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sclerosis associated with infarction in sickle-cell disease. Infection is a more likely possibility, and because of the clinical context, Salmonella might be seriously considered. Salmonella infections are usually more aggressive than this, but the possibility of a chronic infection or a partially treated acute infection should certainly be included in the differential diagnosis.

Neoplastic disease is also a consideration. It is unlikely that the patient had a primary tumor of bone, but a primary neoplastic process of the joint capsule, such as a synovial sarcoma, cannot be excluded. Metastatic tumor is also a possibility. However, metastases to the limbs are uncommon, and in this young patient, a metastasis to the elbow seems statistically unlikely. In this age group, it is also important to mention the possibility of leukemia or lymphoma, for these processes can involve the joint space, producing radiographic findings similar to those found in today's patient.

The gallium scan and the radionuclide bone scan added some important additional information. I will ask Dr. Kumar to give you these results.

Dr. Bharath Kumar: A bone scan was performed with technetium-99m methylene diphosphonate. There was a focus of increased activity superior to the left kidney (Figure 3), which most probably represents accumulation of the tracer in an infarcted, atrophic spleen. This is a well-recognized entity in patients with sickle-cell disease and should not be confused with a lesion in the rib. There was uniform distribution of activity in the lumbar spine and in both sacroiliac joints. There was increased activity in the left elbow compared with the right. This corresponds to the destructive process with some periosteal elevation and mottled luencies in the bony cortex of the distal left humerus that Dr. Jost described. Dr. Jost excluded bony infarction on the basis of the radiographic findings and commented that the primary differential possibilities included infection, metastatic disease, and leukemia or lymphoma that involves bone. The scintigraphic findings in the left elbow were nonspecific in that they were compatible with all three of these possibilities. The pathophysiologic basis for an abnormal bone scan includes increased bone blood flow, increased bone turnover, or both. Therefore, any process that results in either or both of the aforementioned will result in a focus of increased activity in a bone scan. The scan also showed a focus of increased activity in the distal right femur and another in the mid-shaft of the right tibia. In this patient, these foci of increased activity could be secondary either to bone infarction in the reparative phase or to osteomyelitis. It is not possible on a bone scan to differentiate these two entities.

To aid in this distinction, a gallium scan was performed. The anterior image of both tibiae made 48 hours after administration of gallium-67 citrate showed no evidence of increased activity in the mid-shaft of the right tibia, where the focus of increased activity was noted on the bone scan. Similarly, there was no evidence of increased activity in the distal right femur. Increased activity of an intensity greater than that seen on the bone scan would have favored a diagnosis of osteomyelitis. In this patient, the absence of disproportionately increased activity suggests that the bone scan abnormalities were secondary to healing bone infarcts.

The gallium image of the left anterior chest and arm (Figure 4) demonstrated increased activity in the left elbow corresponding to the bone scan abnormality in this region. This patient, however, had undergone biopsy of the lateral epicondyle of the left humerus during the four-day interval between the two scans. This complicates the differential diagnosis, since the focus of increased activity could be secondary to a hyperemic response to the biopsy itself rather than to accumulation of gallium at a site of either skeletal infection or neoplastic infiltration of bone. Additional scintigraphic findings in this patient included increased activity in the soft tissues around the proximal humerus. This was also seen in the soft tissues surrounding both proximal
femora. A history of intramuscular injections in these regions was elicited, and the soft tissue foci of increased activity were believed to represent the injection sites with or without associated soft tissue infection. There was a focus of increased activity in the left breast with additional foci of increased activity in the region of the left axilla. Potential explanations of these findings include either an infectious process in the breast with reactive inflammatory changes in the axillary nodes or a malignant process with metastatic disease in the axillary nodes. The malignant process could well be leukemic or lymphomatous infiltration. Another finding, which may be of some importance in regard to this patient, was the symmetrically increased activity seen in the long bones and joints of both legs. This finding has been reported in patients with leukemia and reflects gallium-67 accumulation in infiltrated bone marrow.

Dr. Deuel asked me to review briefly the mechanism of gallium localization in inflammatory lesions and to comment on its usefulness in the evaluation of patients with either inflammatory or malignant disease. Gallium-67 originally was investigated as a tumor-scanning agent [7,8] and has been widely used for this purpose. Early reports [8,9] were enthusiastic about its potential as a tumor-seeker, even though they also mentioned the problem of nonspecificity, since gallium localizes in many types of inflammatory processes. To give a few examples, gallium-67 studies yield positive results in 80 to 90 percent of primary lesions of bronchogenic carcinoma, irrespective of the cell type of the tumor. Abnormal uptake in one or more lesions was demonstrated in 88 percent of untreated patients with Hodgkin's disease [10]. A sensitivity of 87 percent has been reported for the detection of metastatic sites in patients with seminoma [11]. Although the pattern of diffusely increased bony uptake is not specific for leukemia, 76 percent of patients with more than 75 percent blasts in the marrow demonstrated this pattern in one study [12]. Other tumors in which gallium imaging has been found to be useful include histiocytic and lymphocytic lymphomas, Burkitt's lymphoma, and melanomas. The sensitivity of gallium imaging for detecting hepatomas exceeds 90 percent. A major problem with gallium imaging is that a large fraction of the administered tracer is excreted into the gastrointestinal tract. Residual gallium-67 in the colon may lead to false-positive interpretations or may obscure activity in abdominal tumor foci. This problem has particularly limited the value of gallium-67 imaging for the staging of lymphomas.

Although enthusiasm for gallium-67 as a tumor-seeker has somewhat diminished, enthusiasm for its use in localizing inflammatory disease has increased. Numerous published reports [13–19], including a few from this institution, have attested to the low frequency of false-positive and false-negative diagnoses with this technique. The sensitivity exceeds 90 percent but the false-positive rate tends to increase when gallium imaging is used for routine screening of febrile patients.

In the evaluation of patients with suspected abscesses, gallium-67 citrate is administered intravenously, usually in a dose of 3 to 5 mCi, and imaging is performed 24 and 48 hours later. Images can be made as soon as four to six hours after injection in emergency situations. However, early images are not ordinarily obtained because the body background at this time is rather high. Since the tracer is normally excreted into the intestine, we advocate a bowel preparation similar to that used before barium enema examinations to permit better evaluation of the abdomen and pelvis. Adequate bowel preparation, combined with serial examinations at 24, 48, and sometimes 72 hours, decreases the frequency of false-positive results, since intracolonic activity frequently changes location on serial images.

How does gallium-67 localize in inflammatory lesions? The mechanisms have not been fully elucidated, but the following observations suggest a useful hy-
pothesis. When gallium-67 citrate is injected intravenously, it is bound almost immediately to plasma proteins, especially transferrin [20,21]. Hoffer et al. [22] have shown that there is an exchange of transferrin-bound gallium-67 with lactoferrin. It has also been shown that gallium-67 localization in experimental abscesses is either absent or delayed in leukopenic animals [20]. Tsan et al. [23] have demonstrated that gallium-67 binds to the plasma membrane of neutrophilic leukocytes that migrate to the site of inflammation. Some microorganisms, in particular Staphylococcus aureus, have been shown to accumulate gallium-67 directly [24]. Therefore, increased protein turnover, leukocyte accumulation, and bacterial uptake appear to play important roles in the localization of gallium in abscesses and other infectious processes.

What did the bone and gallium scans contribute to the management of this patient? First, they helped exclude osteomyelitis in the right proximal tibia and distal femur. The scans suggested the presence of an infarcted spleen. Additional sites of increased activity were identified in the breast and in the ipsilateral axilla, thereby raising the possibility of a coexisting infectious or malignant process. Neoplastic and inflammatory lesions cannot be differentiated solely on the basis of gallium-67 uptake. Finally, the possibility of a leukemic process with marrow infiltration was raised by the finding of increased activity in the long bones of both legs.

Dr. Deuel: Infection was considered throughout the hospital course to be a strong possibility as the underlying illness complicating this patient's sickle-cell anemia. Dr. Richard Markham will discuss why patients with sickle-cell anemia have an increased propensity to infection, what infections are likely to occur in these patients, and the diagnostic procedures used in the clinical management of this patient.

Dr. Richard Markham: Before discussing this particular patient, I would like to review briefly the infectious disease problems that are peculiar to patients with sickle-cell disease. The propensity for infections with encapsulated organisms, particularly with pneumococci, to develop in these patients is well established [25]. To understand why patients with sickle-cell disease have this increased risk, it is first necessary to be aware of the basis for natural immunity to these organisms. In the pre-antibiotic era it was determined that protection against pneumococcal infection best correlated with high levels of antibody directed at the polysaccharide capsules of the organisms [26]. At that time, therapeutic trials with pneumococcal capsular-specific antibody were undertaken. It was not until much later that it was discovered that pneumococci possessed the ability to activate the alternative complement pathway, even in the absence of specific antibodies [27]. It was then postulated that opsonization via the alternative complement pathway, by promoting more efficient phagocytosis, could in fact be protective against low-level exposure to these organisms.

In the late 1960s, Winklestein and Drachman [28] showed that serum from patients with sickle-cell disease lacked the ability to promote phagocytosis of pneumococci via the alternative pathway. In these studies, the investigators mixed granulocytes from a normal patient with pneumococci and antibody-free serum from either a patient with sickle-cell disease or a normal patient. It is apparent that in the presence of normal serum, phagocytosis of pneumococci proceeded (Figure 5, left), whereas there is very little evidence of phagocytosis when the organisms were incubated in serum from patients with sickle-cell disease (Figure 5, right). The investigators put these observations in more quantitative terms by looking at the percentage of granulocytes that in fact contained phagocytized pneumococci. In the presence of normal serum, 35 percent of granulocytes contained pneumococci; in the presence of serum from patients with sickle-cell disease, only 10 percent of phagocytes contained bacteria. This defect in the activation of the alternative complement pathway is not specific for pneumococci, and more traditional activators of the alternative complement pathway, such as zymosan, have also been shown to be ineffective in the serum of patients with sickle-cell disease [29].

The component of the alternative complement pathway that is deficient in patients with sickle-cell disease has not been clarified at this time. It is known that when serum from patients with sickle-cell disease is used, normal activation of the classic complement pathway occurs in the presence of specific antibody. The deficiency therefore must involve those complement components that are not shared by the alternative and classic complement pathways. There is some evidence for factor B deficiency in these patients, although there are conflicting results on that observation [30,31]. Because the classic complement pathway is intact, and since this pathway is activated by antibody, it is easy to understand the rationale for giving pneumococcal vaccine to patients with sickle-cell disease to compensate for the defect in alternative complement pathway activation.

Since patients with sickle-cell anemia are functionally asplenic, they would be subject to the same risk of pneumococcal sepsis seen in other asplenic patients [32]. However, the risk of pneumococcal infection appears to be greater in patients with sickle-cell disease, and it is this additional risk that is best explained by the defect in alternative complement pathway activation.

The other infectious disease commonly encountered...