BONE SCANS WITH FLUORINE-18 IN DIAGNOSING OSTEONECROSIS IN DIVERS

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Radionuclide scans are frequently requested clinical procedures because they provide, easily and nontraumatically, information about focal areas of disease in various internal organs. Scans of the skeletal system have achieved clinical acceptance because they demonstrate with considerable sensitivity the presence of primary or metastatic tumors. Considerable interest has developed recently at the University of Texas Medical Branch (UTMB) and its Marine Biomedical Institute in evaluating the sensitivity of bone scans as an additional tool to radiography in the diagnosis of osteonecrosis. Accordingly, some of the Gulf of Mexico divers radiographed by the UTMB for osteonecrosis were also submitted to radionuclide bone-scan surveys.

This type of investigation is possible because of the commercial availability of salts of fluorine-18 (^{18}F), which are safe for human use. This bone-seeking radionuclide has several advantages over the previously used salts of strontium-85 (^{85}Sr). The most significant of them is a markedly reduced radiation dose per millicurie (mCi) to the bone, bone marrow, and total body. In this country, bone scans with ^{85}Sr are permitted only in patients with diagnosed malignancies in whom a search for metastases is warranted. With ^{18}F, on the other hand, it is possible to study with safety a variety of benign disease processes, including osteonecrosis.

The radionuclide used in the UTMB studies was purchased as sterile, pyrogen-free sodium fluoride from Medi-Physics, Inc., in California, where it is produced in a cyclotron by deuteron bombardment of neon (Harper *et al.*, 1971).

The bone-crystal structure shown in simplified form in Fig. 1 demonstrates the mechanism by which radiochemicals can be used as tracers in studies of bone metabolism (Neuman and Neuman, 1958). It is possible to substitute radioactive calcium for the stable calcium normally deposited in bone, but none of the calcium isotopes is suitable for scanning purposes. Therefore, ^{85}Sr and strontium-87m (^{87m}Sr), which follow pathways similar to those of calcium, have been widely used as scan agents (Charkes, 1970; DeNardo *et al.*, 1972).

Fluoride ions, on the other hand, can be exchanged with the hydroxyl ions in bone crystal, as shown in Fig. 1. The process goes through various stages (Neuman and Neuman, 1958). In only a few seconds or minutes, fluoride ions pass from plasma through extracellular fluid to the hydration shell surrounding bone crystal. Rate of transit is limited mainly by the blood supply to a particular portion of a bone. The next step — passage of the ions through the hydration shell to the crystal surface — takes several hours, and actual incorporation into the interior of bone crystal takes days or weeks. But

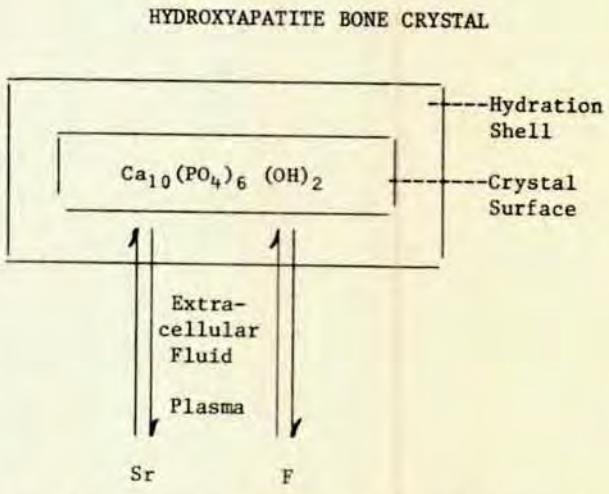

FIG. 1. Simplified schematic of hydroxyapatite crystals, which are deposited in osteoid tissue by proliferating osteoblasts. Arrows show pathways of exchange for the most common bone-seeking chemicals, strontium and fluoride, used for radionuclide scanning.

once the fluoride ions reach the hydration shell, they are sufficiently localized in bone for scanning purposes. At this point, therefore, the distribution of radioactive ^{18}F demonstrates the areas of increased bone metabolism (Blau *et al.*, 1972).

Certain areas in a scan may appear to have greater radioactivity concentration than others, a circumstance thought to be caused either by increased blood supply to that region and/or by increased bone-crystal exposure (Blau *et al.*, 1972; French and McCready, 1967). The latter may be the result of osteoblastic or osteolytic activity in a certain portion of a bone. Osteolytic activity is thought to increase activity in the adjacent bone, and therefore both osteoblastic and osteolytic lesions are demonstrated on a bone scan as areas of increased radioactivity (Blau *et al.*, 1972).

To choose the optimum time to start scanning, one must remember that the uptake of ^{18}F in bone is very rapid, reaching almost maximum within one hour (Blau *et al.*, 1972). On the other hand, only 50% (approximately) of the fluoride becomes concentrated in the skeletal system; the remainder, at this early stage, is still primarily in the blood, which means that some time must be allowed for the blood concentration to be reduced via urinary excretion. This decrease occurs much more rapidly with fluorine than with strontium (Blau *et al.*, 1972). Thus, in addition to the short physical half-life (110 minutes), which permits larger tracer doses, the major advantages of fluorine are its rapid deposition in bone and its rapid clearance from the blood by the kidneys. Compared with the strontium isotopes, fluorine provides much better contrast between focal bone disease and vascular tissues.

The bone-seeking radionuclides used frequently for imaging purposes are compared in Table I. An advantage of ^{85}Sr is its physical half-life of 65 days, making it feasible to purchase the tracer commercially well in advance of intended use. However, the long half-life is also a major disadvantage because it involves protracted radiation exposure to the skeletal system. Since this exposure is significant, ^{85}Sr dosage is generally limited to 0.1 mCi and its use restricted in this country to adult patients with known malignancy (Charkes, 1970). Given the small radioactive dose, the external count rate is understandably low compared with most other modern scan techniques, necessitating rather slow scan speeds and lengthy patient studies. The energy level is somewhat higher than is desirable for imaging, but it is acceptable for rectilinear scanning with properly selected collimators. Strontium's slow blood clearance makes it advisable to wait three to seven days between administration of tracer and performance of the scans. Yet another disadvantage of strontium is that much of it is excreted into the intestinal tract. For examination of the pelvic and lumbosacral region, therefore, the patient must undergo thorough bowel cleansing.

Strontium-87m has a shorter half-life than strontium-85 and can therefore be given in larger

Table I. COMPARISON OF FREQUENTLY USED BONE-SEEKING RADIONUCLIDES

	^{85}Sr	^{87m}Sr	^{18}F	^{99m}Tc
Source	Reactor	^{87}Y generator	Cyclotron reactor	^{99}Mo generator
Chemical form	$SrNo_3$	$SrHCO_3$	NaF	Tc poly-phosphate
Half-life (physical)	65 days	2.8 hr	1.85 hr	6 hr
Photon energy (kev)	513	388	511	140
Dose (mCi)	0.1	4	4	10
Bone localization	30%	30%	50%	40%
Delay	5 days	1 hr	2 hr	4 hr
Preparation	bowel, void	—	void	void
Maximum CPM	2K	—	40K	20K
Radiation dose — bone	3.6r	0.6r	0.6r	0.4r
Radiation dose — marrow	1.1r	0.6r	0.6r	0.1r
Radion dose — body	0.4r	0.2r	0.1r	—

doses — up to 4.0 mCi. Count rates, scan speeds, and radiation exposure to the bone, marrow, and body are within acceptable limits. But its clearance from the blood is very slow, making it more difficult to distinguish focal bone lesions from normal or abnormal vascular regions with elevated count rates (Charkes *et al.*, 1964).

Fluorine-18 overcomes most of these disadvantages. It has a physical half-life of less than two hours, making the radiation exposure quite acceptable for doses in the range of 4.0 mCi. The count rates permit rapid scan speeds. Acceptable scan views can be obtained in a matter of minutes rather than hours. Because excretion is via the urine, the bladder and sometimes the kidneys appear in bone scans. Consequently, a small portion of the pelvis cannot be evaluated completely for focal bone disease.

The value of ^{18}F scans in detecting skeletal abnormalities has been studied mainly in patients with malignant tumors. Scans proved to be in agreement with radiographic findings, or were more sensitive in detecting bony metastases, especially in early stages of disease (Blau *et al.*, 1972). Aseptic necrosis is included in the list of nonmalignant focal bone diseases that may reveal scan abnormalities (O'Mara and Baker, 1973). Little is known about the relationship between stages of development in osteonecrosis and recognizable accumulations of bone-scan tracers. If one were willing to extrapolate what has been described or is known about the mechanisms of scan abnormalities in bone tumors, one would expect that only the more active stages of necrosis would be associated with significant scan findings. This problem deserves further study.

The observations made during the early phase of the UTMB osteonecrosis project involved rapid total-body survey scans and selected regional scans on seven professional divers. The findings in these surveys were compared with roentgenograms made of the same divers, which were interpreted by Dr. Charles Fagan, M.D., and are reported on p. 177 *ff.* of this volume. The scans of two of these subjects will be discussed.

Figure 2*a* shows anterior and posterior total-body scans of one diver. Certain normal areas of fluoride deposition are visible on the anterior view in the skull and facial bones, sternum and sternoclavicular joints, shoulders, bladder, pelvis, and hip joints. On the posterior view, the vertebral column is more easily recognizable, as are the scapulae, rib cage, sacroiliac and hip joints, and, to a lesser extent, the knee joints. A definite abnormal finding is the marked asymmetry of radioactive fluoride concentration in the shoulders; there is much more in the right than in the left. The difference in the pelvic region is more subtle; somewhat more tracer has accumulated in the right ilium and/or the right femoral head than in the contralateral location. The difference, which is more recognizable on the anterior view than on the posterior, is subtle but significant.

X-ray films of this diver revealed evidence of osteonecrosis as manifested by a collapse of the articular cortex and sclerotic and lucent modeling of the right humeral head. There is an associated and complicating osteoarthritis with spur formation (Fig. 2*b*). In location this corresponds to the scan abnormality. A subtle abnormality in the left humeral head seen in the X-ray was not revealed by scanning. X-rays of the hips (Fig. 2*c*) reveal no abnormality.

In the second diver, the difference between the two shoulders in the scan findings is more subtle (Fig. 3*a*). There is slightly more tracer in the right shoulder than in the left. The concentration on the right is not necessarily darker than on the left, but the medium gray area is larger. This difference is so subtle that it was originally interpreted as being within normal limits. The interpretation was made prior to inspection of the roentgenograms. Nothing else on the scans looks asymmetrical or suggests other possible abnormality. But both shoulders of this subject appear abnormal on X-ray, the right much more so than the left (Fig. 3*b*). Radiographs of the hips reveal a lytic lesion in the left femoral neck (Fig. 3*c*).

Of the scans performed on the other four divers, two were normal and two abnormal. In general, correlation between X-rays and scans was similar to that of the first two divers. Wherever a scan showed an abnormality, the X-ray did as well. But several subtle abnormalities were revealed radiographically that were not detected on the bone scans.

Comparison of lesions demonstrated by radiological and scanning techniques suggests that, at this stage of our investigation, scans can detect most areas of aseptic necrosis, but not all. The radionuclide imaging procedures apparently detect early or incipient stages of osteonecrosis. As the disease progresses, however, and scar tissue has formed and blood supply decreased, the scans are less likely to show abnormality than roentgenograms.

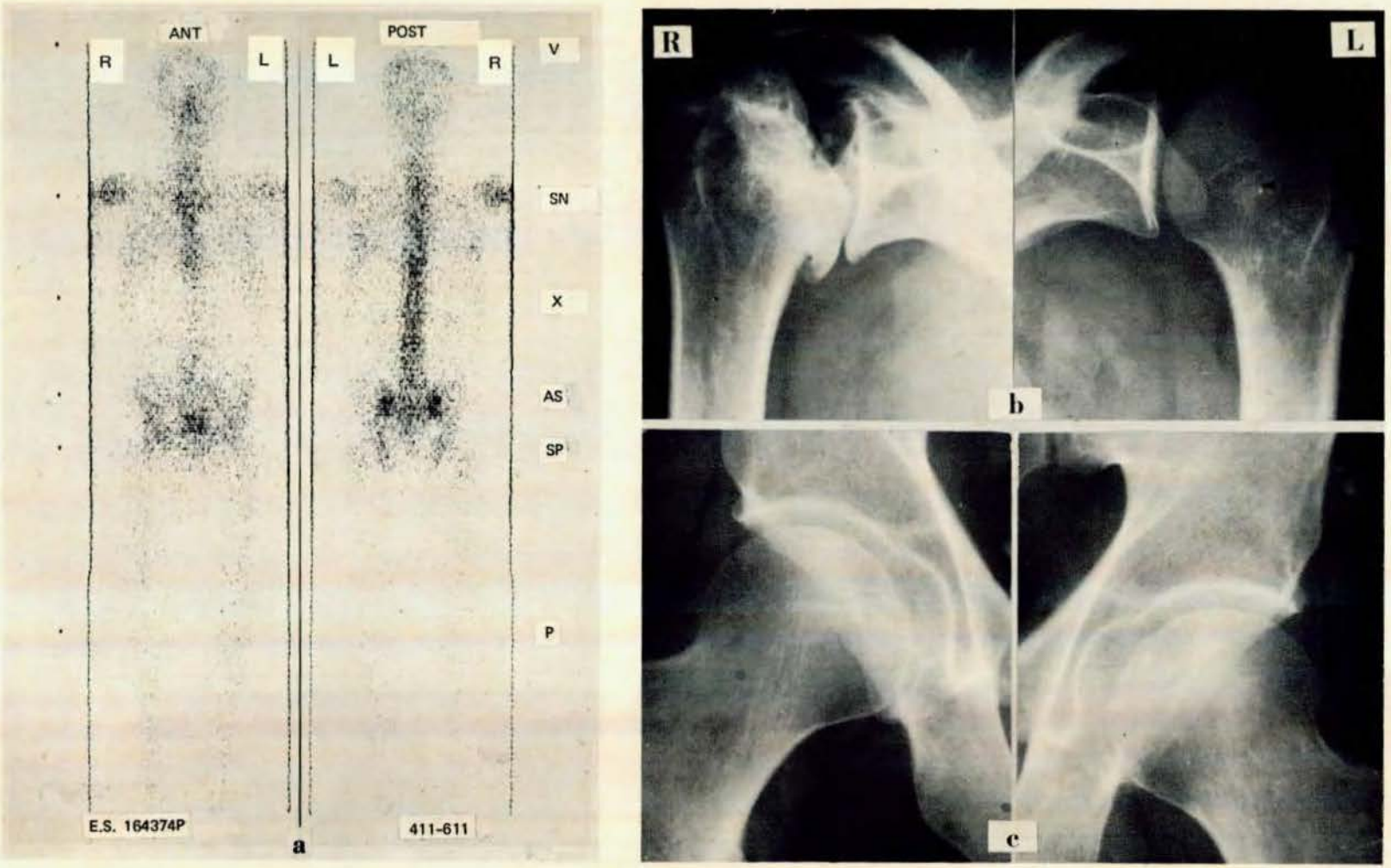

FIG. 2. (*a*) Anterior and posterior total-body survey scans of diver begun 2 hr after an intravenous dose of 2.8 miCi of $Na^{18}F$. Note abnormal areas of increased tracer concentration in R shoulder and in region of R femoral head and/or R ilium. (Abbreviations for anatomic levels: V, vertex; SN, suprasternal notch; X, xiphoid process; AS, anterosuperior iliac spine; SP, symphysis pubis; P, patella.) (*b*) Shoulder radiographs with arrow pointing to abnormally dense area in L humeral head. This area of old osteonecrosis did not appear on radionuclide scans. (*c*) Hip roentgenographs reveal no abnormalities.

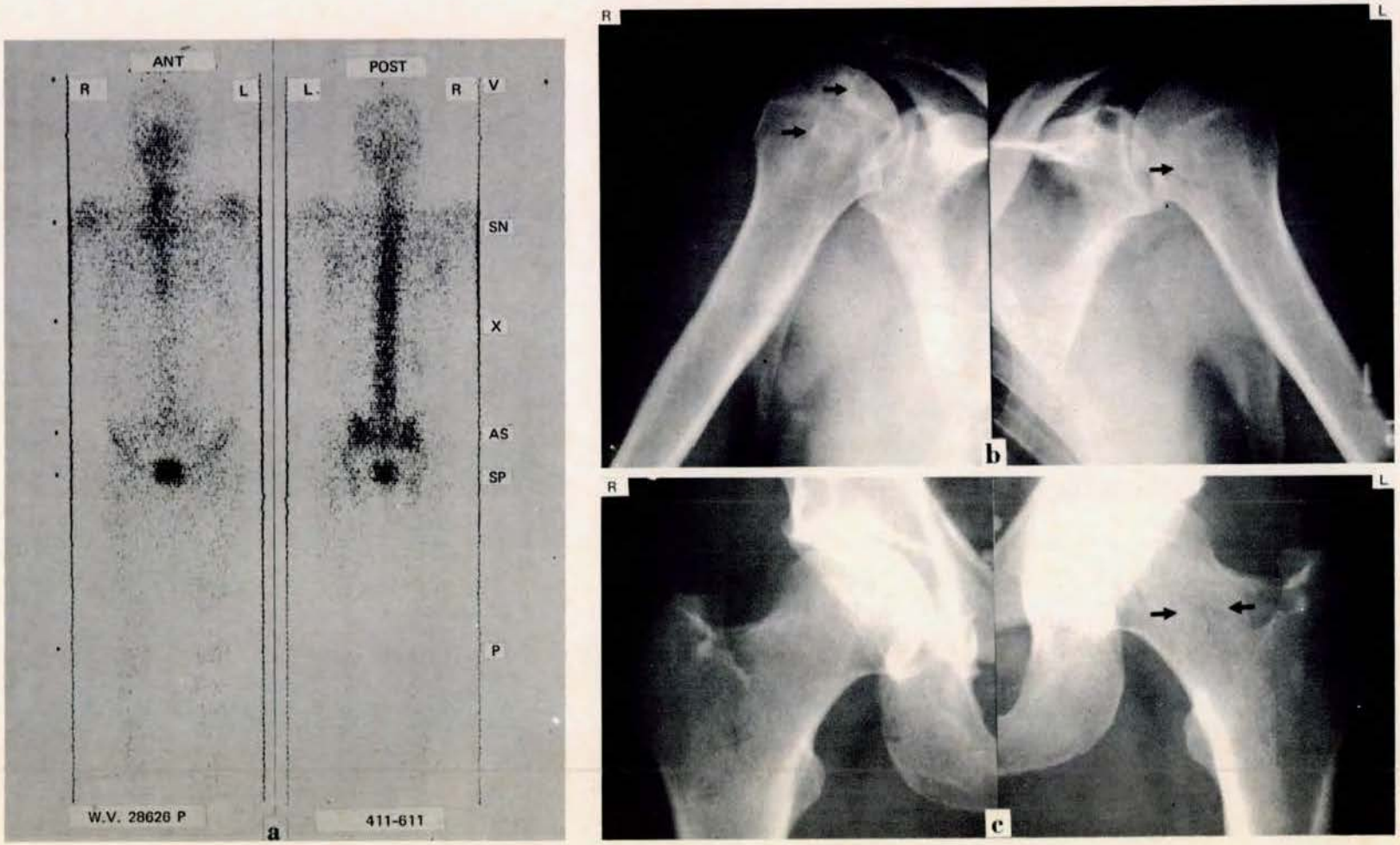

FIG. 3. (*a*) Anterior and posterior total-body survey scans of diver begun 2 hr after intravenous dose of 3.7 mCi of Na^{18}F. Note subtle difference in tracer concentration in the two shoulders. (*b*) Shoulder X-rays revealing radiodensities in R and L humeral heads (arrows). (*c*) Hip X-rays revealing radiolucent area in L femoral neck (arrows).

Scans and radiographs in combination will quite likely enable much more accurate diagnosis of the disease than when one technique alone is used. Experience with serial scans involving larger numbers of divers is required before the actual sensitivity of imaging procedures in detecting various stages of aseptic necrosis can be properly evaluated.

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