Abandoning radiolabeled leukocytes entirely, some investigators have recently turned to other tracers in the pursuit of an agent that can accurately identify the infected prosthesis without the limitations of the current technology. One tracer that has aroused considerable interest is ^{18}F-FDG (*20*–*23*). Uptake of this agent is dependent on glucose metabolism. Activated leukocytes, which are avid consumers of glucose, are present in large numbers around both aseptically loosened and infected prostheses, and this circumstance would seem to pose a serious obstacle to the success of this technique for evaluating the painful joint prosthesis. There are data, in fact, which suggest that regardless of the criteria used, ^{18}F-FDG is significantly less accurate than leukocyte/marrow imaging for diagnosing prosthetic joint infection (*24*).

A novel approach to infection imaging is the use of radiolabeled antibiotics. The prototype of this group of tracers is ^{99m}Tc-ciprofloxacin, or Infecton (Draximage Inc.). The uptake mechanism of this agent, although a subject of some controversy, is presumably the same as that for the unlabeled antibiotic: accumulation and binding by living bacteria with DNA-gyrase inactivation. Initial investigations indicated that ^{99m}Tc-ciprofloxacin is moderately sensitive (70%–85%) but highly specific (91%–96%) (*25*–*30*). Recent data indicate that, at least in orthopedic infections, this agent may be more sensitive than specific (*31*,*32*). The results reported by Sarda et al. in this issue of *The Journal of Nuclear Medicine* indicate that the study may be even less specific than has previously been reported (*33*). The data presented are important, not only because they raise questions about ^{99m}Tc-ciprofloxacin but also because they should move us to reanalyze our approach to the investigation of nuclear medicine techniques for diagnosing orthopedic infections.

It is important to be aware that, currently, no one tracer or combination of tracers is equally satisfactory for all orthopedic infections. An agent that apparently performs well in orthopedic infection in general may be less satisfactory for a specific entity. Labeled leukocyte imaging combined with marrow imaging is extremely useful for the evaluation of the prosthetic joint but is of little or no value in spinal osteomyelitis. Similarly, labeled leukocyte imaging can be used alone to accurately diagnose pedal osteomyelitis in the forefoot of the diabetic patient but must be combined with marrow imaging for accurate evaluation of the mid and hind foot, where the Charcot joint is often present. Although initial broad-based investigations are useful to determine whether an agent merits further evaluation, it is important that these

initial results, no matter how encouraging they might be, not be extrapolated to each of the various entities that we, as nuclear physicians, may be called on to evaluate. Adequate study of a new agent must include focused evaluations of specific entities: the prosthetic joint, the spine, the diabetic forefoot, and the diabetic mid/hind foot.

Another element critical to the successful investigation of any agent is the gold standard by which it is judged. In the case of orthopedic infections in general, and the prosthetic joint in particular, the importance of histopathologic confirmation of the diagnosis cannot be overemphasized. How does one, clinically, determine the presence or absence of infection? Laboratory tests are of limited value. Pain and osteolysis are present in both infection and aseptic loosening and are not likely to resolve with time in either entity. Moreover, what constitutes a sufficiently long period for adequate clinical follow-up: 1 mo, 6 mo, 1 y? Investigations should be limited to patients who are likely to have histopathologic confirmation of the diagnosis.

Finally, the investigational agent should be compared with the radionuclide imaging procedure of choice for a given entity. It is not meaningful, for example, to compare ^{99m}Tc-ciprofloxacin, or ^{18}F-FDG, with labeled leukocyte imaging in spinal osteomyelitis. Similarly, for prosthetic joint infection, the worth of these or any other agents must be judged against leukocyte/marrow imaging in the same population. Certainly, on the basis of the data in this issue of the *Journal*, I could easily conclude that ^{99m}Tc-ciprofloxacin is not likely to supplant leukocyte/marrow imaging for diagnosing prosthetic joint infection. Perhaps, however, there was something unique about the population studied and no study would have performed very well. I would be far more likely to dismiss ^{99m}Tc-ciprofloxacin as a useful agent if these patients had also undergone the dual-tracer study, with the expected results.

In summary, the adequate evaluation of any agent for the diagnosis of orthopedic infection is an almost Herculean, albeit necessary, undertaking. The investigation must include focused, individual evaluations of specific problems, such as the painful replaced joint or the spine, histopathologic confirmation of the diagnosis, and comparison to the radionuclide imaging procedure of choice.

Christopher J. Palestro, MD
Long Island Jewish Medical Center
New Hyde Park, NY

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