Editorial: In Search of the Hot Appendix—A Clinician's View of Inflammation Imaging

The anatomic localization of sites of focal inflammation and infection *in a timely fashion* remains a classic diagnostic problem that prevades all areas of medicine and surgery. There are a number of clinical situations where the ability to accomplish this task is central to patient management such as:

1. The evaluation of a patient with a fever of unknown origin for hidden focal sites of infection in the abdomen, skeletal system, or cardiovascular system.
2. The evaluation of the febrile postoperative patient or the patient who has suffered major trauma for deep wound infection present at the site of previous surgery or trauma. The magnitude of this problem is suggested by the following statistics: the incidence of intraabdominal abscess following abdominal surgery is ~1%–5%, depending on the clinical circumstance (*1–4*); in addition, as many as 20% of patients undergoing major intraabdominal procedures are still febrile 5–7 days postoperatively (Rubin RH, *unpublished data* and Ref. 1). Since these febrile patients include the ones that have the actual focal infections, this is the group of individuals that would be candidates for an effective imaging technique.
3. The evaluation of the patient with fever or defined infection, such as pneumonia or urinary tract infection, who has an orthopedic appliance (such as a hip prosthesis) or a vascular graft in place, and the question of clinical concern is whether this *locus minoris resistentiae* has been infected due to metastatic spread of infection via the bloodstream.
4. The evaluation of the patient who is suspected of having ostemyelitis on the basis of his clinical presentation—the febrile child with symptoms referable to his skeletal system, the diabetic with vascular disease and ischemic lower extremities, the fracture patient with a nonhealing fracture, etc.
5. The evaluation of such immunosuppressed patients as transplant recipients, cancer patients, and those with human immunodeficiency virus infection who present with such subtle signs of possible life-threatening infection as nonproductive cough, fever, malaise, or focal discomfort. As the survival of immunosuppressed patients who actually have infection is dependent upon the speed with which diagnosis is made and effective therapy instituted (*5*), a sensitive noninvasive test that would demonstrate *Pneumocystis* pneumonia in the face of a negative chest x-ray, a perirectal phlegmon in the severely granulocytopenic leukemic patient, and an area of diverticulitis in a transplant patient with mild abdominal pain would be of great clinical utility.
6. The objective measurement of the degree of inflammation present in such noninfectious inflammatory processes as inflammatory bowel disease, rheumatoid arthritis, vasculitis, and such inflammatory lung diseases as sarcoidosis. In this setting, the imaging technique should be useful in two ways—in the establishment of the original diagnosis; and in the assessment of the clinical response of the patient to therapy.

All of these clinical entities, with the exception of the problems of the leukemic and transplant patients, are relatively subacute syndromes, in which an imaging modality that produces reliable answers within 12–24 hr of the time of request is usually satisfactory. In this issue of the *Journal of Nuclear Medicine*, Mountford, et al. (*6*) begin to address another group of clinical problems, those that are much more acute in nature and which must be dealt with immediately. In their study of 41 patients with suspected intraabdominal sepsis, the authors performed scans 4 hr and 24 hr after injection of [^{99m}Tc]HM-PAO-labeled leukocytes and ^{111}In-oxine-labeled leukocytes. Although, as expected (*7–10*), the 24-hr ^{111}In-leukocyte scan gave excellent results, the 4-hr ^{111}In scan was too insensitive to be clinically useful. Conversely, the ^{99m}Tc-leukocyte scans, both at 4 and 24 hr, had too many false-positives due to physiologic bowel uptake (the problem that has seriously limited the clinical utility of [^{67}Ga]citrate scanning for intraabdominal sepsis in sick patients (*11*) to be clinically useful. Thus, neither of these two techniques can be employed for the rapid assessment of the acutely ill patient, in whom a decision must be made regarding the need for emergency surgery.

Is this a clinically important issue with which the nuclear medicine community should be concerned? The answer is clearly yes. One clinical entity, acute appendicitis, provides a perfect paradigm for this problem. Patients undergoing surgery for uncomplicated

Received Dec. 26, 1989; revision accepted Dec. 26, 1989.
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appendicitis, prior to perforation and peritoneal contamination, have a negligible mortality rate and leave the hospital on an average of 3.5 days post-surgery (*12*). When perforation has occurred, which is found in 10%–37% of patients at surgery (particularly the young and the elderly), the hospital stay rises to 10.2 days and the mortality rate to 1%–5% (*13,14*). Thus, a great premium is placed on early surgical therapy, prior to the development of complications. Because of this, and because the clinical presentation of appendicitis can be very occult, it is deemed appropriate surgical practice to find a normal appendix at surgery in 5%–20% of cases; that is, it is far better to remove a certain number of normal appendicies than to risk the complications associated with delaying surgery for true appendicitis (*15,16*).

There is, then a compelling clinical need for an imaging approach that would allow the accurate assessment of a patient with possible acute abdominal sepsis, as exemplified by acute appendicitis. Imaging technologies such as computerized tomography, ultrasonography, and magnetic resonance imaging that rely on anatomical detail are too insensitive in this type of clinical situation where suppuration has not yet caused anatomical distortion (*17,18*). Radionuclide scans that detect inflammation, such as the leukocyte scans described in the Mountford paper and such new techniques as the ^{111}In-IgG scan (*17*) and radionuclide-labeled anti-granulocyte antibody scans (*19*), do not yet have the sensitivity within the first few hours of injection to permit their use in patients with possible appendicitis and allied conditions.

What, then, are the characteristics that the clinician-surgeon, internist or pediatrician is looking for in the next generation of imaging techniques for the delineation of inflammatory processes? The following represents a reasonable "wish list":

1. Easy access to the procedure. Thus, if injection of a radionuclide is involved, reagent preparation is quick and rapidly available and, particularly important in the practice of pediatrics, large volumes of blood do not have to be drawn in order to prepare the reagent.
2. Radioactive dosimetry and lack of toxicity so that serial studies could be carried out to assess response to therapy.
3. Reasonable cost.
4. High sensitivity and specificity of the procedure so that important clinical decisions could be made on the basis of the procedure.
5. Efficacy in each of the clinical situations described above.
6. Timeliness of results—less than 3 hr for situations like appendicitis, less than 24 hr for more subacute processes, and less than 48 hr for chronic processes, without the need to administer purgatives to clean out the bowel.

Clearly, much progress has been made, but more needs to be done. Mountford and his colleagues are to be particularly congratulated for their critical assessment of the utility of presently available techniques in the timely assessment of acute inflammatory processes. For the clinician, timeliness of data is as important as sensitivity and specificity issues, and the introduction of this variable in the evaluation of new technologies is a major step forward.

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