Current Practice in Nuclear Medicine

PEDIATRIC NUCLEAR MEDICINE

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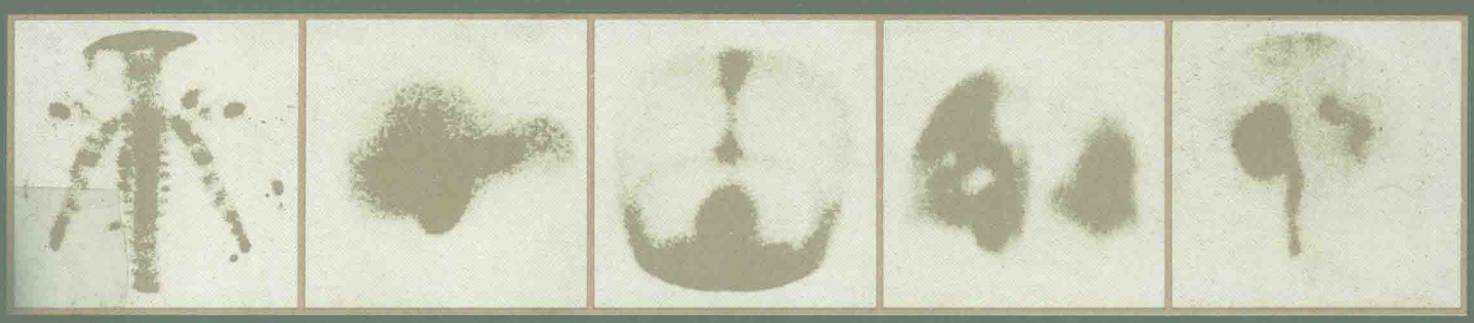

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To my wife Mary

Preface

Major advances in nuclear imaging technology have occurred in recent years. It is now possible to obtain images of excellent spatial resolution and to determine complex organ function. The use of nuclear imaging techniques for the initial diagnosis and serial follow-up of many common and rare pediatric diseases has blossomed. The attractiveness of this method of diagnosis to pediatricians is clear; it is truly noninvasive.

The purpose of this book is to demonstrate to physicians who care for children, pediatricians, surgeons, and radiologists, the great clinical value of nuclear imaging in both the diagnosis and follow-up of childhood diseases. The limitations of this methodology are also enumerated.

An attempt has been made to keep the content consistent throughout the book. The information presented represents the authors' experience of Milwaukee Children's Hospital and Los Angeles Children's Hospital. Both institutions are structured similarly where ultrasonography and nuclear medicine comprise a functional unit. The combined institutions perform approximately 5,000 nuclear examinations on children each year.

Each chapter discusses clinical pediatric problems relating to a specific organ system. The theory and rationale of the procedures as well as pertinent techniques are presented in the initial section of each chapter. These sections are not meant to be exhaustive reviews which are available in many excellent texts of pediatrics or nuclear medicine.

Based primarily on our own experience, helpful hints for preparing the child, the actual performance of the examination, and specific comments concerning diagnostic considerations are reviewed. It is hoped that this text will successfully provide the needed diagnostic information to link nuclear imaging to the daily practice of pediatrics. Such an association will benefit the care of children by expediting diagnosis and treatment.

We wish to thank Seminars in Nuclear Medicine, Clinical Nuclear Medicine, and Journal of Nuclear Medicine for allowing us to use previously published case illustrations. An important contribution was also made by Ruth Brummond, our secretarial assistant at Milwaukee Children's Hospital who helped in locating the case material used in this publication.

PEDIATRIC NUCLEAR MEDICINE

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Chapter 1

Bone Scintigraphy

Since the introduction of Tc-99m phosphate bone-seeking tracers, skeletal scintigraphy has become a routine procedure in pediatrics. It is the most frequent examination performed in a pediatric nuclear medicine department. The technique readily identifies all abnormal regions in the skeletal system where vascularity or osteogenesis is disturbed. The sensitivity of lesion detection is far superior to standard radiography because skeletal scintigraphy identifies pathophysiologic rather than morphologic abnormalities and has been used extensively in children to identify both malignant and benign bone disorders. These changes occur in many diseases that are more common or unique to children and adolescents than adults. Bone imaging offers the most accurate means of establishing an early diagnosis, evaluating extent of disease, and assessing therapeutic response of skeletal disorders that are the result of infection, trauma, vascular insult, bone tumors, metastatic disease, disturbances of growth and development, or congenital lesions.[1–4] Although the basic principles of radionuclide bone imaging apply to both children and adults, the approach to skeletal imaging in children differs substantially because of developmental differences and the unique diseases encountered.

THEORY, TECHNIQUE, AND INTERPRETATION

The factors affecting the exchange or sorption of Tc-99m bone-seeking tracers on the hydroxyapatite crystal and certain other large molecules are vascularity and the rate of growth and remodeling of bone. Sites of rapid osteogenesis, such as the epiphyseal plate region (growth plate), and other regions of rapid bone turnover with a large surface for exchange and sorption usually have high enzyme activity and rapid matrix formation. Bone areas that accumulate tracers to a lesser degree have slow resorption of bone, high acid phosphatase activity, and low metabolic activity.[5–9] Unlike radiographs, which require a reduction of 30 to 50 percent of the calcium content of bone to be visually appreciated, bone-seeking tracers localize in the mineral phase and are significantly less dependent on overall change in calcium content. Capillary permeability, reactive bone formation, metabolic activity, and increased tracer extraction efficiency are factors that contribute to accumulation of bone-seeking tracers in sites of abnormal bone. The major determinant, however, is localized increased bone blood flow.[10–13] Charkes[14] has enu-

merated the mechanisms of abnormal skeletal uptake (Table 1–1). The data provided by bone imaging are not highly lesion specific either positive or negative; the value of the technique is the detection of the lesion rather than the determination of its cause. An abnormal scan must be correlated with clinical history, physical examination, and pertinent radiographic examinations.

To obtain a satisfactory bone scan in a child, it is essential that the child remain immobile during the examination. Because infants and young children cannot always cooperate, sedation may be necessary. As a rule, sedation is not needed for an older child when images are acquired with a gamma camera because the complete study is divided into multiple images. Each interval of imaging is relatively short, and the child is able to relax between imaging periods. If bone images are acquired with a whole body imaging system, sedation may be required for children up to six years of age. Rapport between the technologist and child will lessen the need for sedation.

A dose of 8.3 mCi/m² of bone-seeking tracer is administered intravenously to a well-hydrated child. Delayed images are acquired one-and-a-half to three hours after tracer administration. Skeletal uptake is greater in the growing skeleton of a child than an adult. At two hours postinjection, 40 to 50 percent of the administered dose has been excreted in the urine, thereby resulting in a significant bladder concentration. Approximately 2 to 5 percent of the administered dose is retained in the renal parenchyma, allowing visualization of the kidneys. In general, Tc-99m labeled diphosphonates seem to be better bone-seeking tracers than other phosphate radiopharmaceuticals, including pyrophosphate. Of the diphosphonates, methylene diphosphonate (MDP) is superior to ethylene hydroxydiphosphonate (EHDP) in visual image quality.[15–18] In the following list are the ideal characteristics of a bone-seeking tracer.

1. Readily available.
2. Nonpyrogenic.
3. Lack of adverse reactions.
4. Low radiation dose.
5. No pharmacologic effect.
6. High extraction and uptake by bone.
7. Rapid vascular and soft tissue clearance.
8. Efficient imaging characteristics.

The interpretation of bone images of children is challenging and requires meticulous attention to detail. Bone images are viewed to evaluate bone to soft tissue ratio, assess skeletal symmetry, detect focal abnormalities, assess the kidneys, and detect any extraosseous accumulation of tracer. In addition to the standard criteria used in the interpretation of adult bone scans, interpretation of pediatric images requires knowledge of the age of the child because developmental variations occur from one age group to another. Awareness of the pitfalls in bone imaging is critical.[19] In the metabolically active growth plate, there is increased tracer uptake until closure of the growth plate occurs. This accumulation results in greater radiation dose to this region.[20]

Care must be exercised in the positioning of the child, since minor malpositioning may simulate a focal abnormality. In general, in children under 15 months of age, the epiphyseal-metaphyseal region demonstrates an increase in radioactivity when compared to the adjacent diaphysis. If the extremities are flexed and the growth plate is not perpendicular to the collimator, these regions will assume a globular shape. Kaufman et al.[21] demonstrated that improper positioning of the knee will produce an inadequate demonstration of the epiphyseal-metaphyseal complex due to superimposition of the growth plate on the epiphysis and metaphysis.

After 12 months of age, the growth plate can be identified as a transverse band of increase in radioactivity if the extremity is positioned perpendicular to the collimator. The activity in the metaphysis and epiphyseal ossification center is approximately equal. Although there is a gradual decline in intensity between the

TABLE 1-1
Mechanics of Skeletal Tracer Uptake

Mechanisms	*Example*
1. Reactive bone	Metastasis, infection, fracture, infarction
2. Malignant new bone	Osteosarcoma, chondrosarcoma
3. Heterotopic new bone	Myositis ossificans, pulmonary ossification, cancer (lymph nodes)
4. Decreased bone blood flow	Infarction
5. Increased bone blood flow ("recruitment")	Stroke, sympathectomy, fractures, osteomyelitis, neuropathy, adrenergic drugs
6. Decreased cardiac output	Congestive heart failure, cardiomyopathy
7. Dystrophic calcification	Hypercalcemia, uremia (stomach, lung, kidney, joints)
8. Blood content	Tumors, cellulitis
9. Soft tissue	Aspergillosis, tumor, stroke, synovitis, myocardial infarction
10. Hormonal	Hyperparathyroidism, hyperthyroidism
11. Accretion	Delayed uptake into hydroxyapatite
12. Increased bone surface	Myeloma
13. Destruction without reaction	Tumor, infection, infarction

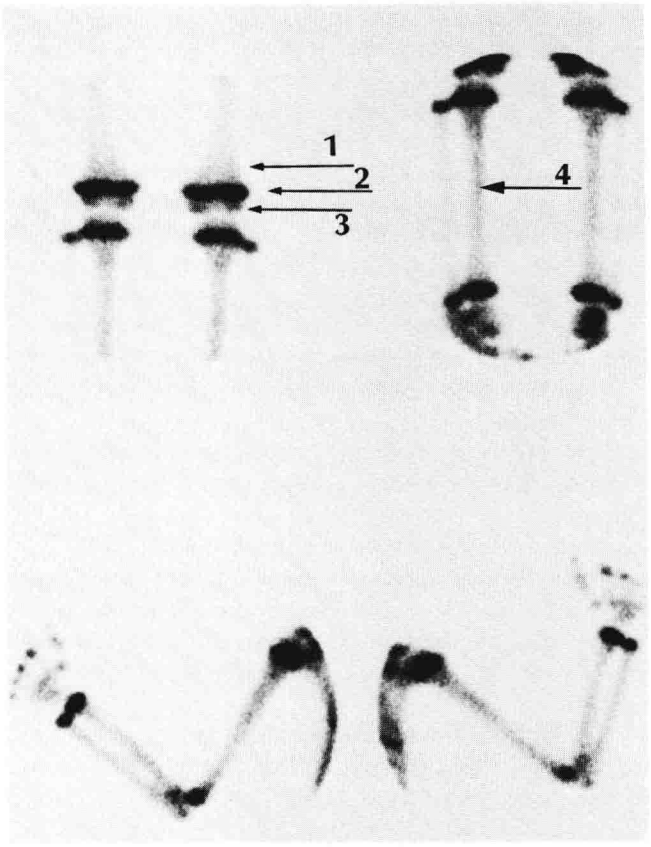


FIGURE 1-1.
Normal bone scan. Age four years. (1) Metaphysis, (2) growth plate (physis), (3) epiphysis. Note that the growth plate is sharply demarcated and uniform in activity. (4) Note slight increase in activity in the midshaft of the tibia.

growth plate and diaphysis, the edges of the growth plate should always be sharply demarcated (Fig. 1-1). Any alteration in the intensity or shape of the growth plate suggests a pathologic process that warrants further investigation. These regions are extremely important to evaluate since they are frequent sites of malignancy, infection, and trauma. Disease processes early in their course cause very subtle changes in the bone image. Additional views are sometimes essential for clarification of an equivocal finding.

In addition to increase in radioactivity in the regions of the growth plate, physiologic preferential uptake may be noted at the base of the skull, the temporomandibular joints, the sutures of the skull, the orbits (Fig. 1-2), the costochondral junctions, and the midshaft of the tibia.

Besides knowledge of the normal scintigraphic anatomy and variation in appearance with age, technical attention to exposure is important. Overexposure of the epiphyseal-metaphyseal complex will result in blooming of the image and can obscure minimal abnormality in these regions.

Proper selection of collimators is an important part of pediatric imaging. The small size of the bones of infants and young children requires the frequent use of pinhole and converging collimators for magnification. This is particularly important when one is obtaining images of the hips[22,23] (Fig. 1-3).

Last, in addition to standard delayed bone images, initial tissue-phase or "blood pool" images are useful in specific clinical situations. This technique will give the physician information about the character of many of the bone abnormalities that occur in children. In general, blood pool images should be obtained whenever the examination is performed to identify a painful region. They have been successful in the differential diagnosis of osteomyelitis, septic arthritis, cellulitis, and bone infarction. Blood pool images are more valuable early in the course of disease, before marked pathophysiologic change occurs. However, the overall yield is not great enough to warrant its routine use other than for the conditions enumerated.

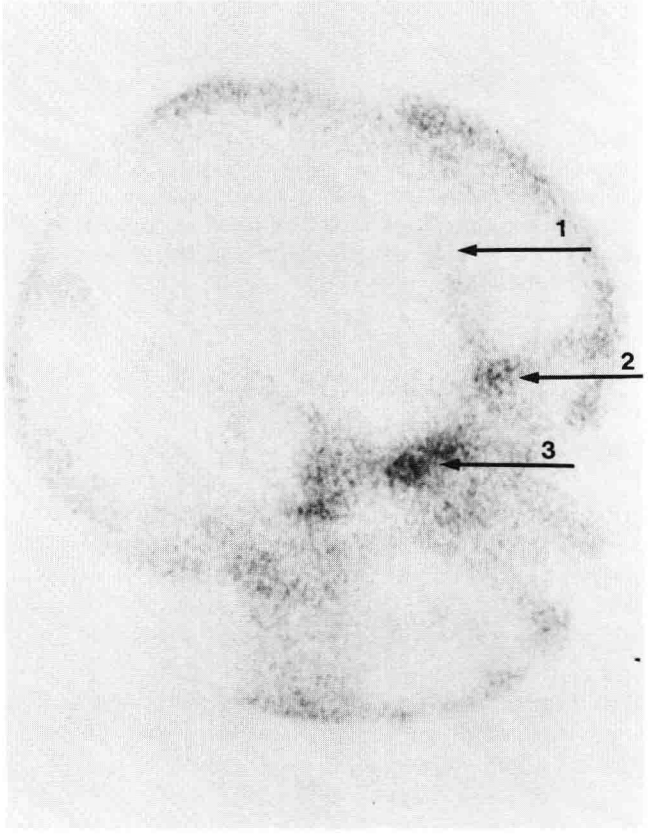


FIGURE 1-2.
Normal bone scan. Skull age six years. (1) coronal suture, (2) orbit, (3) temporomandibular joint.

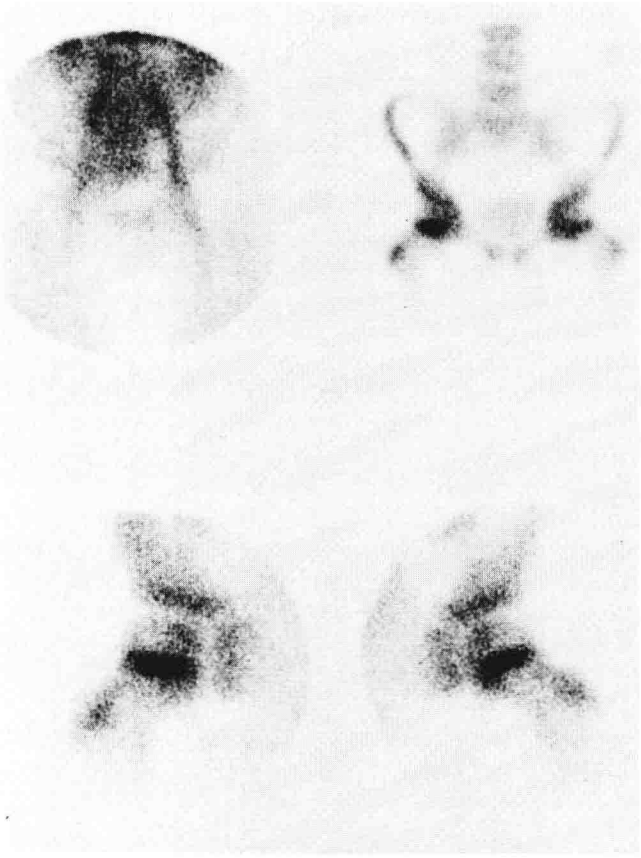


FIGURE 1-3.
Normal bone images of hips. Blood pool (upper left) and delayed images with parallel hole collimator (upper right). Pinhold images (below). Note clear delineation of acetabulum, femoral capital epiphysis, metaphysis, and greater trochanter.

CLINICAL APPLICATION

Bone Tumors

Primary bone tumors constitute less than 1 percent of the malignant disease that occurs in all age groups. In an analysis of 1,000 children with cancer seen at the University of Texas, MD Anderson Hospital and Tumor Institute (Houston, Texas), primary malignant bone tumors accounted for 10 percent of all malignancies and 18 percent of all solid tumors among the children. The mortality data for the United States show that the death rates from bone cancer of all types are 2.87 per million in the 0- to 14-year age group, and 11.97 per million in the 15- to 19-year group.[24,25] The two most frequent primary malignant bone tumors in children are osteosarcoma and Ewing's sarcoma.

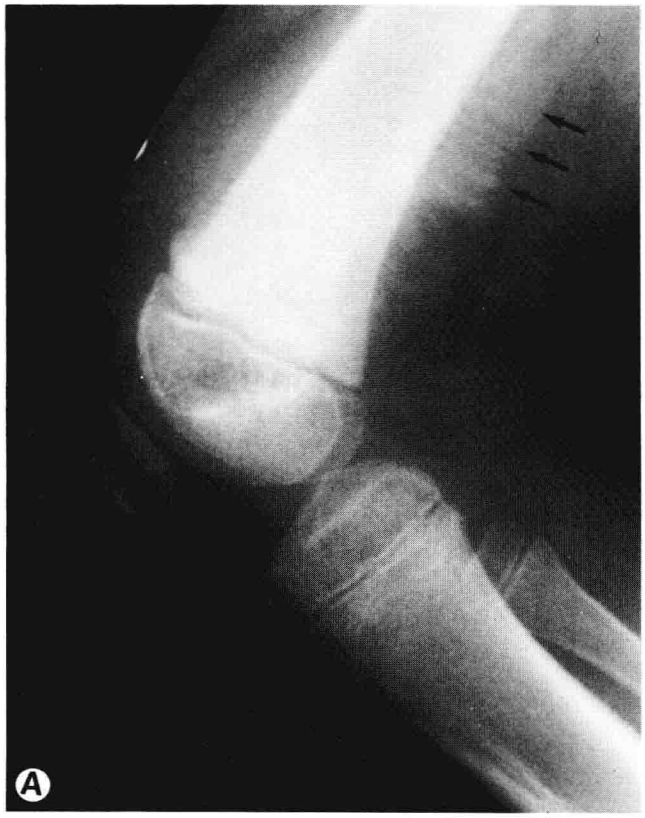
Conventional radiography is superior to other techniques in predicting the nature of a primary bone tumor. Computed tomography is the most effective method for assessing the soft tissue extent of musculoskeletal tumor and consequently has significantly influenced management (Fig. 1-4). In general, computed tomography is more informative than angiography and provides more anatomic detail than ultrasound. Radionuclide bone imaging is mainly of value in detecting unsuspected skeletal metastases in patients with a solitary bone tumor[26] or evaluating the skeletal system if radiographs are normal or equivocal (Fig. 1-5).

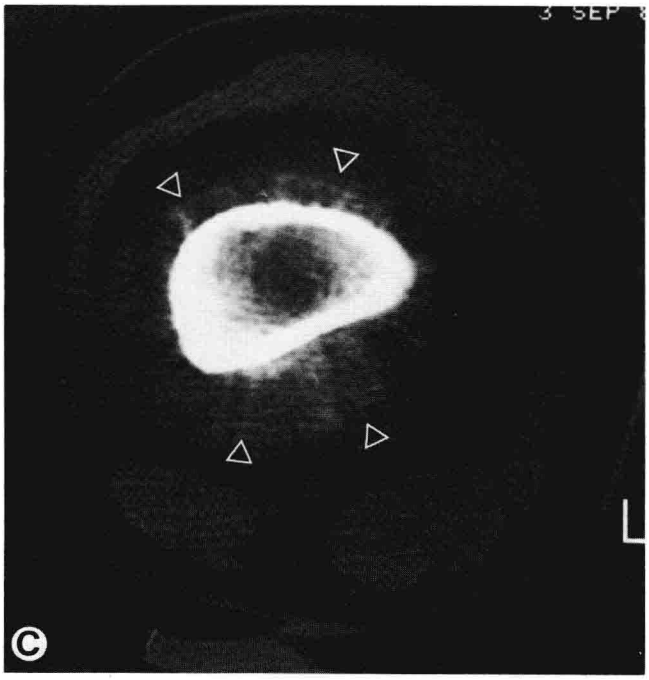
Primary malignant bone tumors are demonstrated with bone-seeking tracers as regions of increased bone uptake and if blood pool images are part of the examination these areas are hyperemic. Scintigraphy does not provide diagnostic information about the pathology of a lesion as does standard radiography. Although bone scintigraphy is not lesion specific, it has a high rate of detection of malignant bone disease. Gilday et al.[27] reported an accuracy approaching 100 percent with bone scanning in the detection of primary malignant bone tumors in children. This has been verified by several clinical studies[28–30]; however, radiography has similar sensitivity.

In the past it was thought that bone scintigraphy provided more information than radiography about the osseous extent of a primary bone tumor. However, vascularity and reaction of the bone to the tumor obscure the boundary of lesion.[31] Goldman and Braunstein[32] reported increased radionuclide uptake in either the affected or unaffected limb in 10 out of 13 patients with osteosarcoma. In five of these, histologic examination of abnormal areas failed to identify malignancy. The abnormal radionuclide accumulation has also been noted to cross joint spaces into the opposed epiphysis. Consequently, one should consider that bone imaging usually exaggerates the extent of a primary malignant bone lesion. Nonspecific and diffuse uptake of radiotracer probably is related to abnormal biomechanics of the skeleton induced by the pain caused by the malignant process.

Benign bone tumors such as osteoid osteoma, nonossifying fibroma, osteochondroma, fibrous dysplasia, giant cell tumor, bone cyst, and eosinophilic granuloma have been successfully detected scintigraphically.[33]

Bone imaging is of particular value in children who have atypical bone pain or pain in the spine, sacrum, hip, or the small bones of the hands or feet. In these circumstances, conventional radiography may be indeterminate. Uptake of tracer may vary from marked to absent in benign bone lesions. It may be necessary to obtain special views with magnification before a painful region can be declared negative. Once the area of involvement has been identified scintigraphically, radiographic tomograms usually, but not always, demonstrate the lesion.[34] If the etiology is not definitely established, biopsy may be necessary.





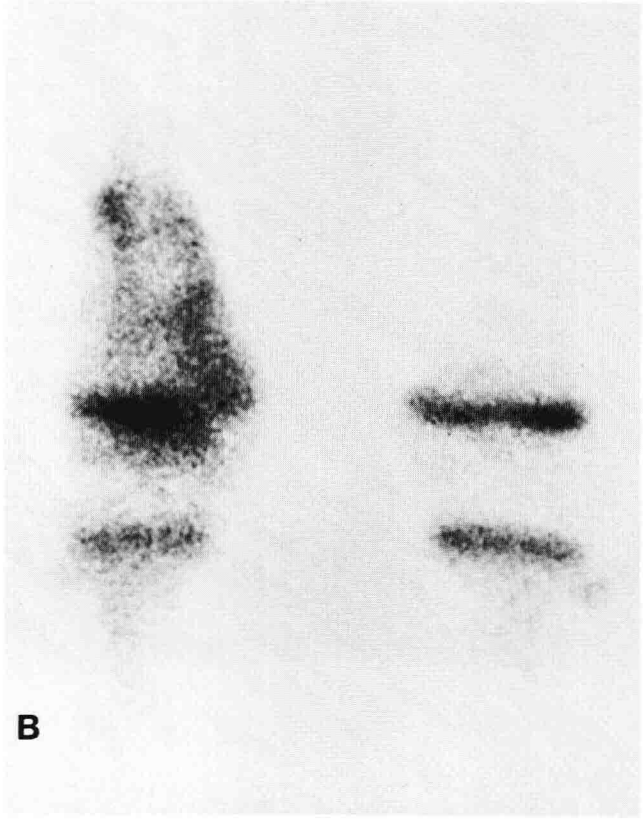


FIGURE 1-4.
A. *Lateral radiograph of knee. Note "sunburst" appearance of osteosarcoma of distal femur (arrows).* **B.** *Anterior bone image. Note increased activity in metaphysis, which extends into epiphysis. Scan appearance is that of a malignant bone tumor. The lesion cannot be further characterized on the basis of the scan.* **C.** *CT clearly demonstrates the soft tissue extent of osteosarcoma (arrows).*

Osteoid osteoma is a benign tumor of bone that was initially described by Jaffe in 1935.[35] It consists of variable calcified osteoid in a stroma of relatively loose vascular connective tissue. Surrounding this osteoid nidus is a zone of "normal" sclerotic bone. This benign tumor constitutes 10 percent of all benign bone tumors.[36] Swee et al.[37] reported 100 surgically proven cases of osteoid osteoma and stated that bone imaging is necessary when no abnormality is visable on the radiographs. In a review of 42 cases, Smith and Gilday[38] found a well-localized area of increased activity at the tumor site in both blood pool and standard two-hour delayed images. The blood pool images, obtained immediately after injection of Tc-99m MDP, showed a small hyperemic lesion in these osteomas. This distinguishes this tumor from other bone lesions that may only show abnormal uptake of tracer after two hours. Similar observations regarding the accuracy of radionuclide bone imaging in osteoid osteoma have been noted by other investigators (Fig. 1-6).[39,40]

In those cases in which scintigraphy is positive and radiography is negative, intraoperative radionuclide ex-

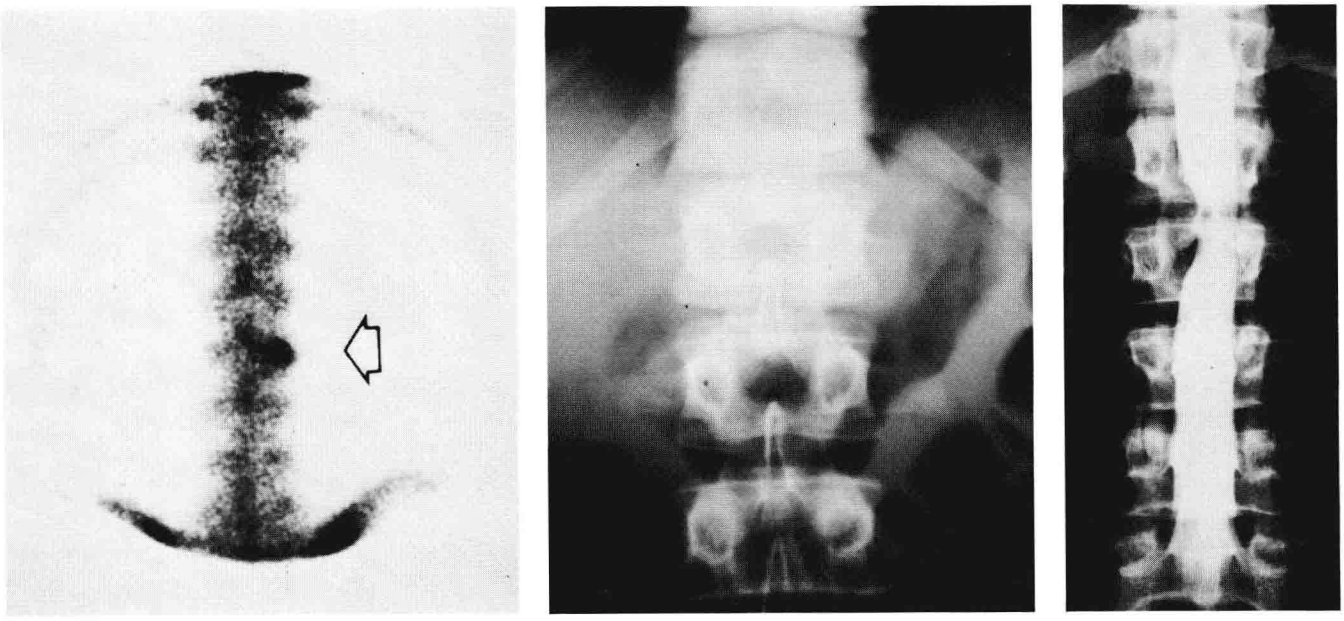


FIGURE 1-5.
Left. *Posterior bone image of cervical spine. Note metastatic lesion from Ewing's sarcoma in L-2.* **Middle.** *Radiograph of lumbar spine is normal.* **Right.** *Lumbar myelogram shows extradural lesion at site of metastasis to right pedicle of L-2.*

amination may be necessary to guide the surgical approach.[41] Infrequently, a bone island may be demonstrated with bone scintigraphy.[42] This is not a surgical disease, and it must be distinguished from an osteoid osteoma on radiographic grounds.

Nonossifying fibroma, fibrous cortical defect, or avulsive cortical irregularity are common lesions found in healthy children between the ages of 2 and 20. Radiographs of the lesion typically demonstrate a well-circumscribed radiolucent area with sclerotic borders located in the posteromedial aspect of the distal femoral metaphysis for the avulsive cortical irregularity or in the metaphysis of other large tubular bones for the other two lesions. Scintigraphy demonstrates minimal or normal uptake of bone-seeking tracers and consequently can aid in distinguishing these lesions from other benign or malignant abnormalities.[43,44]

An osteochondroma generally is visualized by the bone scan only when it is actively growing (Fig. 1-7). This correlates with its cellular activity and vascularity. Multiple endochondromata and exostoses are identified readily as numerous focal areas of increased uptake in the metaphyses.[45,46] Although bone scans cannot identify malignant degeneration as such, they will accurately distinguish growing osteocartilaginous exostoses from those that are quiescent. Scintigraphy is of particular use for lesions that are remote from the skin surface and whose growth might otherwise not be noted. Bone scintigraphy is preferable to conventional radiography for periodic routine follow-up for patients with heredity multiple exostoses because a change in a lesion may indicate malignant degeneration, a recognized complication of this disease.

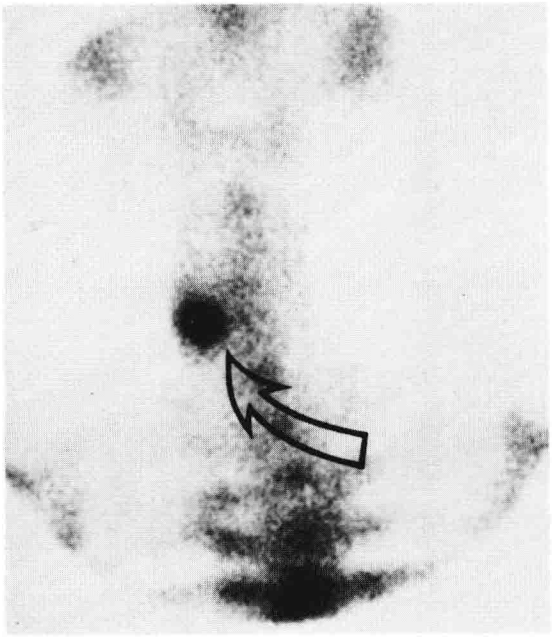


FIGURE 1-6.
Posterior bone image of lumbar spine. Note focal intense tracer accumulation in osteoid osteoma.

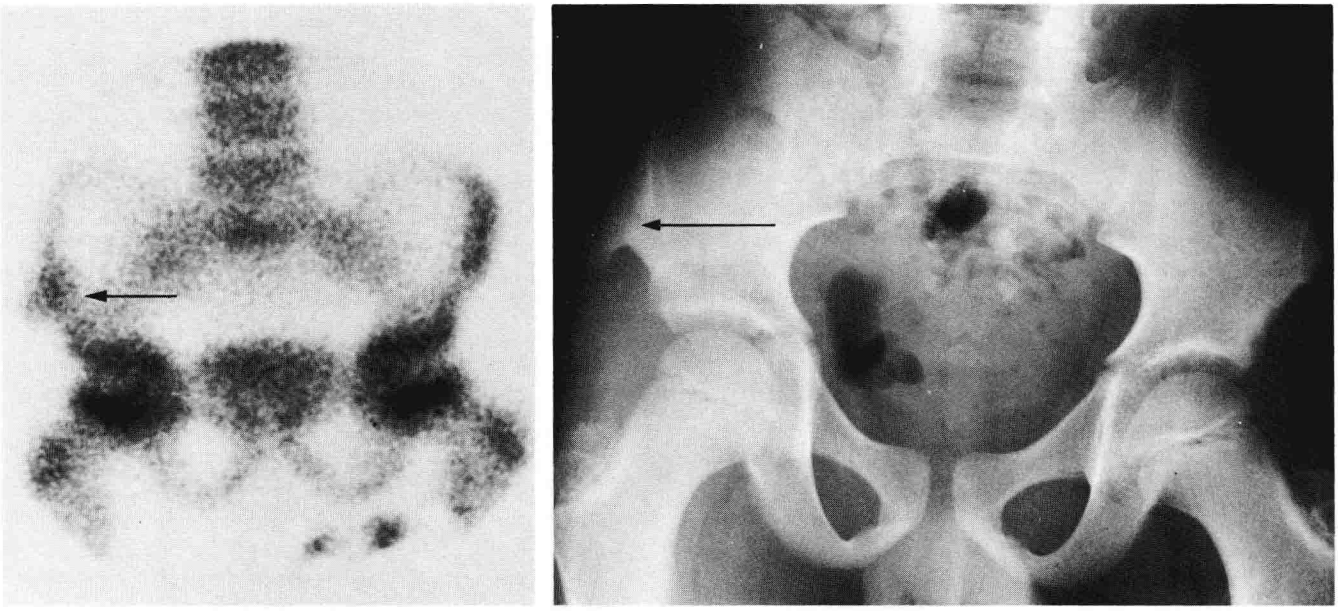


FIGURE 1-7.
Left. *Anterior bone image of pelvis. Arrow marks osteochondroma arising from iliac bone.* **Right.** *Anterior pelvic radiograph. Arrow marks osteochondroma.*

Fibrous dysplasia, a vascular bone abnormality, shows marked uptake of tracer, making it difficult to distinguish from malignant bone tumors, long-standing osteomyelitis, or trauma. Bone imaging will delineate the extent of the lesion and can document postoperative recurrence. Since up to 27 percent of patients with craniofacial fibrous dysplasia have at least one other site of skeletal involvement, scintigraphy can be useful to assess the extent of this disorder.[47,48]

Two types of bone cysts occur in children: the simple bone cyst and the aneurysmal bone cyst. There appears to be no significant difference between these lesions with bone scintigraphy even though each has a distinct histologic appearance. Scintigraphically these lesions show either minimal or normal radioactivity. Gilday and Ash[33] suggests that a simple bone cyst is not "hot" unless it has been traumatized. When a cyst has been fractured, plain radiographs can be normal and tomographic evaluation equivocal, whereas the bone scan is extremely sensitive in determining whether fracture has occurred.

Metastatic Bone Disease

Perhaps the greatest contribution of radionuclide bone imaging is its superiority over conventional radiography in the detection of bone metastases.[49–51] Bone imaging is considerably more sensitive in detecting early osseous abnormality than is the radiologic skeletal survey. In general, the radionuclide examination identifies metastases not visualized by conventional radiography in more than 30 percent of adults with malignancy.[52] Its sensitivity is greater in children with solid tumors. Gilday et al.[27] reported 159 children with malignancy and found that metastases were present in 44, 68 percent being detected only by the bone scan. When a radionuclide bone scan reveals focal abnormal osseous accumulation in a patient with a malignant disease and the cause is uncertain, percutaneous bone biopsy can be performed.[53] The procedure is safe and effective, and a positive biopsy result for malignancy has major therapeutic and prognostic implications.

Detection of distant skeletal metastases from a primary bone tumor significantly alters therapy and consequently a radionuclide skeletal survey is mandatory (Table 1-2).[1,27] This is particularly relevant is osteosarcoma and Ewing's sarcoma.

McNeil[54] reported the experience with osteosar-

TABLE 1-2
Bone Scan Demonstration of Metastases in 1° Bone Tumor

	Gilday et al.[27]	*Murray*[1]
Osteosarcoma	7/19	8/35
Ewing's sarcoma	2/18	8/20
Chrondrosarcoma	1/1	0/8
Fibrosarcoma	0/2	1/4
	10/30	17/67

coma of the Sidney Farber Cancer Institute over a 10-year period. Two percent of the patients had distant bone metastases at the time of presentation. This included children with multifocal osteosarcoma. The use of adjuvant chemotherapy since 1971 has also changed the incidence of bone metastases that develop during treatment. Before current therapeutic regimens, approximately 75 percent of patients developed pulmonary metastases within the first year of treatment, and 50 percent of these later developed bone metastases. The development of bone metastases prior to lung metastases was thought to be very rare. Consequently, bone imaging was used primarily to indicate additional sites of relapse beyond the lung. Of patients treated with adjuvant therapy at the Sidney Farber Cancer Institute over the past five years, 50 percent had lung metastases, but 75 percent developed bone metastases. Sixteen percent developed bone metastases in the absence of or before clinically apparent lung metastases. Approximately 25 percent of all bone lesions were evident by 7 months after initial presentation, 50 percent by 14 months, and 75 percent by 24 months.[55–57] Therefore, careful bone imaging is essential in following the clinical course of children with osteosarcoma (Fig. 1-8).

Bone imaging is also necessary in evaluating a child with Ewing's sarcoma, which shows bone metastases more often than osteosarcoma. Approximately 12 percent of patients with Ewing's sarcoma present with bone metastases, and not all of these have demonstrable lung metastases. During follow-up evaluation, approximately 30 percent will develop bone metastases, half of them in the absence of or before the development of lung metastases,[54] thus making the bone scan a critical diagnostic tool.

In addition to primary bone tumors, other solid tumors of children frequently metastasize to bone; these primary malignancies include neuroblastoma, Wilms' tumor, rhabdomyosarcoma, thyroid carcinoma, nasopharyngeal lymphoepithelioma, retinoblastoma, and hepatoblastoma.

Neuroblastoma is one of the most common malignant tumors in children. Staging is critical in management because bone metastases specifically indicate a poor prognosis, especially in children over the age of one year. Radionuclide bone imaging has proven to be extremely useful in evaluating this tumor. It detects skeletal metastases with greater sensitivity than radiographic studies and frequently identifies the primary tumor.[58]

Howman-Giles et al.[59] reviewed the bone scans of 49 patients with neuroblastoma. Forty-one abnormal bone images were obtained. Seventeen showed tracer accumulation within the primary tumor. Three of 12 children with tumor calcification seen on radiographs failed to concentrate tracer. Bone metastases were evident in 29 children. In 28, areas of focally increased radioactivity were seen and 1 had multiple "cold" areas. In 24 children, the metastases were asymmetric. Radiologic studies were abnormal in only 11 cases. Sty et al.[60] reported detecting bone metastases in 7 of 13 children with bone imaging while the radiographic skeletal survey documented only 4. The metastatic deposits are usually disseminated, but typically involve the metaphyseal region (Fig. 1-9). Because of the usual location of metastatic lesions in the metaphysis, extreme caution must be exercised when viewing this area. Whenever the growth plate demonstrates change in intensity or blurring, metastatic involvement should be considered. Some authors have reported significant false negative radionuclide skeletal surveys.[21] They ascribe the scintigraphic results to small lesion size, lytic radiographic appearance, and metaphyseal location. This underscores the difficulty in detecting small lesions close to the growth plate.

Sty et al.,[60] Spencer,[61] and Fawcett and McDougall[62] reported photopenic lesions due to metastatic neu-

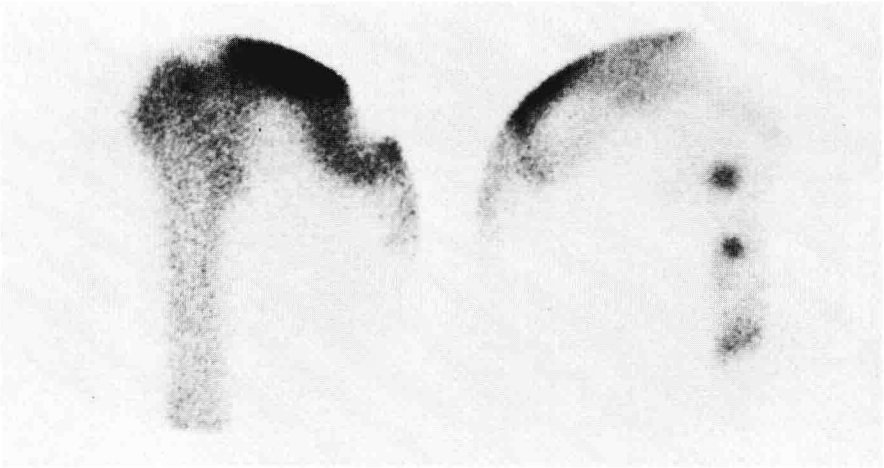


FIGURE 1-8.
Anterior bone images of hips. Patient had amputation for osteosarcoma of distal femur. Note "skip" metastases in stump.