TECHNETIUM - 99M METHYLENE-DIPHOSPHONATE BONE SCAN: MECHANISMS AND CLINICAL APPLICATIONS

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SYNOPSIS

Modern day bone scanning utilises the bone-seeker technetium - 99m methylenediphosphonate. The accumulation of this radioisotope in a piece of bone is influenced by blood flow and bone metabolism, and the final pattern of localisation in the skeletal system provides valuable information about structure and function. Bone scanning complements radiology - the sensitivity of the former complements the specificity of the latter. The experience of the first 100 technetium bone scans in our department has confirmed its greater sensitivity in the detection of skeletal metastases. The increasing use of bone scans in other areas has prompted us to review the mechanics and clinical applications of this modality; examples are drawn from our 100 cases.

INTRODUCTION

Conventional radiology has long remained the most widely used diagnostic tool in diseases of the skeletal system. The excellent anatomical detail provided by radiographs is unsurpassed by any other noninvasive technique. There remains, however, many areas in which greater sensitivity and more information about function and metabolism are required. Xrays cannot detect osteolytic lesions until 30% to 60% of bone has been destroyed. And in many disorders like osteomyelitis, avascular necrosis, inflammatory joint diseases and metabolic bone diseases, radiologically detectable changes occur late and often persist even when the disease process has run its full course. Radioisotope bone scanning attempts to fill this gap by detecting the earliest metabolic changes in diseased bone.

The Technique

10-15 mCi of technetium-methylenediphosphonate (200-300 uCi/kg body weight) is administered intravenously. About half of this dose is rapidly taken up by the skeleton and the rest excreted in the urine. The progressive accumulation of the isotope in the skeleton and progressive elimination of serum activity enables optimal visualisation of the skeleton 3-4 hours after injection. The gamma camera is positioned over the regions of interest and images are obtained with up to 200,000 counts per view. A whole body scan includes anterior and posterior views. This usually takes about 45 minutes to 1 hour to complete.

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The Radiopharmaceutical

The earliest bone seeking radioisotopes were phosphorus-32 and calcium-45. These were subsequently replaced by strontium-85, strontium-87 and fluorine-18. These latter isotopes permitted diagnostically useful imaging but presented problems of high radiation dose or costs. It was the development of technetium labelled phosphate compounds by Subramanian et al (1) in 1971 that transformed bone scanning into a highly sensitive and widely available procedure. The technetium label confers the advantages of widespread availability (far from nuclear reactors and cyclotrons), ideal gamma emission energy of 140 KeV and short half life (permitting higher activity which in turn allows the high count rates necessary for good resolution images).

The radiation dose incurred in the course of a bone scan is small and compares favourably with a full skeletal survey. Table 1 gives us an idea of the radiation risks from these two modalities.

Mechanisms and kinetics of skeletal tracer uptake

The amount of technetium-methylendiphosphonate which accumulates in a specific area of the skeleton is determined by two variables. The first variable is the amount of tracer delivered to that site. Computer perturbation studies of fluoride-18 kinetics in man supports the concept of five compartments (4) as shown in figure 1. The most important single determinant of tracer delivery to a specific site is the blood supply. It was originally thought that there was a proportional relationship between volume of blood flow to a bone and its uptake: that is, if blood flow is doubled, tracer uptake would also be doubled. The experimental work of Sagar, Piccone and Charkes (5), however, showed that there is a limit beyond which an increased skeletal blood flow would only contribute to a minimal increase in tracer uptake. They showed that a four fold increase in femoral artery flow in dogs only increased tibial skeletal uptake by 33%.

It has been suggested that this saturation effect is due to a rate limiting step in the delivery of the tracer. Experimental evidence suggests that the rate limiting step lies in the slow diffusion of tracer from bone extracellular fluid into the bony matrix.

Cutting the nerve supply to a bone, however, raised the limit at which this saturation effect occured. It appears that approximately a third of the arterioles in bone are normally closed by sympathetic vasomotor tone. When this sympathetic tone is interrupted, these "dormant" arterioles are "recruited" and the consequent increase in surface area of bone matrix available for uptake is responsible for the increased accumulation of tracer. This phenomenon has been reported in strokes, after sympathectomy, in peripheral neuropathies and in the reflex sympathetic dystrophy syndrome.

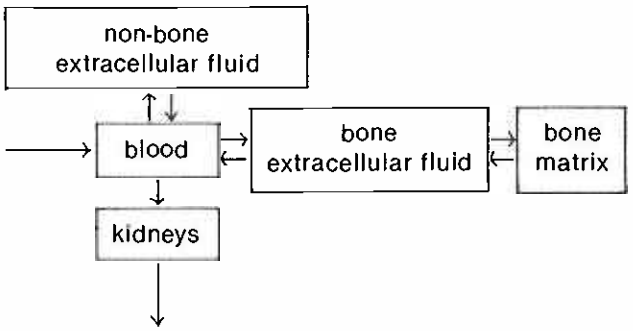


Figure 1: Concept of Five Compartment Kinetics of Fluorine-18 in Man (4)

Table 1. Radiation Doses from Skeletal X-rays and Technetium Bone Scanning (2, 3)

Procedure	Absorbed dose (mrad)		
	Bone Marrow	Male Gonad	Female Gonad
Radiological examination			
Head (including cervical spine)	50	<10	<10
Bony thorax (ribs, sternum, clavicle, shoulder)	100	<10	<10
Arm (including forearm and hand)	<10	<10	<10
Dorsal spine	200	<10	<10
Lumbar spine, lumbo-sacral	200	1000	400
Pelvis	100	700	250
Hip and femur (upper third)	50	1200	500
Lower leg, foot	<10	<10	<10
Full Skeletal Survey	700	2900	1150
Bone scan Tc^{99m} - polyphosphate 10-15 mCi (adult dose)*	375 - 560	400 - 600	300 - 450

*Organ of greatest exposure is the bladder (3,000 - 4,500 mrad if no voiding is assumed).

The tremendous increase in bone tracer accumulation in many disease states could not be accounted for by an increased blood flow. In many cases of Paget's disease the uptake in an affected bone would often be ten times that of normal bone. The second variable in determing skeletal tracer uptake is the avidity of the bone for the tracer. The most "metabolically active" areas take up the greatest amount of tracer and there are suggestions that immature bone has the greatest affinity for skeletal tracer. Nowhere is this ability to reflect "function" better seen than in Paget's disease. New bone formation in response to local insult (from tumour infiltration, infection or fracture) is the basis for the focal abnormalities seen so frequently in bone scans. Merrick (6) suggests that immature bone is associated with well hydrated bone crystals. As bone matures, there is a progressive loss of the hydration shells and the bone interfaces become less and less accessible to bone seeking isotopes. Mature compact bone, therefore, has the least affinity for bone tracers.

Bone scan images: variation of normal and the abnormal

A normal bone scan is characterised by homogenous and symmetrical radiopharmaceutical uptake in the skeleton Region to region variation should reflect thickness of bone and the relative proportion of compact and cancellous bone. Minor increases may be appreciated in joints subjected to increased usage e.g. right shoulder joint. In the growing child, regions of growth will show an increased uptake - this decreases progressively till fusion occurs.

The most common abnormality detected is one or more focal areas of increased uptake ("hot spots"). Certain patterns of uptake are highly specific for certain disorders: a haphazard, asymmetrical pattern of multiple "hot spots" is typical of metastatic bone disease; intense uptake involving large areas of the skeleton or the whole of a bone with curvature in the long axis is seen in Paget's disease; increased pericortical activity in the limbs in hypertrophic pulmonary osteoarthropathy.

Improvements in instrumentation have permitted the detection of "photon-deficient areas" or "cold spots" where a purely osteolytic lesion is surrounded by normal bone. When the blood supply is compromised, radioisotopes cannot reach the area and decreased uptake is expected. In the early phase of avascular necrosis (before revascularisation occurs) decreased uptake is indeed registered and this is the basis for early detection. Bone infarcts are similarly characterised by "photon-deficient areas".

Clinical applications of bone scan

The value of bone scans has been well established in many areas. The ability to demonstrate an osteoid osteoma not seen radiologically or a pseudarthrosis developing after spinal fusion are well known. Table 2 lists some of the current applications of bone scanning. Increasing experience in these areas will continue to redefine its role in relation to radiology, biochemistry, etcetera.

The value of bone scanning is in no way confined to the skeleton - bone seeking radioisotopes will accumulate wherever new bone forms (as in the pulmonary metastases of osteogenic sarcoma (7) or where calcium is laid down (as in dystrophic calcification in necrotic tissues or metastatic calcification in hypercalcaemia (8, 9). Nor is the technetium phosphate compound restricted to the study of bone. As early as 1978 Tc-99m pyrophosphate has been found useful in delineating lower extremity muscle necrosis and perfusion (to help determine amputation level in atherosclerotic peripheral vascular disease) (10).

The increasing use of quantitative measurements and computer processing promises to open a new dimension in bone scanning. Increasing use of whole body counters in determing the sequential body retention of Tc-99m HEDP (11, 12, 13) and the use of bone to soft tissue uptake ratios may provide the first means of quantifying the severity of metabolic bone diseases.

Our intention, however, is to look closer at 3 main areas in which bone scanning has achieved its greatest value viz secondary malignant bone disease, bone infection and exercise related stress fractures.

SECONDARY MALIGNANT BONE DISEASE

By sheer volume of cases and diagnostic yield, scanning for skeletal metastases is the raison d'etat for bone scanning. Of the first 100 bone scans performed in our department 85 were on patients with malignant disease. Table 3 summarises 74 of these patients who had radiological examination (either a full skeletal survey or regional xrays of symptomatic sites) in addition to bone scans. 41 patients had no radiological evidence of metastases and of these, 21 (51.2%) had bone scans interpreted as demonstrating metastases. The value of bone scan was even greater in those patients with nasopharyngeal carcinoma - 11 of 12 patients without xray evidence of metastases had positive bone scans.

We did not encounter any patient with lesions detected by xrays and not by bone scan. This may, however, be a reflection of our restricted sample of patients. When both xray and scan were positive, a high proportion of the patients had many more metastases demonstrated on bone scan.

One patient had an equivocal bone scan and equivocal xrays - there were features of hyperparathyroidism, some of which could also result from osteolytic metastases.

It is now widely accepted that radioisotope bone scan is the most sensitive method currently available for the detection of skeletal metastases Galasko (31) and Citrin et al (32) have convincingly demonstrated the greater accuracy and sensitivity of bone scan in comparison with radiological skeletal survey.

Citrin et al (32) studied 372 patients with known malignant disease. Out of a total of 260 patients with no evidence of metastases on skeletal survey, 63 (24%) had positive bone scans. Of those with both positive bone scans and positive skeletal surveys, almost half had scintigraphic evidence of additional metastases not seen on xrays. Followup studies by other workers showed that the scan abnormalities

Table 2: Indications for Bone Scanning

Diseases	Indications for scan	Comments
INFECTIONS & INFLAMMATIONS		
acute osteomyelitis	- early detection	- greatest value in absence of classical signs and symptoms - least value in neonatal osteomyelitis - of special value in the axial skeleton
	- differentiation from cellulitis or septic arthritis	
chronic osteomyelitis	- detects resurgence of infection	
osseous sarcoidosis	- detects bone involvement	- not known if it carries the same prognostic significance as xray lesions (14)
TRAUMA AND THEIR COMPLICATIONS		
stress fractures	- early confirmation of clinical diagnosis	
battered child	- diagnosis	- scintigraphic evidence of a fracture may persist for up to 1 year (15) - has been suggested as a screening test
pseudarthrosis	- detection	- of particular value after spinal fusion
delayed union or non-union	- prediction of response to intervention	- findings useful in predicting success of percutaneous direct current electrical stimulation (16)
avascular necrosis following fracture	- early detection	
NON-TRAUMATIC VASCULAR DISORDERS		
Perthe's disease	- early detection (17)	
bone infarction		
BENIGN BONE TUMORS		
osteoid osteoma	- detection in absence of xray changes	
MALIGNANT BONE TUMORS AND THEIR EXTRA OSSEOUS METASTASES		
osteosarcoma	- delineate extent of tumor and its skeletal metastases - detection of pulmonary metastases	- problem of extralesional uptake adjacent to tumor (18) - most cases are detected earlier by xrays but small diffuse metastases may be seen only on bone scan (7)
multiple myeloma	- detection	- "purely osteolytic" lesion may only be seen in xrays (19, 20)
SECONDARY MALIGNANT BONE DISEASE (Skeletal metastases from extraosseous malignancies)		
bone-seeking tumors (breast, prostate, kidney, lung)	- staging of disease - baseline for future scans - serial scans to evaluate response to therapy	- purely osteolytic lesions (rare) may not be detected by current equipment (21)
JOINT DISEASES		
rheumatoid arthritis (22, 23)	- detects subclinical joint involvement - objective evaluation of drug-therapy in clinical trials	- useful in relatively inaccessible joints
sero-negative arthritides	- assessment of sacroiliac joint (24)	
post protheses pain	- detection of loosening and infection	
METABOLIC BONE DISEASE		
osteomalacia (25), hyperparathyroidism (26), renal osteodystrophy (27)	- detects presence of a metabolic bone disease and some of its complications (28)	- current quantitative measurements cannot confidently differentiate the different metabolic bone diseases (25, 12, 13)
Paget's disease of bone	- define extent of involvement and stage of evolution of disease (29)	
MISCELLANEOUS		
bone grafts	- assess viability	
Caisson's disease of bone	- surveillance of deep sea divers to detect sub-clinical disease (30)	
metastatic calcification	- diagnosis and assessment of response to therapy (8, 9)	

Table 3: Results of Radiological Examination and Bone Scans in 74 patients with established Malignant Disease

Disease	X-ray Negative			X-ray Positive		X-ray Equivocal		
	No. of patients	Bone Scan negative	Bone Scan positive	No. of patients	Bone Scan positive	No. of patients	Bone Scan positive	Bone Scan equivocal
Nasopharyngeal Carcinoma	12	1	11	5	5	2	2	0
Carcinoma of Breast	9	6	3	7	7	2	1	1
Carcinoma of Lung	4	3	1	4	4	0	0	0
Colo-rectal Carcinoma	4	2	2	1	1	0	0	0
Metastatic Disease from unknown primary	1	1	0	3	3	0	0	0
Osteosarcoma	2	1	1	1	1	0	0	0
Soft Tissue Sarcomas	1	0	1	1	1	1	1	0
Carcinoma of Kidney	1	0	1	1	1	0	0	0
Carcinoma of Cervix	2	2	0	0	0	0	0	0
Giant Cell Tumor	0	0	0	2	2	0	0	0
Carcinoma of Prostate	2	1	1	0	0	0	0	0
Others	3	3	0	3	3	0	0	0
Total	41 (100%)	20 (48.8%)	21 (51.2%)	28 (100%)	28 (100%)	5 (100%)	4 (80%)	1 (20%)

could precede symptoms or xray changes by 3 months to 18 months.

By 1975 it had become evident that many cases of clinically early breast carcinoma (considered "curable" by local surgical treatment) had already spread to the bones. Could this be one of the major reasons why 10-20% of patients with stage I or II carcinoma of the breast fared badly even after extensive surgery? Galasko (31) studied 50 patients with "early" breast cancer. All these patients (except 2 with T_3 tumors) had T_1 or T_2 tumors, N_0 or N_1 lymph nodes, and normal radiographic skeletal survey, chest xray and liver function tests. A quarter of these patients had positive bone scans and none of them were alive and free of disease 5 years after mastectomy. Of those with negative bone scans, two-thirds were alive and free of disease 5 years after mastectomy. The grave prognostic implications of a positive bone scan in breast cancer has been further confirmed by McKillop (33) who demonstrated a very poor short term prognosis when a positive scan was reported in clinical stage I or II disease. The reported incidence of positive scans in early breast cancer varies from 6% to 30%.

The value of bone scans in the initial assessment of carcinoma of the prostate has also been verified. McGregor et al (34) studied 50 newly diagnosed cases of prostatic carcinoma. Bone scans revealed the presence of skeletal metastases in almost half of these patients while radiological skeletal survey was positive in only 12% and serum acid phosphatase levels were elevated in only half of those patients with positive bone scans.

Many centres now consider it important (33, 35) to perform a bone scan in the initial assessment of a patient presenting with a "bone-seeking" malignancy (e.g. breast cancer, prostatic cancer, lung cancer). The clinical worth of some therapeutic trials is now open to criticism as bone scan was not incorporated into the protocol. Gerber et al (36) consider pre-operative scanning combined with sequential post-operative scans "one of the most sensitive indicators of evolving metastatic disease". The suggestion of serial scans, however, raises tremendous problems in logistics and costs.

The value of bone scans in nasopharyngeal carcinoma has not been well defined. In a study of 340 patients with confirmed nasopharyngeal carcinoma, Tan and Oon (37) established an incidence of 17% on the basis of clinical and radiological evidence. They took xrays of localised regions (not skeletal surveys) only on clinical suspicion of metastases (symptoms of local pain or neurological deficits from cord compression).

This predilection of nasopharyngeal carcinoma for bone metastases has been further confirmed by Khor et al (38). They studied 352 consecutive cases of nasopharyngeal carcinoma and obtained an incidence rate of 13.6% for bone metastases (based wholly on clinical examination and radiology). Of those patients with bone as the single organ of metastasis, median survival was 3 months 4 days. The incidence of positive routine bone scans can be expected to be 2 to 3 times this figure for a large group of similar patients at various stages of the disease.

The value of bone scanning in a patient with radiological evidence of skeletal metastases at one or more sites is a subject of considerable debate. Can the additional information justify the costs. Additional information about the extent of skeletal involvement can certainly help the radiotherapist in planning treatment fields. When the primary site is unknown, bone scanning may reveal other areas more accessible to biopsy. The ability of serial bone scans to monitor response to chemotherapy or hormonal therapy has not been sufficiently tested to recommend its use on a wide scale. Indeed, the ability of any method to accurately assess response to chemotherapy has been questioned (39).

The grave prognostic and therapeutic implications

of a positive bone scan in malignant disease imposes a heavy responsibility on the physician who performs and interprets the scan. The reported incidence of false-positive bone scans in assessing skeletal metastases varies from 1% to 6%. While McGregor et al (34) experienced no difficulty in distinguishing benign bone disease for metastatic prostatic cancer, Citrin et al (32) had a 5.3% incidence of false positive scans from 75 control subjects (half of these false positives were due to localised areas of Paget's disease in the pelvis. The incidence of false negative scans is lower and arises chiefly from purely osteolytic lesions. Improvements in imaging techniques, however, are permitting the detection of osteolytic lesions as "cold areas" (21). Careful interpretation with full clinical history and radiographs of solitary abnormal areas can decrease the incidence of false-positives.

The commonest diagnostic dilemma occurs when a solitary abnormality is detected in the bone scan of a patient with an extraosseous malignancy. Corcoran et al (40) reviewed the bone scan of 1,129 patients with extraosseous primary malignancies and found solitary abnormalities in 15% (172 cases). The aetiology of this scan abnormality was established by biopsy or followup in 90 cases: two-thirds were due to metastatic disease and one-third due to benign bone disease (degenerative bone disease, monostotic Paget's disease, healing fracture etc). 80% of the solitary abnormalities in the axial skeleton were due to metastatic disease compare to 17% of rib lesions. The presence of pain and tenderness on examination of the abnormal site was found to be a fairly reliable indication of metastatic disease (23 of 25 patients with these features proved to have metastatic disease).

It is clear that the greatest disadvantage of bone scanning is its non-specificity. We wait eagerly for the development of a truly tumor specific radioisotope. Figure 2 suggests an approach to the use of bone scan in extraosseous malignancy.

BONE INFECTION

Early and adequate chemotherapy is the cornerstone of success in the treatment of acute osteomyelitis. The absence of early radiological changes is a hindrance to early diagnosis and therapy must often be started before blood cultures or cultures of aspirates from the septic focus becomes available. This problem has been compounded by increasing awareness that osteomyelitis can exist without positive cultures or xray changes when appropriate therapy has been started early. Bone scanning has achieved considerable success in this area (41).

The scintigraphic detection of osteomyelitis hinges on two consistent features of bone infection. Firstly, there is a reactive hyperaemia. This is usually limited to the septic region of the bone but sometimes extends into the surrounding soft tissues. This can be seen on the "blood pool" image obtained immediately after intravenous administration of the isotope. Secondly there is bone destruction and new bone formation proceeding side by side. The newly formed or immature bone takes up activity intensely and 2 to 4 hours later, an intense focus of activity appears (on what is known as the "delayed bone" image).

In May 1975 Gilday et al (42) had considerable success in the use of combined blood pool and delayed bone imaging in the differential diagnosis of childhood osteomyelitis, cellulitis and septic arthritis. He based his interpretation of the scans on the pattern of uptake in bone as well as the surrounding soft tissues.

In their series, 70 out of 71 children with acute osteomyelitis had positive bone scans. They recommend bone scanning as the most reliable investigation in early osteomyelitis (especially of the axial skeleton).

Six months later, Duszynski et al (43) reported on 19 patients with acute osteomyelitis - 18 of them had positive bone scans while only one had radiological evidence. However, this degree of accuracy could not be reproduced in neonatal osteomyelitis. Ash and Gilday (44) studied 2 groups of infants over a 4 year period. The first group were neonates with onset of disease within 30 days of birth - the accuracy of bone scan by site was only 31.5% (6 out of 20 proven sites). The second group of infants were aged 40 days to 1 year with onset of disease after the neonatal period - the bone scans were positive in all 19 infants subsequently proved to have osteomyelitis (and there was no false negative). They feel that neonatal osteomyelitis is a different disorder from that seen at older age groups and would not recommend bone scan if onset of disease is within 30 days of birth.

Increasing experience from various centres suggests that there is a wide spectrum of scan abnormalities in osteomyelitis (45, 46). This is related to the intensity of the initial inflammatory response and the degree of bone destruction and formation. In acute, severe osteomyelitis, the rise in intraosseous pressure may produce local ischaemia and prevent delivery of tracer to the site. This may produce a faintly visualised lesion or even an area of decreased uptake.

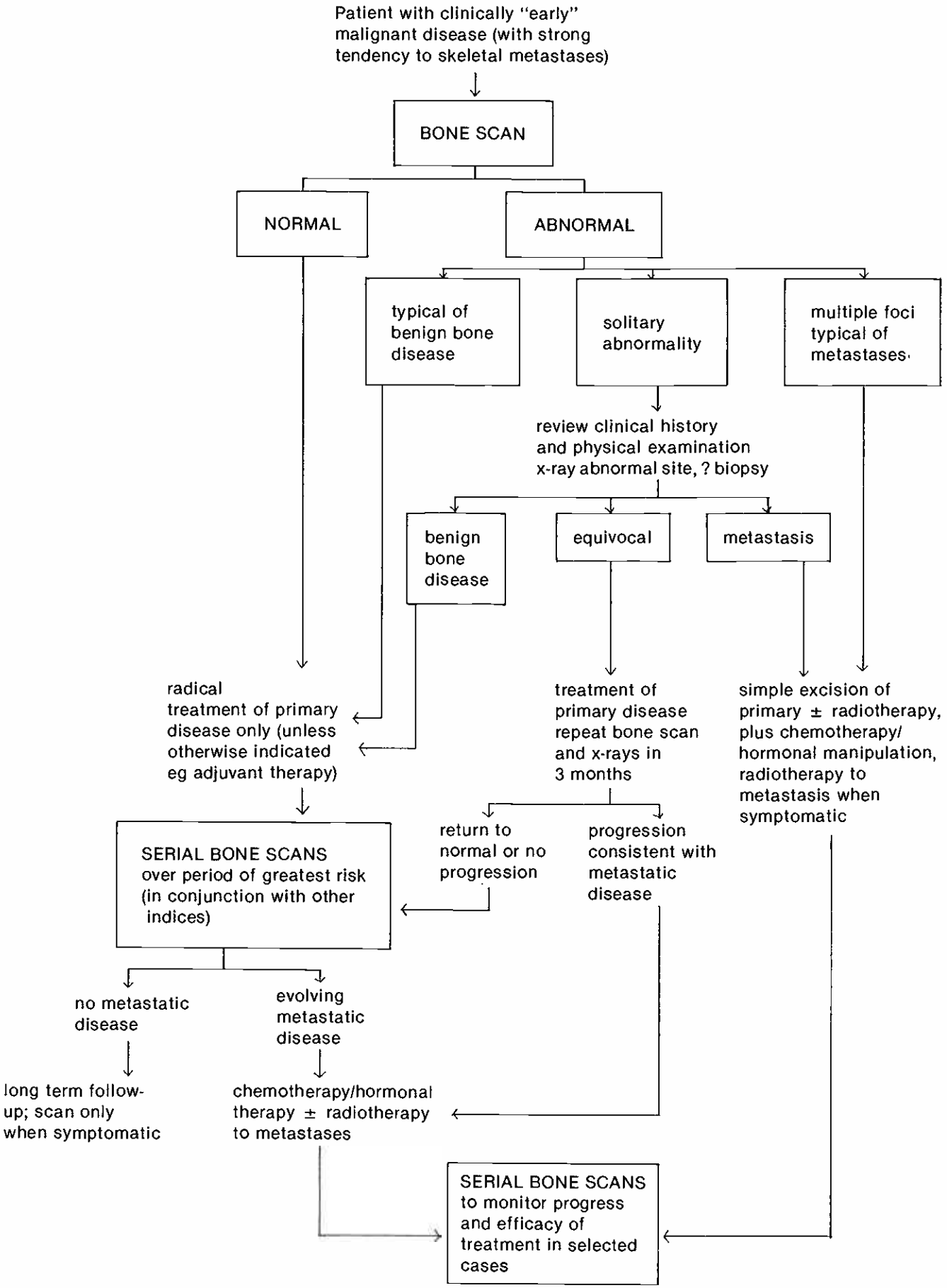
Most workers are agreed on the following:

- an early negative bone scan (absence of an intense focus of activity) does not rule out osteomyelitis. A scan repeated 3-4 days later may show the full blown features.
- bone scanning is most useful in the absence of classical signs and symptoms. The less severe the local symptoms (or when these are masked by indiscriminate use of antibiotics) the more likely it is to obtain a positive scan.
- Bone scans are also most useful in areas difficult to evaluate by xrays or clinical means (e.g. axial skeleton, sacroiliac joint).

STRESS FRACTURE

Military service and increasing health-consciousness invariably leads to an increase in the incidence of exercise related stress fractures. Fortunately, most stress fractures heal well without complications. The complications (and considerable misery in the new military recruit) arise when the undiagnosed fracture is subjected to continuing stress. An undiagnosed

FIG 2 AN APPROACH TO THE USE OF BONE SCAN IN THE MANAGEMENT OF MALIGNANT DISEASE WITH A STRONG TENDENCY TO SKELETAL METASTASIS



femoral neck stress may then proceed to complete fracture with displacement.

The absence of early xray changes is well known. Radiological signs of new bone formation may be delayed for 3 weeks or longer. The role of bone scan is to establish or exclude a diagnosis of stress fracture early.

Wilcox et al (47) evaluated bone scanning in 34 patients with a clinical diagnosis of stress fracture of the lower extremity. They found bone scans to be highly sensitive and they encountered no false negative. They felt that a normal bone scan in the appropriate clinical setting excludes the diagnosis of stress fracture and the patient can be treated symptomatically only.

Mills et al (48) demonstrated the superiority of bone scan in the diagnosis of stress fracture of the shin splint variety. Their scans were able to demonstrate a discrete focus of hyperactivity at the site of origin or insertion of a particular muscle. This excellent anatomical detail permitted planned rehabilitation programmes that minimise the use of the muscles concerned. The implications of these studies for professional and amateur athletes are clear.

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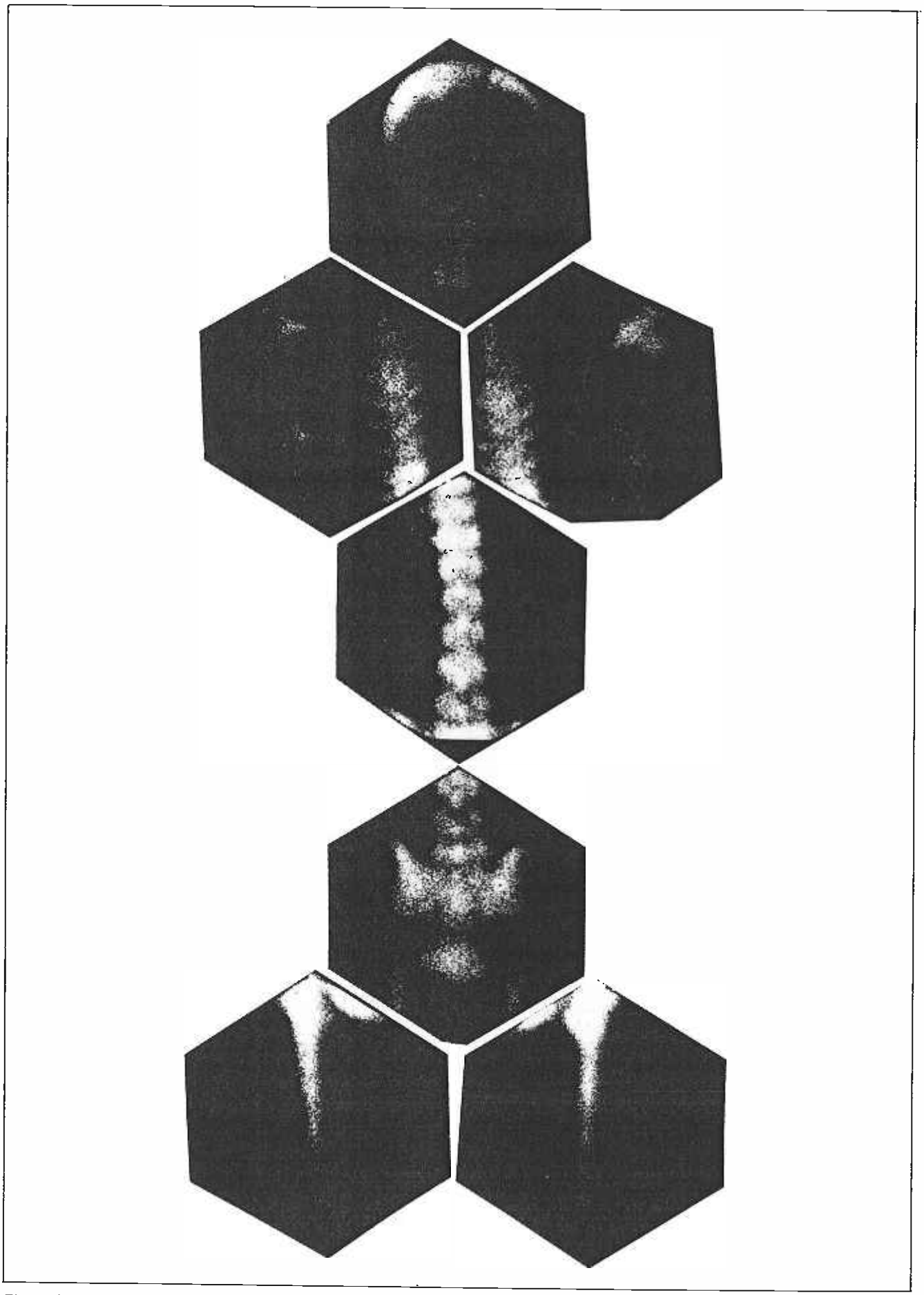

Figure 3: Bone Scan of a 38 year old male with skeletal metastases from nasopharyngeal carcinoma. Multiple hot spots are demonstrated in the parietal bones, both femurs, thoracic and lumbar vertebrae, and the sacrum.

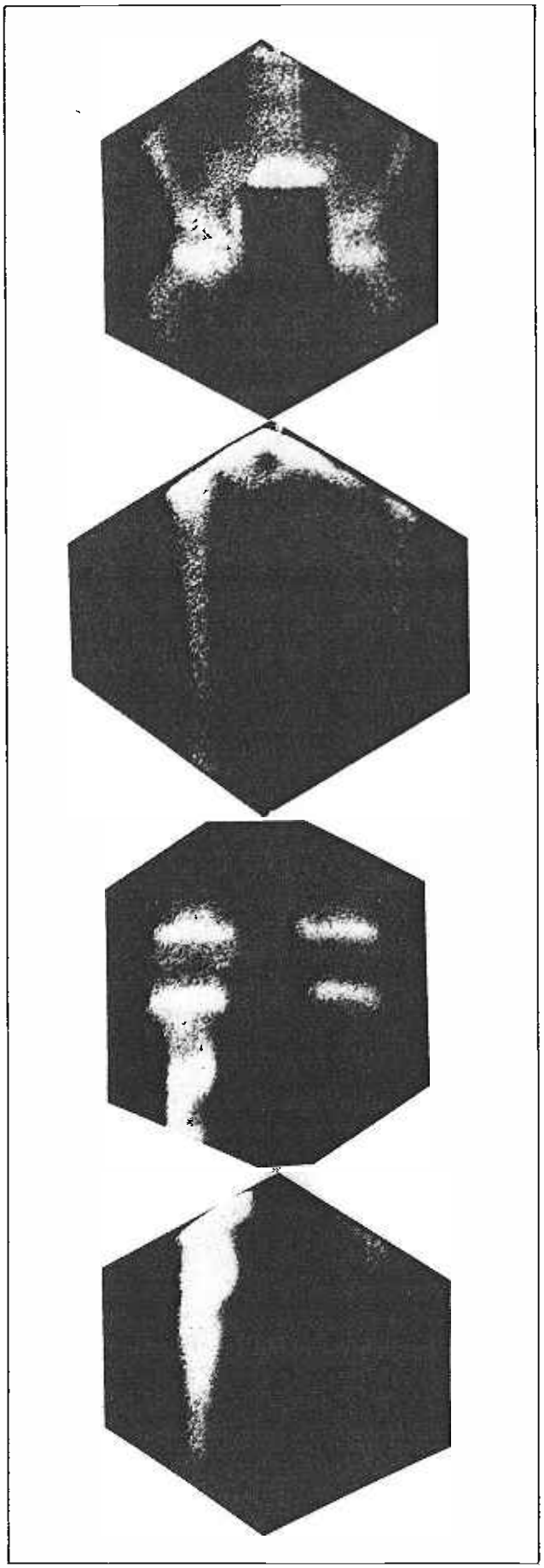

Figure 4: Osteomyelitis of the right tibia in a 11 year old boy. Note the intense activity extending along the marrow cavity. The epiphyses are clearly defined.

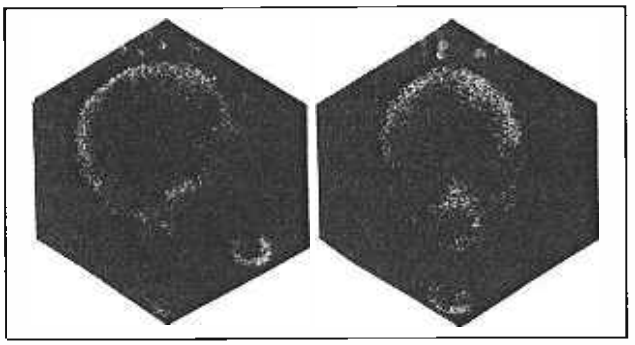

Figure 5: Giant cell tumour of the mandible with the "doughnut" sign on bone scan.

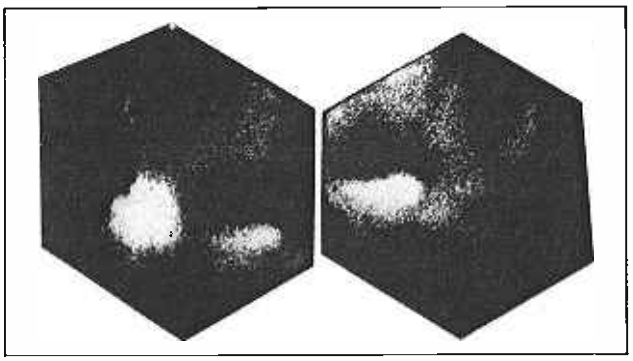

Figure 6: Late features of avascular necrosis of the right femoral head are seen in this patient. The activity reflects revascularisation and new bone formation.

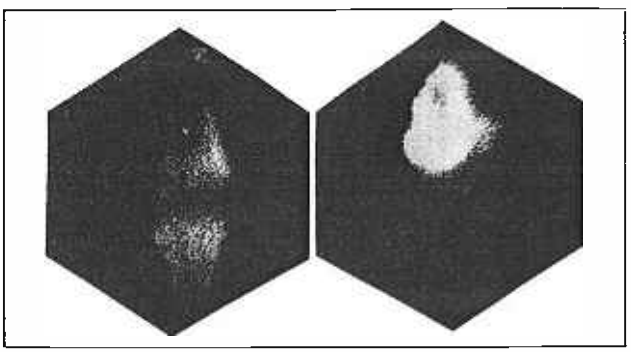

Figure 7: Intense uptake of bone-seeker by osteogenic sarcoma of the lower end of the left femur.

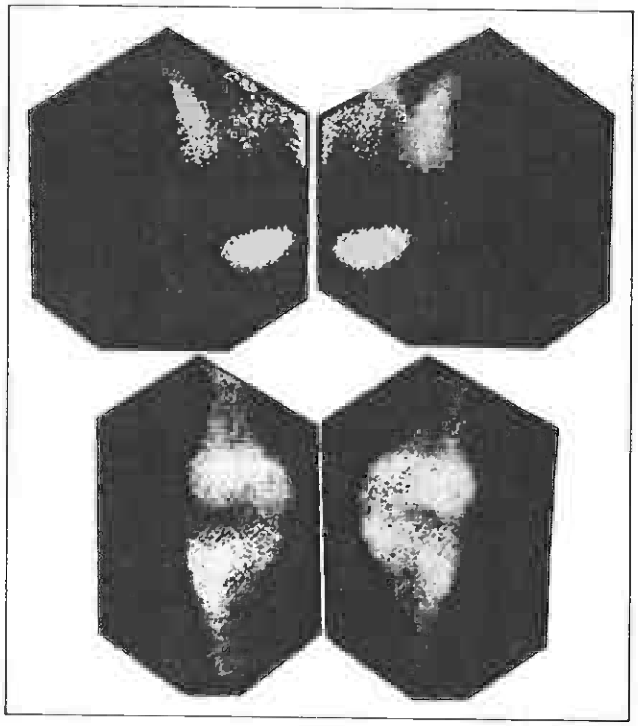

Figure 8: Bone scan of a 28 year old man with disseminated pyogenic infection. The scan shows features of septic arthritis in both sacroiliac joints and both knees. A liver scan had earlier demonstrated multiple small filling defects in the liver.

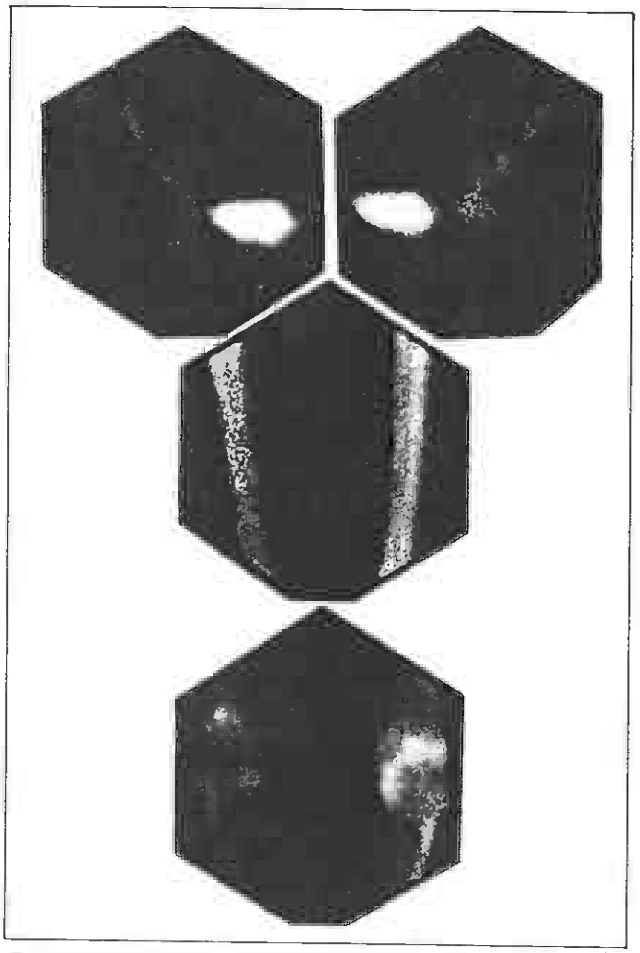

Figure 10: The bone scan of this 57 year old housewife demonstrates an uniform increase in uptake by all the bones of the left lower limb. This is the result of interruption of the sympathetic supply to the left lower limb from diabetic neuritis.

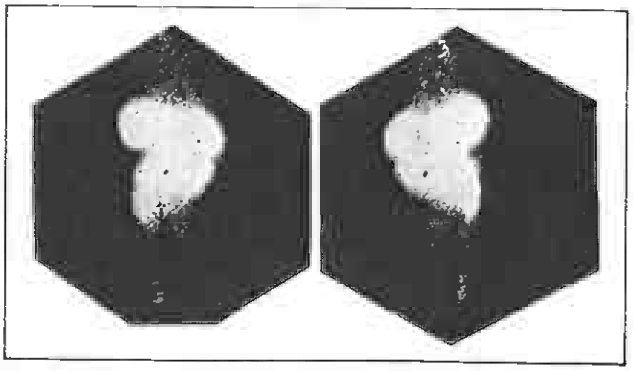

Figure 9: Bone scan of a patient with rheumatoid arthritis of both knees.

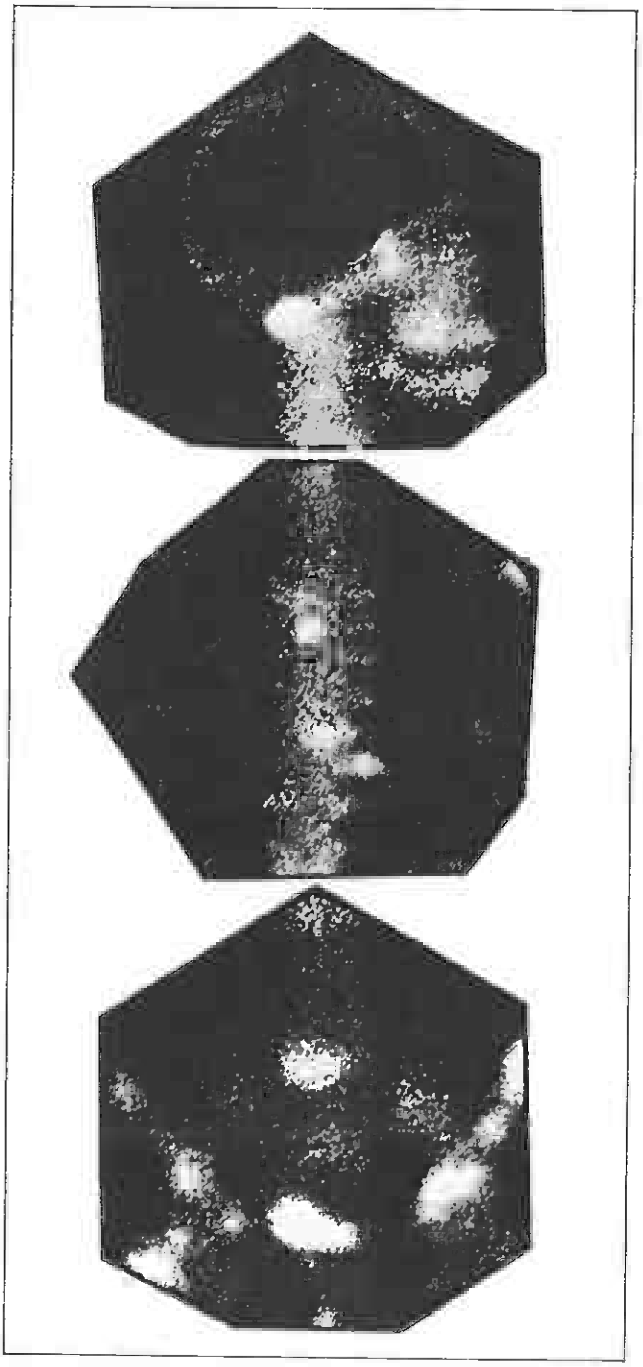

Figure 11: Bone scan of a 40 year old female with simple mastectomy performed for carcinoma of the breast 2 years previously. Multiple metastases are present in the skull, vertebrae, ribs and pelvis.