SKELETAL SCINTIGRAPHY AND QUANTITATIVE TRACER STUDIES IN METABOLIC BONE DISEASE

A thesis submitted to the Faculty of Medicine,
University of Glasgow for the degree of
Doctor of Medicine

by

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TABLE OF CONTENTS

Page No.

LIST OF FIGURES

This thesis is dedicated

to

my Mother and late Father

for

their love, unfailing support and belief

in the importance of education.

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DECLARATION

The work described in this thesis was performed in Glasgow Royal Infirmary, both in the University Department of Medicine and the Department of Nuclear Medicine, from June 1976 to June 1982. All of the studies have been published or are in press in learned journals and are presented in their original form as reprints or photo-copies. In most cases, these studies are the work of several authors. I can affirm, however, that in all studies I have played the major part and where opinions are given these opinions are mine. The detailed planning of the work, the clinical execution and the writing of the papers were performed by myself. The only exceptions to this are papers 2, 10 and 12, which were planned and written in conjunction with Drs J H McKillop, R G Bessent and W Martin respectively.

The following oral communications based on work in this thesis have been presented personally by the author:-

1. The use of whole-body retention of 99m Tc-diphosphonate in metabolic bone disease.
   Scottish Society for Experimental Medicine, Edinburgh. October, 1977.

2. The role of bone scanning and quantitation of skeletal uptake of radiopharmaceutical in metabolic bone disease.
   Radioactive Isotopes in Clinical Medicine and Research, 13th International Symposium, Bad Gastein.
   January, 1978.
3. Skeletal uptake of 99m Tc-Diphosphonate in Metabolic Bone disease.
   The 3rd International Workshop on Calcified Tissues, Jerusalem. March, 1978.
4. The potential value of 24 hour whole body retention of 99m Tc-diphosphonate in the search for metabolic bone disease.
   Joint 2nd Congress of the European Society of Nuclear Medicine and 6th Annual British Nuclear Medicine Society Meeting, London. April, 1978.
5. The bone scan in acromegaly.
   Combined British Institute of Radiology and British Orthopaedic Association Meeting, London. May, 1978.
6. The use of 99m Technetium Diphosphonate in the evaluation of metabolic bone disease. Combined British Institute of Radiology and British Orthopaedic Association Meeting, London. May, 1978.

7. The Metabolic Index: A diagnostic index derived from the bone scan.
   Society of Nuclear Medicine, 16th International Annual Meeting, Madrid. October, 1978.
8. Twenty-four hour whole body retention of 99m Technetium Diphosphonate in the diagnosis of primary hyperparathyroidism.
   Scottish Society for Experimental Medicine, Edinburgh. February, 1979.
9. Comparison of bone scanning and radiology in metabolic bone disease.
   British Nuclear Medicine Society, 7th Annual Meeting, London. April, 1979.
10. Comparison of bone scanning and radiology in metabolic bone disease.
    Society of Nuclear Medicine, 26th Annual Meeting, Atlanta. June, 1979.
11. *The bone scan in metabolic bone disease.
    Fort Wayne Radiology Association, Fort Wayne. June, 1979.
12. *Studies with technetium diphosphonate in the qualitative and quantitative assessment of metabolic bone disease.
    Division of Endocrinology, Mayo Clinic, Rochester. July, 1979.
13. *Quantitative tracer techniques in skeletal disease.
    Division of Nuclear Medicine, Stanford University, Palo Alto. July, 1979.

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14. *Nuclear Medicine techniques in metabolic bone disease. 3rd National Congress of the Italian Society of Radiology and Nuclear Medicine, Milan. November, 1979.
15. *Bone scintigraphy in metabolic disease. Boerhaave course on bone scintigraphy, Leiden. January, 1980.
16. *Skeletal avidity for diphosphonate: A measure of bone metabolism. Divisions of Endocrinology and Nuclear Medicine, Indiana University, Indianapolis. January, 1980.
17. *Technical uses of whole body counter. Division of Nuclear Medicine, University of Cincinnati, Cincinnati. February, 1980.
18. *Advances in evaluation of metabolic bone disease. Division of Endocrinology, University of Cincinnati, Cincinnati. February, 1980.
19. *Whole body retention of diphosphonate: A measure of skeletal metabolism. Hospital Physicists' Association Meeting on: Quantitation in Radionuclide Skeletal Studies, London. February, 1980.
20. Skeletal uptake of diphosphonate: A new method for prediction of post-menopausal osteoporosis. 10th Steenbock Symposium - Osteoporosis: Recent Advances in Pathogenesis and Treatment, Madison. June, 1980.

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21. *Advances using quantitative tracer techniques in metabolic bone disease.
Division of Medicine and Radiology, Columbia University, New York. June, 1980.

22. *Advances in the assessment of skeletal metabolism.
Society of Nuclear Medicine, 27th Annual Meeting, Detroit. June, 1980.

23. *Investigation of metabolic bone disease with diphosphonates.
Department of Human Metabolism, University of Sheffield, Sheffield. October, 1980.

24. *Bone imaging.
West of Scotland Health Boards Department of Clinical Physics and Bioengineering Colloquium, Glasgow. February, 1981.

25. *The short-term evaluation of sex hormone effect on skeletal metabolism by 24 hour whole body retention of diphosphonate.
Bone and Tooth Society, Leeds. March, 1981.

26. *The bone scan in Paget's disease.
Symposium - Diphosphonates and Paget's Disease of Bone, York. April, 1981.

27. A comparison of skeletal uptake of three Tc-99m labelled diphosphonates.
British Nuclear Medicine Society, 9th Annual Meeting, London. April, 1981.

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28. *Clinical applications of 24 hour whole body retention of diphosphonate.
Workshop on the Diphosphonates in Clinical Disorders of Calcium Metabolism, American Society for Bone and Mineral Research, Cincinnati. June, 1981.

29. *Use of 24 hour whole-body retention of diphosphonate in metabolic bone disease.
Division of Nuclear Medicine, University of Cincinnati, Cincinnati. June, 1981.

30. The use of 24 hour whole body retention of diphosphonate in the evaluation of sex hormone effect on skeletal metabolism.
International Symposium on Osteoporosis, Jerusalem. June, 1981.

31. *Radionuclide assessment of skeletal metabolism.
16th European Symposium on Calcified Tissues, Knokke. September, 1981.

32. *Bone scintigraphy as a diagnostic tool in metabolic bone disease.
Leuven University, Leuven. September, 1981.

33. *Use of Tc-99m labelled diphosphonate in the evaluation of metabolic bone disease.
Division of Radiology, Columbia University, New York. September, 1981.

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34. Evaluation of sex hormone effect on skeletal metabolism by 24 hour whole body retention of diphosphonate.
Scottish Society of Physicians, Ayr. October, 1981.

35. *The bone scan in clinical practice.
Diphosphonates, Fourth Symposium CEMO, Nyon.
November, 1981.

36. A critical evaluation of 24 hour whole-body (skeletal) retention of diphosphonate measurements.
Radioactive Isotopes in Clinical Medicine and Research, 15th International Symposium, Bad Gastein.
January, 1982.

37. *A comparison of diphosphonate bone scanning agents.
Bone and Joint Scintigraphy, Oswestry. April, 1982.

38. *Paget's disease and sarcoma.
Bone and Joint Scintigraphy, Oswestry. April, 1982.

39. *The role of whole body retention.
Bone and Joint Scintigraphy, Oswestry. April, 1982.

40. *Clinical comparisons of the diphosphonate bone scanning agents.
Joint Meeting of the Dutch and Belgian Societies of Nuclear Medicine, Breda. May, 1982.

41. *Technetium bone scanning in osteoporosis.
Osteoporosis: A multi-disciplinary problem.
The Royal Society, London. June, 1982.

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PREFACE

The objectives of this thesis are to develop and assess critically methods of using the radiopharmaceutical technetium-99m labelled diphosphonate in the reliable detection of metabolic bone disease.

The work described commenced in 1976 at a time when bone scanning with the 'new' phosphate and phosphonate compounds had only recently become established in clinical practice. Most early studies were carried out in patients with metastatic disease. This is understandable, and indeed the evaluation of a patient with known or suspected malignancy remains the most important indication for a bone scan today. By 1976 the clear superiority of bone scanning over radiology in the detection of skeletal metastases was well documented and attention was turning towards the application of scintigraphy in benign disease. In my own field of interest, metabolic bone disease, several individual articles on bone scanning were available but no one had specifically investigated this group of disorders.

From initial studies in osteomalacia I observed that the bone scan appearances were often similar to those obtained in other conditions such as renal osteodystrophy and primary hyperparathyroidism. Thus the concept of "metabolic features" being present on a bone scan was suggested by

myself and it was observed that such features are non-specific and may be found in any condition where there is generalised increased bone turnover.

An awareness of abnormality on the bone scan in metabolic bone disease does however depend upon a subjective impression of increased tracer uptake throughout the whole skeleton, and this is not always readily apparent. I suggested that a more sensitive index of abnormality in metabolic bone disease would be obtained if skeletal uptake of tracer were quantitated. Initially a semi-quantitative index for metabolic bone disease was derived from the bone scan image. This metabolic index was evaluated and while some favourable results were obtained, the technique did not provide a sensitive means of identifying altered skeletal metabolism in individual patients.

It had been suggested by several authors that measurement of bone to soft-tissue ratios from the bone scan image, using a computer programme to select appropriate regions of interest, might provide a satisfactory means of quantitating bone uptake of tracer. It was my belief, however, that use of bone to soft-tissue ratios was likely to be of limited value in the identification of metabolic bone disease. Nevertheless, critical studies of this technique had not been performed; such studies were undertaken and are reported in the thesis.

In the continuing search for a more accurate means of quantitating skeletal uptake of diphosphonate, I developed a new technique whereby the 24-hour whole-body retention of Tc-99m diphosphonate was measured using a shadow-shield whole-body monitor. It is generally held that Tc-99m diphosphonate is either taken up by the skeleton or else excreted via the urinary tract and by 24 hours after injection most of the tracer initially present in soft-tissue has been excreted, with the great majority of the remaining activity in the body being in bone. Various studies detailing the development, evaluation and clinical application of this technique are described in the thesis and I believe represent the most original and important aspect of my work.

For the past six years, during which time these studies were carried out, I have maintained a keen interest in developments relating to the bone scanning agents. It is clear that differences in skeletal affinity exist between various diphosphonates and this may have important implications for bone scanning both in malignant and benign disease. Currently there is a trend for bone seeking radiopharmaceuticals to have increased skeletal affinity, leading to higher absolute uptake of tracer by bone. While this may lead to more satisfactory views of the skeleton being obtained in normal subjects, higher bone uptake of

tracer may not necessarily be desirable for the identification of disease. Several studies comparing different diphosphonates in clinical practice are therefore reported in this thesis.

The application of quantitative techniques utilising Tc-99m diphosphonate in metabolic bone disease is still relatively in its infancy. This task has stimulated me and maintained my enthusiasm to this day, and is likely to occupy my further attention in years to come.

CHAPTER 1

THE BONE SCAN IN CLINICAL PRACTICE

THE BONE SCAN - Historical aspects

At the present time the bone scan is generally accepted as an extremely powerful investigational tool in the evaluation of patients with both benign and malignant skeletal disease. However it is worth reflecting that it is only a matter of some ten years since the introduction of the "new" bone seeking agents which made clear visualisation of the skeleton possible. The bone scan as we recognise it today results from the development of technetium-99m (Tc-99m) labelled polyphosphate by Subramanian in 1971 (Subramanian and McAfee, 1971). That report is the foundation on which subsequent development of Tc-99m labelled bone seeking agents is based. The excellent physical characteristics of Tc-99m are well documented (Harper et al, 1965; McAfee and Subramanian, 1975). The short physical half life of 6.02 hours is ideal for many studies. The monoenergetic gamma emission of 140 keV is easily collimated and the absence of biologically hazardous beta decay reduces the absorbed dose of radiation. Thus the introduction of a bone scanning agent which could be labelled with Tc-99m was clearly a major advance, and indeed ideal physical properties combined with relatively low cost and easy availability make Tc-99m the radionuclide of choice in

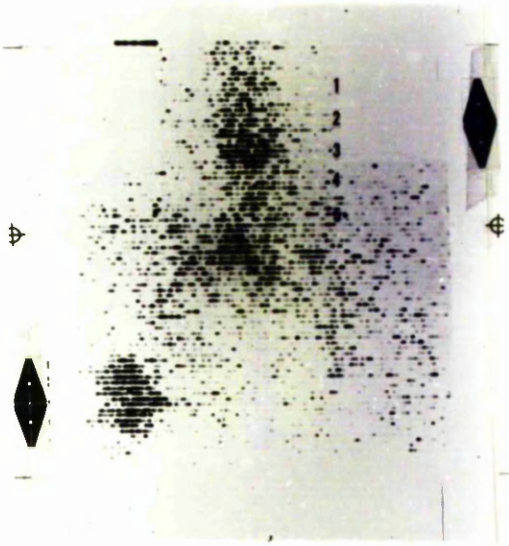
radioisotope imaging procedures for nearly every major organ system in man (Harper et al, 1965). In addition to the introduction of Tc-99m labelled bone scanning agents there was continuing development of nuclear medicine imaging devices with improvement in their resolution (Anger 1964; Cooke and Kaplan, 1972). These factors combined to allow clear visualisation of the skeleton and to produce the bone scan that we are familiar with today.

The history of bone scanning, however, commences some ten years earlier than Subramanian's important publication and the first report of skeletal imaging with a radionuclide was from Fleming et al (1961) using strontium-85 (Sr-85). They found that Sr-85 localised at areas of increased osteoblastic activity, and the scan could be used as an index of bone repair; they concluded that scanning of bone lesions was practical and informative. The increasing use of bone scanning in clinical practice throughout the 1960's was, however, largely due to D M Sklaroff and N D Charkes. In many articles (Sklaroff and Charkes, 1964; Charkes and Sklaroff, 1964; Charkes et al, 1964; Charkes et al, 1966; Sklaroff and Charkes, 1968; Charkes et al, 1968) and innumerable talks they demonstrated to perhaps at that time unbelieving audiences, that bone scan imaging had a primary role in the detection of skeletal

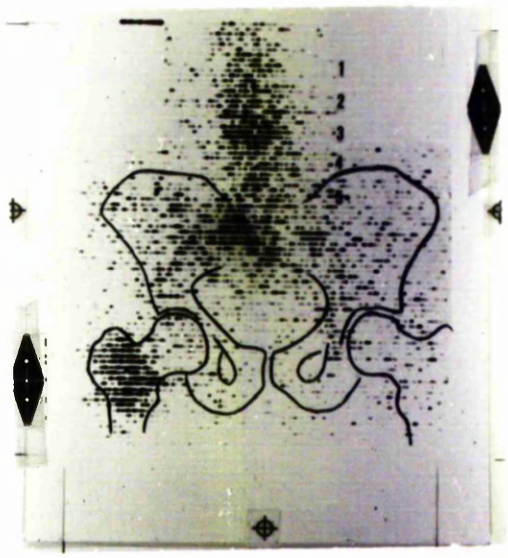
metastases. Their extensive experience was supported by a series of reports from De Nardo and colleagues (De Nardo 1966; De Nardo et al, 1966; De Nardo 1968; De Nardo et al, 1972) confirming the practicality and usefulness of bone imaging. The cumulative experience with Sr-85 showed clearly that bone scanning consistently detected lesions months before radiographs of the skeleton became abnormal. Thus by 1970 the bone scan had already become a clinically acceptable procedure but radiostrontium, initially Sr-85 and later Sr-87m (Charkes, 1969), the most practical bone agent available was far from ideal (figure 1). The low gamma yield, gut excretion of tracer which could interfere with lesion visualisation, limitation of use to patients with malignant disease because of high radiation dose, and prolonged delay from injection to imaging, led to increasing dissatisfaction with Sr-85. It is of interest today that a bone scan with Sr-85 could only be obtained after a delay of some 24-48 hours following injection to allow excretion of non-skeletal tracer via bowel and urinary tract (Sklaroff and Charkes, 1964) and a single view of pelvis could take 30-45 minutes to obtain (De Nardo 1966). Sr-87m, on the other hand, had a short physical half-life (2.8 hours) and larger activities could be injected obtaining scans of high information density with relatively short patient scanning times

Figure 1

a) Sr-85 scan of anterior pelvis with metastases present in pelvis, spine and femora.
(April, 1963)



b) As above, with overlay to define outline of pelvis.



c) Tc-99m diphosphonate scan of anterior pelvis with metastases present in pelvis, spine and femora.
(April, 1982)

(Figures 1a and b provided by Dr N D Charkes.
Figure 1b from the Journal of the American Medical Association 1964, volume 188, pp 1-4, with permission.

(Volpe 1971). However the main disadvantage of Sr-87m was the slow blood clearance of tracer. High background activities in blood and soft-tissues resulted in low target to background ratios and thus relatively poor visualisation of normal and pathological bone until many hours after injection (Weber et al, 1969). The short physical half-life of Sr-87m however precluded waiting until background levels were low, when optimum target to background ratios would be obtained. It was reported that the high blood and extra-cellular fluid activities of Sr-87m could lead to erroneous false-positive diagnoses (Charkes 1969).

Some of the disadvantages of imaging with the strontium isotopes had already been overcome with the introduction of fluorine-18 (F-18) by Blau and associates (Blau et al, 1962). With more favourable radiation dosimetry and faster blood clearance, it was possible to administer larger activities resulting in greater information density and faster scanning speeds. Visualisation of the entire skeleton thus became practical with F-18. F-18 quickly replaced the strontium isotopes as the scanning agent of choice and extensive experience was accumulated with its use (Blau et al, 1962; French and McCready, 1967; Sharma and Quinn, 1972; Blau et al., 1972; Shirazi et al, 1974; Fordham and Ramachandran, 1974).

However F-18 required cyclotron production, was expensive, and with its short physical half-life (1.83 hours) insoluble problems arose regarding widespread distribution of this radionuclide. Thus only relatively few centres could use F-18, which precluded general acceptance of this reliable and effective radionuclide.

The search for a satisfactory bone scan compound continued. Many alternative nuclides and radiopharmaceuticals were considered. These included gallium-68 (Hayes et al, 1965; Edwards et al, 1966) and Tc-99m pertechnetate (Tow and Wagner, 1967). Because of the chemical similarity to calcium, several nuclides of the alkaline earth element barium (Ba) were evaluated. Both Ba-131 and Ba-135m were found to have excellent physical characteristics and rapid blood clearance (Spencer et al, 1970; Lange et al, 1970; Subramanian 1970). Another promising group of agents were chelates of the rare earth elements (the lanthanides) (O'Mara et al, 1969). Of these compounds the HEDTA (N-hydroxy ethylenediamine triacetic acid) chelate of dysprosium-157 appeared to have the most suitable properties (Subramanian et al, 1971; Yano et al, 1971).

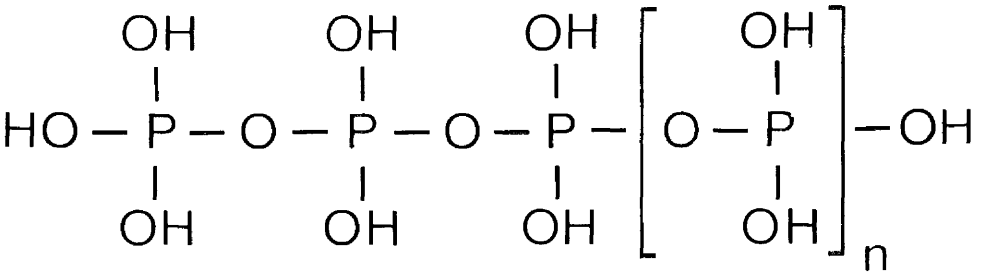
While some initial excitement was generated by the agents described above, their roles as bone scanning agents in clinical practice were completely supplanted by the

introduction of Tc-99m polyphosphate by Subramanian and McAfee (1971).

Introduction of Tc-99m phosphate

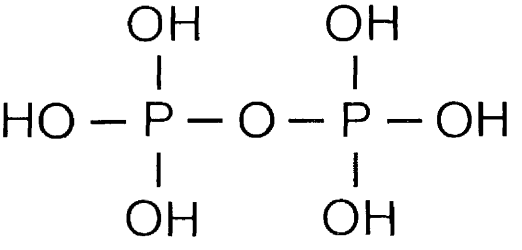
Animal studies using polyphosphate labelled with phosphorus-32 (P-32) were first carried out by Fels and co-workers in 1959 (Fels et al, 1959). They demonstrated that the accumulation of tracer in bone relative to soft tissue was greater for polyphosphate than orthophosphate. There were major therapeutic implications from this work regarding the possibility of delivering higher amounts of P-32 selectively to sites of bone metastases, and indeed subsequent studies (Kaplan et al, 1960) on human subjects with carcinoma of the prostate verified increased localisation of polyphosphate P-32 in bone in proportion to the severity of malignant disease. If polyphosphate with increased skeletal affinity had applications in the realm of therapy, could it not also be of use in the diagnosis of disease?

Many years earlier Neuman and Neuman (1953) had described localisation of anionic metal complexes in bone. As Tc-99m readily forms anionic complexes, it was considered feasible to obtain selective osseous localisation of this radionuclide (Subramanian and McAfee, 1971). The polyphosphates, also known as condensed phosphates, are compounds which possess chains of -P-O-P-units (figure 2) joined together. Their ability to prevent deposition of

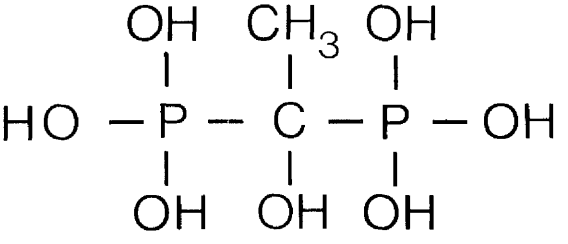


POLYPHOSPHATE

n = number of recurring units



PYROPHOSPHATE



DIPHOSPHONATE (hydroxyethylidene diphosphonate)

Figure 2

Chemical structure of polyphosphate, pyrophosphate and diphosphonate.

calcium carbonate from solution is well known (Fleisch and Russell, 1970) and it was predicted that polyphosphates would have strong affinity for hydroxyapatite crystals in the mineral phase of bone, and in particular for sites of new bone formation. Such affinity had been previously demonstrated in autoradiographic studies using P-32 labelled polyphosphate (Fels et al, 1959).

Techniques were already available for reducing Tc-99m pertechnetate with stannous chloride (Eckelman and Richards, 1970) which made it possible to label phosphate compounds with Tc-99m.

This was the background to that initial publication from Subramanian and McAfee (1971). Thus a compound with high skeletal affinity was combined with a radionuclide with near perfect physical properties; introducing Tc-99m labelled phosphate bone scanning agents to clinical practice (Subramanian et al, 1972a). While the first bone scans may have had some irritating body background activity, the skeleton was nevertheless clearly discernible.

Following the initial development and introduction of Tc-99m polyphosphate, attention turned to other phosphates which could be suitable bone scanning agents. Technetium-99m pyrophosphate appeared promising. Pyrophosphate is believed to be important in regulating the calcification process in bone, although its precise role in calcium metabolism and

in disorders of bones and teeth is not well defined (Fleisch and Russell, 1970; 1972). When labelled with Tc-99m, pyrophosphate provided improved bone to background activity ratios, and satisfactory scans were obtained in experimental animal and early patient studies (Perez et al, 1972; Cohen et al, 1972; Hosain 1973; Fletcher et al, 1973; Huberty et al, 1974). Bone scanning had come of age, the scans looked like bone surveys - an advantage Sklaroff and Charkes did not have with Sr-85 and Sr-87m.

Shortly after the introduction of Tc-99m polyphosphate and Tc-99m pyrophosphate, still another group of bone scanning agents, the diphosphonates, became available. The development of the diphosphonates stemmed from the search for a therapeutic agent in bone disease which combined the biological properties of pyrophosphate and polyphosphate, together with resistance to enzymatic destruction in vivo (Fleisch et al, 1969; Francis et al, 1969). While the possibility of using both polyphosphate and pyrophosphate as therapeutic agents had been considered (Russell and Smith, 1973), their rapid destruction by tissue phosphatases made this impossible. During the late 1960's, however, a diphosphonate (hydroxyethylidene diphosphonate) was shown to be of value in the treatment of myositis ossificans (Bassett et al, 1969) and was soon after evaluated in

Paget's disease (Smith et al, 1971). Today, diphosphonates are a standard therapy for Paget's disease (Russell et al, 1974; Khairi et al, 1977) and many other potential clinical applications have been suggested (Russell and Smith, 1973). Tc-99m labelled diphosphonate (hydroxyethylidene diphosphonate) as a bone scanning agent was independently proposed and evaluated by several groups of workers (Tofe and Francis, 1972; Castronovo and Callahan, 1972; Subramanian et al, 1972b; Yano et al, 1973) and evidence was obtained that diphosphonate provided improved scans when compared with either Tc-99m pyrophosphate (Citrin et al, 1975; Fogelman et al, 1977) or F-18 (Silberstein et al, 1973). Within a year a major clinical study from Pendegrass et al (1973) using Tc-99m diphosphonate summarised their experience with 500 bone scans. It had taken Sklaroff and Charkes almost eight years to obtain similar numbers of patient studies using Sr-85 (Charkes et al, 1968).

Thus within a short period of time, three new, good bone scanning agents had become available (Tc-99m polyphosphate, pyrophosphate and diphosphonate) and a brief report from Subramanian in 1971 had led to as many as 50 publications reporting on their use by 1973. Since that time cumulative experience has suggested that the diphosphonates are the bone scanning agents of choice

(Dunson et al, 1973; Serafini et al, 1974; Krishnamurthy et al, 1974; Lundell et al, 1975) with superior detection of lesions in metastatic disease (Citrin et al, 1975; Fogelman et al, 1977; Silberstein et al, 1978). While other agents such as Tc-99m monofluorophosphate (Citrin et al, 1974), Tc-99m sodium trimetaphosphate (Nelson et al, 1975), and Tc-99m imidodiphosphate (Subramanian et al, 1975a) have since been evaluated, none presented a serious challenge to Tc-99m hydroxyethylidene diphosphonate. Subramanian and colleagues in 1975 however introduced a new diphosphonate, methylene diphosphonate (Subramanian et al, 1975b). This compound had more rapid blood clearance than hydroxyethylidene diphosphonate and also appeared to have higher skeletal affinity. Certainly it became a great commercial success and is currently the most widely used bone scanning agent. However, the search for a better scanning agent has by no means stopped and at present two further diphosphonate compounds (hydroxymethylene diphosphonate and dicarboxypropane diphosphonate) are available. Each appears to have higher absolute bone uptake than methylene diphosphonate but any advantage to their use in clinical practice has still to be shown. However, there seems little point in quibbling over which is the very best agent when we are truly fortunate to have bone scanning agents which perform their job so superbly well.

Paper 1. Skeletal uptake of diphosphonate: A review (1980)

European Journal of Nuclear Medicine 5: 473-476

I Fogelman

Purpose of Investigation

This paper reviews the current literature relating to mechanisms of diphosphonate uptake by bone. Several important concepts are discussed. Firstly, whether alterations in local vascularity or skeletal metabolism are primarily responsible for variations in bone uptake of tracer. While accepting the importance of vascularity in the regulation of tracer delivery to the skeleton it is seen that markedly increased uptake of tracer cannot be adequately explained by alterations in vascularity alone. The evidence supporting the importance of increased bone turnover for tracer uptake is presented. Secondly, it is recognised that considerable controversy exists as to the exact site of localisation of tracer in bone, and the available evidence regarding this is summarised.

Eur. J. Nucl. Med. 5, 473–476 (1980)

European Journal of Nuclear Medicine

Skeletal Uptake of Diphosphonate: A Review

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Abstract. The diphosphonates are currently the skeletal imaging agents of choice and while extremely sensitive for bony abnormality their mechanism of action remains poorly understood. The current concepts in bone uptake mechanisms are reviewed and it is concluded that diphosphonate uptake is most likely related to sites of newly forming bone with diphosphonate adsorbed onto the surface of hydroxyapatite crystals. In situations where there is markedly increased skeletal uptake of tracer, increased vascularity alone cannot account for changes in tracer uptake and changes in skeletal extraction, related to newly forming bone are more important.

Introduction

Bone scanning has revolutionised the investigation of patients with skeletal disease and it is now well recognised that in the search for metastatic involvement of bone, the scan may become positive 6 months, 1 year or even 18 months before changes are seen on X-ray (Tofe et al. 1975; Citrin et al. 1977). Also the use of bone scanning is established in Paget's disease (Serafini 1976) and various other benign bone disorders (Handmaker and Leonards 1976), with recent interest in the evaluation of patients with metabolic bone disease (Sy and Mittal 1975; Fogelman et al. 1978b). While there is universal agreement that the currently available bone seeking radiopharmaceuticals (the diphosphonates) are extremely sensitive for skeletal abnormality, their mechanism of action remains poorly understood. The purpose of this review is to summarise the evidence that is presently available as to their mode of action and site of localisation and to discuss some of the remaining problems which exist in clarifying the processes that occur at the bone surface.

Several of the earlier studies which will be quoted have been carried out with phospate compounds, while in clinical practice today, the diphosphonates are virtually exclusively used. However, it is likely that both groups of agents behave at least in a qualitatively similar manner in relation to bone (Charkes 1979).

Stability of Bone Seeking Radiopharmaceuticals

Several studies have now shown that the diphosphonate compounds have excellent physical and chemical properties as bone scanning agents (Dunson et al. 1973; Citrin et al. 1975b). They provide highly reproducible bone scans despite variations in technetium presentation, labelling and injection procedures (Citrin 1977). In addition prolonged shelf life and variations in temperature and pH apparently have minimal effect on stability (Garnett et al. 1975). It is generally assumed that the technetium diphosphonate complex travels to bone and stays there as a unit (Jones et al. 1976). It is likely that this is indeed the case and Tofe and Francis (1974) have shown that the ratio of technetium to diphosphonate which is deposited in bone is the same at 3 and 24 h following injection.

Tissue Distribution of Diphosphonate

The diphosphonates are either taken up by bone or else rapidly cleared through the kidneys (McDougall and Citrin 1975) and in a normal subject approximately 70% of the injected activity will be excreted via the urinary tract within 6 h of injection (Citrin et al. 1975a). However renal clearance is not the primary determinant of skeletal uptake of tracer. This depends upon the intrinsic affinity of the tracer for

0340-6997/80/0005/0473/$01.00

bone modified by other factors which wil be discussed later. It has been shown that the uptake of diphosphonate in bone compared to other soft tissue varies between a factor of ×20 and ×1,000 (Rohlin and Nosslin 1977).

Factors Involved in Skeletal Uptake of Diphosphonate

a) Vascularity. Before a radiopharmaceutical can be taken up by a bone, it must be delivered there by its vascular supply. Skeletal vascularity is therefore of fundamental importance but the question arises as to whether increased uptake of tracer can be fully explained by an eqivalent increase in the blood supply to bone. It is known that following a sympathectomy to a limb there is increased tracer uptake (thought to be related to vessel dilatation) (Charkes 1979) and that in Paget's disease where there is high blood flow to the involved sites, there is also intense uptake of tracer (Serafini 1976). Genant et al. (1974) found correspondingly increased tracer uptake and vascularity with thermal-induced alterations in blood flow to bone in rats. They also found increased skeletal tracer uptake in rachitic rats and argued that this was due to increased vascularity as mineralisation is generally reduced in rickets. However, Kaye et al. (1975) found that skeletal vascularity was normal in rachitic rats and although the mineralisation rate is reduced in rickets, there is so much excess osteoid present throughout the whole skeleton which is mineralising, albeit at a slower rate, that the total mineralisation in the whole animal is increased (Nordin 1978). Siegel et al. (1976) studied various groups of rats in whom femoral artery ligation and fractures of bone were carried out and found that skeletal uptake of tracer correlated with change in vascularity. However, if one reduces blood flow to a bone then tracer uptake will obviously be reduced and their findings in the fracture situation where tracer uptake is increased were less convincing.

Recent studies from the Mayo Clinic have correlated capillary extraction of bone tracers with their diffusion coefficients (Hughes et al. 1977; Kelly and Bassingthwaighte 1977). It was suggested that the principal mechanism for the movement of tracer from blood to bone is passive diffusion through the clefts in the capillary walls into the extravascular, extracellular fluid. This type of diffusion is proportional to molecular size and smaller ions such as strontium and fluorine spread more rapidly than the technetium phosphonate agents. Nevertheless it seems likely that the initial dilution process does not determine the ultimate degree of tracer uptake on bone. Wootton (1974) has shown that fluorine-18 is 100% extracted by normal bone in a single passage and Garnett et al. (1975) subsequently showed that technetium-pyrophosphate has 64% extraction in bone compared to fluorine-18. They suggested that the capillary membrane reduced the efficiency with which pyrophosphate was extracted by normal bone and that in abnormal bone increased tracer uptake was due to a combination of increased blood flow and more efficient extraction.

Hughes et al. (1978) have shown that the skeletal uptake of diphosphonate when injected as a bolus compared to constant infusion over a thirty minute interval was equivalent and this is of real interest as it appears the contact time of tracer with bone may not be of importance. This has relevance eg, in chronic renal failure where increased blood levels of tracer occur due to soft tissue retention (Fogelman et al. 1978a) and suggests that high skeletal tracer uptake in such patients (Sy and Mittal 1975) reflects skeletal avidity rather than prolonged exposure of bone to tracer.

Lavender et al. (1979) in a series of elegant experiments using a canine tibia in which an osteotomy had been carried out with an isolated tibial artery showed that a moderate increase in blood flow (by 100%) was associated with a much greater increase in the diphosphonate residue (by 800%). They concluded that vascularity may increase tracer uptake (potentially by 100%) but that for higher uptake some other factor related to newly forming bone was responsible for increased extraction. Similar results and conclusions were obtained by Sagar et al. (1978) who showed that increased vascularity (by 400%) led to an increase in diphosphonate uptake of only 70%. Charkes et al. (1978) devised a 5 compartmental model for radiopharmaceutical uptake by bone and it was deduced that for a significant increase of blood flow (by 500%) there was only relatively little increase in skeletal uptake of tracer.

The conclusion from these findings is that while increased vascularity is certainly a factor in increased skeletal uptake of tracer, markedly increased uptake (by more than a factor of 100%) cannot simply be explained by alterations in vascularity alone.

b) Skeletal Metabolism. It is well recognised that conditions with accelerated bone turnover e.g., Paget's disease, primary hyperparathyroidism, and renal osteodystrophy show increased skeletal uptake of tracer (Fogelman et al. 1978a) and if vascularity alone cannot fully explain this uptake then it must be related in some way to the increased modelling and remodelling of bone (Jones et al. 1976). Garcia et al. (1976) have shown in an animal model that only a bone

forming system can lead to increased tracer uptake and they concluded that where an osteolytic lesion existed in bone it led to increased tracer uptake by a compensatory osteogenic response.

We have shown that total skeletal uptake of tracer (as measured by 24 h whole-body retention of diphosphonate) correlated well with plasma immunoreactive parathyroid hormone in patients with primary hyperparathyroidism and that skeletal uptake fell with time following parathyroidectomy, i.e., skeletal uptake of tracer fell as skeletal metabolic activity gradually returned towards normal (Fogelman et al., in press).

The importance of skeletal metabolism is accepted (Jones et al. 1976; Bell 1972) but some controversy exists as to the mechanisms and site of localisation of tracer. It is generally believed that uptake is related to the mineral phase of bone (Jones et al. 1976) but recently it has been suggested that uptake by enzyme systems (Zimmer et al. 1975) and immature collagen may also be important (Rosenthall and Kaye 1975).

Bone Mineral

It has been shown in vitro that diphosphonate uptake is related to bone mineral and it has been suggested that diphosphonate chemi-adsorbs on to hydroxyapatite crystals (Francis 1969). It is likely that the reactivity of tracer is different for the various phases and hydration states of forming hydroxyapatite (Khan et al. 1979). It would seem that uptake of tracer is mainly associated with "newly forming bone" and that there is little uptake in mature bone (Jones et al. 1976; Tilden et al. 1973). It is also attractive to postulate that in high bone turnover states increased tracer uptake is due to increased bone resorption which effectively causes an increase in exposure of potentially available binding sites.

Several groups have performed autoradiography on bone or cartilage using diphosphonate (Jones et al. 1976; Khan et al. 1979; Tilden et al. 1973; van Langevelde et al. 1977; Guillemart et al. 1978) and have shown that uptake is related to the interphase between osteoid and mineralised bone i.e., at the site of active mineralisation. While Jones et al. (1976) found no activity in osteoid, Guillemart et al. (1978) and Tilden et al. (1973) did note some scattered activity throughout osteoid.

Enzymes Systems

Zimmer et al. (1975) have suggested that enzymes such as alkaline phosphatase complexing with diphosphonate may explain uptake of tracer on bone surfaces. However, this seems unlikely for in Paget's disease, for example, there are extremely high blood levels of alkaline phosphatase and if diphosphonate complexed with this enzyme there would be considerable delay in blood clearance of diphosphonate, and this does not occur (Jones et al. 1976).

Immature Collagen (Osteoid)

Kaye et al. (1975) in a series of in vitro studies showed a striking increase in tracer uptake on to demineralised bone and they concluded that there was preferential binding of tracer by immature collagen. However, bone was exposed to various chemical and physical traumas and these findings cannot necessarily be related to the physiological state. Also the same group (Rosenthall and Kaye, 1975) found no correlation of 5 h bone to soft tissue ratios (reflecting skeletal uptake of tracer) with the percentage of bone surface covered by osteoid. We have reported a case of Paget's osteosarcoma where the tumour (with malignant osteoid present) did not appear to take up any tracer with the lesion cold on bone scanning (McKillop et al. 1977). We have also studied a case of adult hypophosphatasia (the essential problem here is very low alkaline phosphatase levels with a basic mineralisation defect leading to excess osteoid (Birtwell et al. 1967)) and this patient's bone scan appeared normal in terms of tracer uptake. However, hot spots were seen in the femora where pseudofractures were present. We also measured the total skeletal uptake of tracer using our whole-body retention technique (Fogelman et al. 1978a) and found this to be in the normal range. We, therefore, have a situation where there is excess osteoid present but skeletal uptake of tracer is normal and this seems to suggest that mineralisation may be the more important factor. Also the autoradiographic findings reported above are further strong evidence in support of this. Where technetium deposition has been seen in osteoid on autoradiography (Tilden et al. 1973; Guillemart et al. 1978), it was probably due to nuclei of calcium phosphate present rather than strong specific adsorption with the organic matrix itself.

The evidence to date strongly supports the view that diphosphonate uptake is related to sites of newly forming bone with the diphosphonate being adsorbed on to the surface of hydroxyapatite crystals. Nevertheless high turnover states eg, Paget's disease, primary hyperparathyroidism and renal osteodystrophy do have excess osteoid present and it will be necessary to perform autoradiography in these conditions and, in particular, in osteomalacia (where osteoid is greatly

increased) to localise the specific site of uptake. Even then it may not be possible to differentiate uptake by immature collagen and calcium phosphate crystals present in the osteoid, and the final answer may have to await electron microscopy studies of bone.

References

Bell EG (1972) Nuclear Medicine and Skeletal Disease. Hosp Pract 7:49–60

Birtwell Jr WM, Riggs BL, Peterson LFA, Jones JD (1967) Hypophosphatasia in an Adult. Arch Intern Med 120:90–93

Charkes ND (1979) Mechanisms of Skeletal Tracer Uptake. J Nucl Med 20:794–795

Charkes ND, Makler Jr PT, Philips C (1978) Studies of Skeletal Tracer Kinetics. 1. Digital Computer Solution of a Five-compartment Model of (^{18}F) Fluoride Kinetics in Humans. J Nucl Med, 19:1301–1309

Citrin DL (1977) An Evaluation of the in vitro Properties of 99m Tc-HEDP. Radiology 122:255–258

Citrin DL, Bessent RG, Greig WR (1977) A Comparison of the Sensitivity and Accuracy of the 99m-Tc-phosphate Bone Scan and Skeletal Radiography in the Diagnosis of Bone Metastases. Clin Radiol 28:107–117

Citrin DL, Bessent RG, McGinlay E, Gordon D (1975a) Dynamic Studies with 99m Tc HEDP in Normal Subjects and in Patients with Bone Tumours. J Nucl Med 16:886–890

Citrin DL, Bessent RG, Tuohy JB, Elms ST, McGinlay E, Greig WR, Blumgart LH (1975b) A Comparison of Phosphate Bone-scanning Agents in Normal Subjects and Patients with Malignant Disease. Br J Radiol 48:118–121

Dunson GL, Stevenson JS, Cole CM, Mellor MK, Hosain F (1973) Preparation and Comparison of Technetium-99m Diphosphonate, Polyphosphate and Pyrophosphate Nuclear Bone Imaging Radiopharmaceuticals. Drug Intell Clin Pharm 7:470–474

Fogelman I, Bessent RG, Beastall G, Boyle IT (in press) Estimation of Skeletal Involvement in Primary Hyperparathyroidism. Use of 24-hour Whole Body Retention of Technetium-99m Diphosphonate. Ann Int Med

Fogelman I, Bessent RG Turner JG, Citrin DL, Boyle IT, Greig WR (1978a) The Use of Whole-Body Retention of Tc-99m Diphosphonate in the Diagnosis of Metabolic Bone Disease. J Nucl Med 19:270–275

Fogelman I, McKillop JH, Bessent RG, Boyle IT, Turner JG, Greig WR (1978b) The Role of Bone Scanning in Osteomalacia. J Nucl Med 19:245–248

Francis MD (1969) The inhibition of calcium hydroxyapatite crystal growth by polyphosphonates and polyphosphates. Calcif Tissue Res 3:151–162

Garcia DA, Tow DE, Kapur KK, Wells H (1976) Relative accretion of 99m Tc-polyphosphate by forming and resorbing bone systems in rats: Its significance in the pathologic basis of bone scanning. J Nucl Med 17:93–97

Garnett ES, Bowen BM, Coates G, Nahmias C (1975) An analysis of factors which influence the local accumulation of bone-seeking radiopharmaceuticals. Invest Radiol 10:564–568

Genant HK, Bautovich GJ, Singh M, Lathrop KA, Harper PV (1974) Bone-seeking radionuclides: An in vivo study of factors affecting skeletal uptake. Radiology 113:373–382

Guillemart A, Besnard JC, Le Pape A, Galy G, Fetissoff F (1978) Skeletal uptake of pyrophosphate labelled with technetium-95m and technetium-96m, as evaluated by autoradiography. J Nucl Med 19:895–899

Handmaker H, Leonards R (1976) The bone scan in inflammatory osseous disease. Semin Nucl Med 6:95–105

Hughes SPF, Davies DR, Bassingthwaighte JB, Knox FG, Kelly PJ (1977) Bone extraction and blood clearance of diphosphonate in the dog. Am J Physiol 232:H341–H347

Hughes S, Khan R, Davies R, Lavender P (1978) The uptake by the canine tibia of the bone-scanning agent 99m Tc-MDP before and after an osteotomy. J Bone Joint Surg 60B:579–582

Jones AG, Francis MD, Davis MA (1976) Bone scanning: Radionuclide reaction mechanisms. Semin Nucl Med 6:3–18

Kaye M, Silverton S, Rosenthall L (1975) Technetium-99m-pyrophosphate: Studies in vivo and in vitro. J Nucl Med 16:40–45

Kelly PJ, Bassingthwaighte JB (1977) Studies on bone ion exchanges using multiple tracer indicator-dilution techniques. Fed Proc 36:2634–2639

Khan RA, Hughes S, Lavender P, Leon M, Spyrou N (1979) Autoradiography of technetium-labelled diphosphonate in rat bone. J Bone Joint Surg 61B:221–224

Lavender JP, Khan RAA, Hughes SPF (1979) Blood flow and tracer uptake in normal and abnormal canine bone: Comparisons with Sr-85 microspheres, Kr-81m, and Tc-99m MDP. J Nucl Med: 20:413–418

McDougall IR, Citrin DL (1975) Bone scanning: The current position. Scott Med J 20:149–151

McKillop JH, Fogelman I, Boyle IT, Greig WR (1977) Bone scan appearances of a paget's osteosarcoma: Failure to concentrate HEDP. J Nucl Med 18:1039–1040

Nordin BEC (1978) Diagnostic procedures in disorders of calcium metabolism. Clin Endocrinol 8:55–67

Rohlin M, Nosslin B (1977) Quantitative analysis of the distribution of 99m Tc-labelled ethylene hydroxy diphosphonate in young rats. Eur J Nucl Med 2:113–115

Rosenthall L, Kaye M (1975) Technetium-99m-pyrophosphate kinetics and imaging in metabolic bone disease. J Nucl Med 16:33–39

Sagar V, Piccone JM, Charkes ND, Makler Jr PT (1978) Skeletal tracer uptake and bone blood flow in dogs. J Nucl Med 19:705–706

Serafini AN (1976) Paget's disease of bone. Semin Nucl Med 6:47–58

Siegel BA, Donovan RL, Alderson PO, Mack GR (1976) Skeletal uptake of 99m Tc-diphosphonate in relation to local bone blood flow. Radiology 120:121–123

Sy WM, Mittal AK (1975) Bone scan in chronic dialysis patients with evidence of secondary hyperparathyroidism and renal osteodystrophy. Br J Radiol 48:878–884

Tilden RL, Jackson Jr J, Enneking WF, De Land FH, McVey JT (1973) 99m Tc-polyphosphonate: Histological localisation in human femurs by autoradiography. J Nucl Med 14:576–578

Tofe AJ, Francis MD (1974) Optimisation of the ratio of stannous tin: Ethane-1-hydroxy-1, 1-diphosphonate for bone scanning with 99m Tc-pertechnetate. J Nucl Med 15:69–74

Tofe AJ, Francis MD, Harvey WJ (1975) Correlation of neoplasms with incidence and localisation of skeletal metastases: An analysis of 1355 diphosphonate bone scans. J Nucl Med 16:986–989

Van Langevelde A, Driessen OMJ, Pauwels EKJ, Thesingh CW (1977) Aspects of 99m technetium binding from an ethane-1-hydroxy-1, 1-diphosphonate-99m complex to bone. Eur J Nucl Med 2:47–51

Wootton R (1974) The single-passage extraction of ^{18}F in rabbit bone. Clin Sci Mol Med 47:73–77

Zimmer AM, Isitman AT, Holmes R (1975) Enzymatic inhibition of diphosphonate: A proposed mechanism of tissue uptake. J Nucl Med 16:352–356

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Comment

The two main contenders as regards site of localisation of diphosphonate in bone are immature collagen (osteoid) and bone mineral, particularly at sites of new bone formation. I believe that the available evidence strongly favours diphosphonate uptake in association with bone mineral.

Since the present review further work has become available supporting this view. Francis et al (1981) reacted technetium-99m (Tc-99m) diphosphonate with a mixture of pure inorganic hydroxyapatite and pure organic bone matrix to provide a competitive adsorption environment for the diphosphonate. It was found that while some adsorption of diphosphonate to matrix alone does occur, when hydroxyapatite and matrix compete in the same system, as happens in vivo, then diphosphonate is adsorbed preferentially to hydroxyapatite (the ratio of Tc-99m hydroxyapatite to Tc-99m matrix being 40:1).

Christensen and Krogsgaard (1981) using epiphyseal growth plates of rats have again confirmed by autoradiography that Tc-99m labelled diphosphonate localises primarily at sites of active mineralisation. In addition, labelling of diphosphonate corresponded with the fluorescence of tetracycline, a known marker of bone mineralisation (Teitelbaum and Nichols, 1977), but did not coincide with new production of collagen, as judged by localisation of tritium labelled proline. When sections labelled in vivo

with Tc-99m diphosphonate were decalcified using ethylene diamine tetraacetic acid (EDTA), loss of radioactivity was shown. This is in contrast to those sections incubated in water where no loss was seen, thus providing further evidence of the affinity of diphosphonate for the mineral phase of bone.

While there is strong evidence supporting the view that diphosphonate adsorbs on to the surface of hydroxyapatite crystals, it is important to realise that the exact mechanism by which diphosphonate binds to bone is not yet fully understood. In addition, as will be shown in the thesis, differences in skeletal affinity exist amongst the various diphosphonates. This has been attributed to differences in binding characteristics, perhaps related to those molecules present on the central carbon atom of the diphosphonate (Deutsch and Barnett, 1980). However, such explanations are neither proven nor wholly satisfactory and it is clear that much basic research is still required to answer the 'simple' question of what happens to diphosphonate on bone.

Paper 2. Bone scanning in clinical practice: A review

Diphosphonates, Fourth Symposium CEMO (in press)

I Fogelman, J H McKillop

Purpose of Investigation

The bone scan is still most commonly used in the search for metastatic disease but increasingly there is recognition of the value of bone scanning in benign bone disorders. This paper identifies and summarises some of the more important applications of the bone scan in clinical practice.

BONE SCANNING IN CLINICAL PRACTICE: A REVIEW

Ignac Fogelman, James H McKillop

The isotope bone scan is a relatively new method of imaging the skeleton which has rapidly assumed major clinical importance. It provides a simple, sensitive test for the localisation and evaluation of skeletal disease, and will often present diagnostic information which cannot be obtained from other non-invasive procedures. In this review the pathophysiology of bone uptake of radiopharmaceutical, the relative sensitivity of bone scan and radiograph, and the more important indications for bone scanning in clinical practice are described.

PATHOPHYSIOLOGY OF BONE UPTAKE OF RADIOPHARMACEUTICAL

A skeletal radiograph indicates the net result of bone resorption and repair and a destructive lesion in trabecular bone must be greater than 1 to 1.5 cm in diameter with loss of approximately 50% of bone mineral before it becomes apparent on x-ray (1). The bone scan, however, reflects skeletal metabolic activity and while the exact mechanism of uptake of tracer (technetium - 99m labelled diphosphonate) by bone remains incompletely understood, it is thought most likely that diphosphonate adsorbs onto the calcium of hydroxyapatite (2). The major factors which affect this adsorption on to bone are believed to be osteoblastic activity and skeletal vascularity (3). Rather than bone destruction the bone scan, therefore, reflects the reaction of normal bone to a variety of disease processes, be they neoplastic, metabolic, traumatic, or inflammatory (4). Early in bone resorption reactive bone may not be present in sufficient quantities to be detected radiographically, although the bone scan may be strongly positive. This ability to detect functional change, which occurs earlier than structural change is the reason why bone scanning is so much more sensitive than conventional radiology. However, bone scans are relatively non-specific because almost any disease process in bone results in a change in osteoblastic activity and blood flow. Nevertheless, the pattern of abnormality in the bone scan may be sufficiently characteristic in many conditions to allow a specific diagnosis, but often the scan findings do require to be correlated with corresponding radiographs.

THE BONE SCAN IN MALIGNANT DISEASE

The most common use of the radionuclide bone scan in clinical practice has been in the evaluation of patients with suspected or established malignant disease (Figure 1). The bone scan is superior to skeletal x-rays for screening for bony involvement in most tumours for two reasons. Firstly, in most tumours the bone scan is more sensitive than skeletal x-rays for the detection of

early bone involvement, because of the ability of the isotope method to demonstrate the change in skeletal metabolism occurring in response to tumour invasion. The radiological studies are dependent upon structural changes which occur later. Citrin et al (5) reported a series of 16 patients with normal x-rays at the time of a bone scan demonstrating metastatic disease in whom the x-rays subsequently confirmed malignant involvement of the skeleton. The mean time between an abnormal scan and development of radiological abnormality was 6 months. One notable exception to increased sensitivity for bone scanning is multiple myeloma (6). In this group of patients the boene scan is usually abnormal, but at fewer sites than skeletal x-rays from the same patients. The lack of sensitivity of the bone scan in myeloma is presumed to be due to failure of the tumour process to elicit an osteoblastic response in the bone. The second main advantage of the bone scan over skeletal radiology for screening for malignant disease in bone is the greater ease with which the whole skeleton can be evaluated by the former method. This is important in view of the widespread dissemination found in many tumours (7). The principal disadvantage of the bone scan in detecting bone metastases is the lack of specificity (Figure 2), making it essential to correlate bone scan findings with x-rays and, if necessary, with bone biopsy (8). This correlation is especially important in patients with extra osseous primaries in whom the bone scan shows a single abnormality (9, 10).

Bone involvement in extra osseous malignancy

Breast cancer patients have been extensively studied by bone scans in many centres. Though it is generally agreed that there is a high incidence of bone metastases in clinically advanced disease, widely differing figures have been reported for the frequency of bone involvement in patients with clinically early disease (11). Many workers would now accept that the frequency of bone scan abnormality is less than 2% in clinical stage I and around 2-5% in stage II. Some authors have advocated that bone scans be performed only in stage I and II patients who have symptoms of bone metastases (12). In view of the non traumatic nature of the procedure we believe bone scans are still indicated in all breast cancer patients for the following reasons:

a. extensive surgery is not indicated when bone metastases are demonstrated as it cannot be curative

b. bone pain is a poor guide as to the presence of metastases (13).

c. patients with bone metastases at presentation have a poor prognosis (14, 15)

d. the initial bone scan is useful for comparing with scans during follow-up.

Bone scans have also been used extensively in the follow-up after mastectomy. Many workers believe routine bone scanning is indicated during follow-up; others disagree, and suggest that routine studies be reserved for patients with adverse prognostic factors such as positive axillary nodes or evidence of vascular invasion. The bone scan should be the first investigation in the patient with a clinical suspicion of metastases (11).

The use of bone scans is well established in prostatic cancer and the study is valuable in the initial and follow-up assessment of all patients (16). It is unclear whether the intensity of tracer uptake within metastatic lesions can be used to monitor the response to hormonal therapy. In renal tumours bone scans appear to be of value in the screening for metastatic disease (17). It should also be remembered that renal tract pathology may be detected as an incidental finding on a bone scan (Figure 3). In patients with carcinoma of the cervix bone scans produce a useful yield of occult metastases only in patients with locally advanced disease (18).

The role of bone scans in evaluation of patients with lung cancer remains controversial, though the consensus of opinion is that a bone scan should be obtained prior to thoracotomy (19). The bone scan is a useful method of detecting hypertrophic pulmonary osteoarthropathy (8).

Primary bone tumours

Bone scans are valuable in the detection of osteoid osteoma, and should be performed in all patients in whom the diagnosis is suspected but x-rays are negative (20). Figure 4 shows a patient with an x-ray negative osteoid osteoma detected by bone scanning.

The bone scan is markedly abnormal at the site of primary osteosarcoma, but it has no advantage over x-rays in demonstrating the extent of the primary tumour (21). The frequency of distant metastases at presentation is less than 5% (22, 23), but a bone scan should be obtained at this time in view of the radical change in therapy necessitated by this finding. Since the introduction of adjuvant chemotherapy, a significant proportion of osteosarcoma patients (15-20%) have bone metastases as their first tumour recurrence (22, 23) and serial bone scans should be performed during follow-up. Bone scanning agents may accumulate in soft tissue metastases from osteosarcoma, but they are an unreliable means of screening for such recurrences (23).

BONE SCANNING IN OSTEOMYELITIS

Acute osteomyelitis remains a difficult diagnosis. Acute osteomyelitis produces an intensely increased uptake of bone

scanning agents within 24 hours of the onset of symptoms (24). Occasionally the first indication of osteomyelitis on the scan is an area of decreased tracer uptake which is thought to represent an area of septic infarction (25). A bone scan should be obtained in all patients with a suspicion of acute osteomyelitis and negative x-rays. The bone scan appears to be unreliable, however, in the diagnosis of acute osteomyelitis in infants (26).

Difficulty may be experienced in differentiating acute osteomyelitis and overlying cellulitis on standard bone scan images. This problem can sometimes be overcome by taking blood pool images, immediately after administering the tracer, in addition to delayed images. In cellulitis there will be an initial high activity on the blood pool image but less intense focal activity on the delayed image whereas the initial high activity will be sustained in the case of acute osteomyelitis (27).

The bone scan is less useful in separating acute osteomyelitis from chronic osteomyelitis in remission, as both will be associated with a focal hot spot. Gallium-67 citrate imaging may be helpful as an abnormal Ga-67 image usually indicates an acute exacerbation (28). Recent work suggests that imaging with Indium-111 labelled polymorphonuclear leucocytes may also be valuable in this context (29).

A specialised problem in the diagnosis of osteomyelitis is the evaluation of the patient with a painful prosthetic joint, particularly a hip replacement. The symptom may be due either to loosening of the prosthesis or to infection around it. It has been suggested that the pattern of bone scan uptake around the prosthesis can allow differentiation of these two diagnoses from standard bone scans (30), though there is debate about this. From recent work it appears that Gallium-67 citrate images may yield false positive results in joint loosening. It has been suggested that the likelihood of infection is increased if the bone scan agent and Gallium-67 show incongruent distribution, while congruent distribution, unless very intense is more likely to indicate prosthetic loosening (28).

BONE SCAN APPEARANCES IN THE METABOLIC BONE DISORDERS

As skeletal uptake of tracer is related to osteoblastic activity and blood flow, the bone scan essentially displays a functional image of skeletal metabolic activity and one would predict that the bone scan would be of considerable value in metabolic bone disease.

However, in contrast to metastatic disease where the characteristic feature of the bone scan is the irregularity of

image (Figure 1) in metabolic bone disease the whole skeleton is often involved by the metabolic process and typically there is diffusely increased skeletal uptake of tracer. Nevertheless, while focal lesions may not be present, certain recognisable patterns of bone scan abnormality and metabolic features are particularly common in the metabolic bone disorders (31-33).

Osteomalacia

The bone scan appearances in vitamin D deficient osteomalacia are often strongly suggestive of a metabolic bone disorder (32). However, the scan features are non-specific and can be seen in other metabolic bone conditions (eg renal osteodystrophy). Recognisable scan features include generalised increased tracer uptake by the axial skeleton, long bones, periarticular areas, with the calvarium and mandible appearing prominent. The renal images may appear faint and occasionally are not seen due to competition between the skeleton and the kidneys for the tracer, reflecting increased bone uptake. The costo-chondral junctions often appear prominent ('beading') and a characteristic appearance of the sternum may also be seen where there is increased activity particularly round the lateral borders - the so-called 'tie' sternum (32,33).

Pseudofractures are common in severe osteomalacia and lesions may be symmetrical and characteristically involve the ribs, femora, pelvic rami and scapula. Pseudofractures on the bone scan are seen as focal areas of increased tracer uptake and in particular in the ribs where conventional x-rays may be normal, the bone scan is the more sensitive investigation (34). However, pseudo-fractures in the pelvis may occasionally be missed on the bone scan due either to their symmetrical nature or because they are obscured by bladder activity (32).

Renal Osteodystrophy

Patients with renal osteodystrophy frequently have bone scan images which show the most striking appearances seen in the various metabolic bone disorders. It is thought that most of the abnormal bone scan findings are due to the effect of secondary hyperparathyroidism but co-existing osteomalacia probably contributes. Typically there is markedly increased tracer uptake throughout the whole skeleton (31,35). In keeping with the high bone uptake the renal images are often not visualised on the bone scan (31). The other metabolic features previously described for osteomalacia are also commonly seen. Focal abnormalities are generally not seen although on occasion the osteomalacia component of renal osteodystrophy may be so severe that pseudofractures occur.

Primary Hyperparathyroidism

Patients with primary hyperparathyroidsm can have bone scans ranging from normal to appearances similar to those found in renal osteodystrophy depending on the severity of the bone disease (36, 37). While increased skeletal uptake of tracer can be detected by sensitive quantitative techniques in virtually all patients with primary hyperparathyroidism, at least 50% of patients will have bone scan images which appear subjectively normal (38).

Osteoporosis

In osteoporosis there is usually only a gradual reduction in bone mass which occurs over many years. In keeping with this the bone scan appearances are usually normal. Osteoporotic bones are abnormally brittle and pathological fractures may occur. These appear on the bone scan as focal abnormalities and when vertebral collapse has occurred, the scan appearances are characteristic with linearly increased tracer uptake corresponding to the whole of the collapsed vertebral body (Figure 2). Generally this increased tracer activity fades over the following 12-18 months and by comparing the scan and x-ray some estimation of the interval since collapse may be obtained (38, 39). Occasionally, very poor scan images with low bone to background ratios are noted in severe or "end-stage" osteoporosis and it has been suggested that these occur because of markedly reduced or absent osteoblastic activity (40).

THE BONE SCAN IN PAGET'S DISEASE

Paget's disease is a common condition with an incidence of approximately 4% in hospital patients over the age of 40 years. The bone scan appearances are often characteristic (41) and it is important to recognise this condition as Paget's disease will often be an incidental finding on a scan performed for another reason, for example in the search for tumour or infection. The main feature on the bone scan in Paget's disease is intense uptake of tracer which is usually distributed uniformly throughout the involved bones (Figure 5). Expansion and distortion of the affected bone is also commonly seen. When polyostotic Paget's disease is present there is seldom any doubt as to the correct diagnosis, so much so that it may be possible to detect co-existing Paget's and metastatic disease (8). When monostotic disease is present it may be difficult to differentiate this from other pathology and in particular from a sclerotic lesion in the spine eg from carcinoma of the prostate, but often even the appearance of a single lesion is so characteristic as to be highly suggestive of Paget's disease. While correlation of x-rays and bone scans in Paget's disease have shown that neither method alone detects all lesions, it is clear that the bone scan is the more

sensitive technique (41-43). In addition, those sites that are occasionally missed on the bone scan are metabolically inactive (42, 43). Indications for performing a bone scan in Paget's disease include the investigation of a patient with elevated serum alkaline phosphatase levels and in any case where Paget's disease is clinically suspected. Where the diagnosis has been established a bone scan is of value to demonstrate the extent of skeletal involvement and as a base line for future reference as patients with Paget's disease often have co-existent disorders such as osteo-arthritis, rheumatoid arthritis or on occasion metastatic disease. Patients undergoing therapy for Paget's disease, eg with either calcitonin or diphosphonate may show an improvement in the bone scan that parallels biochemical changes, while x-rays will usually remain unchanged. Nevertheless at the present time, while of some academic interest, there does not appear to be any clear indication for sequential bone scans as a means of monitoring therapy in Paget's disease as this can be more simply gauged by routine biochemistry.

THE BONE SCAN IN ARTHRITIS

Joint Imaging

In the normal skeleton there is some increase of tracer uptake seen on the bone scan in the bone immediately adjacent to joints, and in general this appears symmetrical. For a joint to appear positive on scanning there requires to be increased tracer uptake relative to an uninvolved joint or markedly higher uptake when compared with adjacent non-articular bone.

Rheumatoid Arthritis

Inflammatory synovitis is associated with increased blood flow to the synovium and peri-articular bones, and as hyperaemia is recognised as a cause of increased tracer uptake it is likely that this is an important factor leading to a positive bone scan in rheumatoid arthritis. However, the intensity of uptake of a bone seeking radiopharmaceutical has been shown to be higher than a blood pool imaging agent in acute inflammation suggesting that there is increased uptake of tracer by peri-articular bone, perhaps due to local remodelling following bone resorption (44,45).. Whatever the precise mechanism there is no doubt that in rheumatoid arthritis intense areas of increased tracer uptake are seen at sites of activity on the bone scan, but the appearances in themselves are non-specific and may be seen in a wide variety of conditions including psoriatic and gouty arthritis, ankylosing spondylitis, seronegative polyarthritis, hypertrophic osteoarthropathy, reflex sympathetic dystrophy syndrome and regional migratory osteoporosis (28). However, it has been suggested that certain features on the scan such as symmetrical disease with peripheral joint activity greater than axial activity, uniform involvement of the wrists and proximal

joints of the limbs and feet, and typical skeletal deformities would favour a diagnosis of rheumatoid arthritis (46).

In rheumatoid arthritis the bone scan has been shown to be able to antedate clinical and radiographic manifestation of inflammatory synovitis (45-47). Nevertheless, once a diagnosis of inflammatory synovitis has been established the bone scan will not provide any additional information and therefore its role in the routine management of patients with rheumatoid arthritis is limited (28). While it has been suggested that the bone scan may provide an accurate means of monitoring a patient's response to therapy (28), its advantage in clinical practice over simpler techniques remains to be established.

In children the bone scan has proven to be disappointing in the detection of rheumatoid arthritis. This is thought due to the fact that tracer uptake in the growth plate obscures any increased uptake in peri-articular bone, induced by inflammatory synovitis (45).

Ankylosing Spondylitis

Acute sacro-iliitis will produce a positive bone scan image and it is now well recognised that the bone scan may detect radiologiclally negative sacro-iliitis (28, 48, 49). The difficulty which arises when assessing the sacro-iliac joints on the bone scan is that they usually appear hotter than the surrounding pelvis and sacrum in normal subjects, and even more so in young subjects in whom sacro-iliitis is most frequently seen. Also while sacro-iliitis may be unilateral it is commonly bilateral and in this situation it may not be possible to detect any abnormality on subjective evaluation. To overcome such difficulties a quantitative technique,, using a computer, has been developed whereby a ratio relating the uptake of tracer by each sacro-iliac joint to that of the body of the sacrum is obtained (49, 50). This ratio is abnormally high early in the disease process when x-ray findings are often minimal or absent, but tends to approach normal as end-stage fusion of the joints develops.

In patients with ankylosing spondylitis it may be possible to identify on the bone scan a diffuse increase in spinal uptake of tracer, most often seen in the low dorsal spine and in addition more focal abnormalities at the apophyseal joints are frequently seen. As there is a tendency to bony ankylosis the scan image will often fail to clearly illustrate the normal segmental anatomy of the spine. Ankylosing spondylitis may also be associated with a peripheral arthropathy which will be seen on the bone scan (48).

Osteoarthritis

In osteoarthritis the increased mechanical stresses occurring at altered joint surfaces lead to an osteoblastic reaction and

reactive new bone formation which is readily demonstrated by bone scanning. Typically the scan appearances show asymmetric tracer uptake at sites of involvement, which correspond to the weight bearing joints and the distal joints of the hands and feet. Patchy tracer uptake with more focal areas in the lower lumbar spine is also a common scan finding when degenerative disease is present. As degenerative disease of the spine is common such scan appearances may occasionally lead to some confusion when metastatic disease is suspected. For this reason it is always essential to x-ray any such area of abnormality to confirm the presence of degenerative change.

In the assessment of osteoarthritis of the knee the bone scan has been shown to be more sensitive than physical examination, radiography and double-contrast arthrography (51) and it was shown that the scan provided important supplementary information in those patients in whom surgery was contemplated.

ASEPTIC NECROSIS AND INFARCTION

Bone scans can be helpful in the diagnosis of aseptic necrosis and infarction, in disorders such as Legg-Perthe's disease, sickle cell anaemia and caisson disease (28). The initial pathological process in each is bone ischaemia, and bone images obtained at this stage will show a zone of decreased tracer uptake. As the pathological process continues a peripheral zone of increased uptake develops and slowly replaces the photon deficient area. The bone scan should be performed as an early investigation in patients with suspected avascular necrosis, as it will often confirm the diagnosis at a time when x-rays are negative or equivocal. It should be noted that special views may be required on occasion eg pinhole images of the hips in the "frog leg" position in children with suspected Legg-Perthe's disease. The value of a bone scan in predicting aseptic necrosis of the femoral head after femoral neck fracture is currently being assessed.

THE BONE SCAN IN TRAUMA

Bone scanning is not a primary diagnostic modality in patients with bony trauma. However, it can be useful in some particular situations, such as assessment of radiologically difficult sites such as the wrists, hips, ribs and sternum, where a persistently negative bone scan virtually excludes a fracture. A positive scan is not completely diagnostic of fracture as it may be seen due to other trauma induced pathologies such as sub-periosteal haematoma. Bone scans may remain abnormal for some time after a fracture (39) but persistently positive scans beyond about 18 months are usually associated either with secondary degenerative disease or healing in poor alignment. The use of the bone scan in studying adequacy of fracture healing has been evaluated in a number of animal models but has not yet found wide acceptance in clinical practice.

Two specialised areas of trauma where bone scanning is very valuable are diagnosis of stress fractures and assessment of battered babies. In stress fractures, characteristically found in athletes, recurring episodes of minor stress lead to some disorganisation of the bone trabeculae. This causes sufficient osteoblastic response to give an abnormal bone scan, some two or three weeks prior to the onset of radiological signs of subperiosteal new bone or sclerosis along a line of healing (52). Thus the bone scan enables earlier restriction of activity, allowing healing to occur and preventing progression to a more gross fracture. The bone scan is helpful in the diagnosis of the "battered baby syndrome" where multiple scan abnormalities may be found throughout the skeleton, resulting both from frank fracture and from subperiosteal haematoma (53).

FIGURE 1a

Normal posterior view

thoracic spine.

FIGURE 1b

Multiple bony metastases

in patient with carcinoma

of breast.

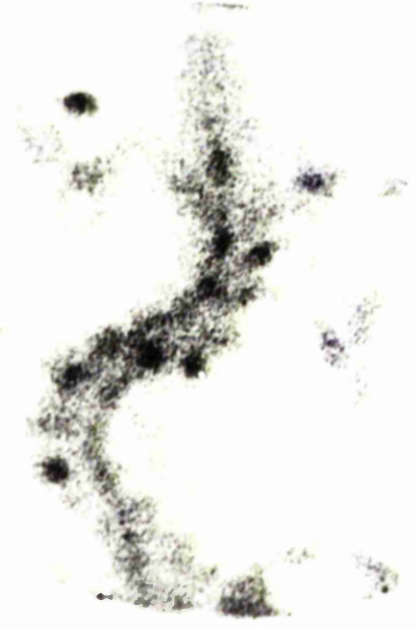


FIGURE 2

Posterior view thoracic spine in osteoporotic subject showing multiple collapsed vertebrae with multiple focal abnormalities in ribs due to trauma and fracture.

FIGURE 3

Anterior view pelvis showing retention of tracer in left urinary tract due to hydronephrosis and hydroureter.

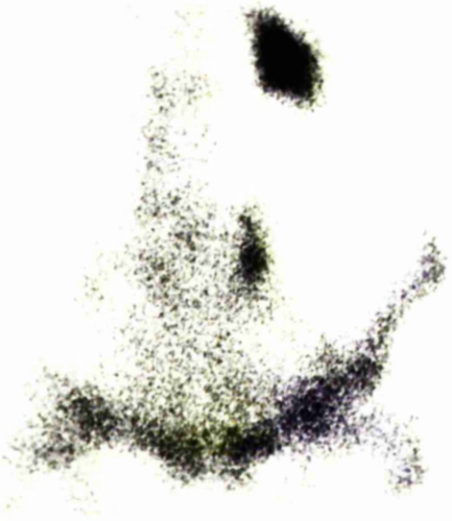


FIGURE 4

Anterior view pelvis showing osteoid osteoma left femoral neck. X-ray negative.

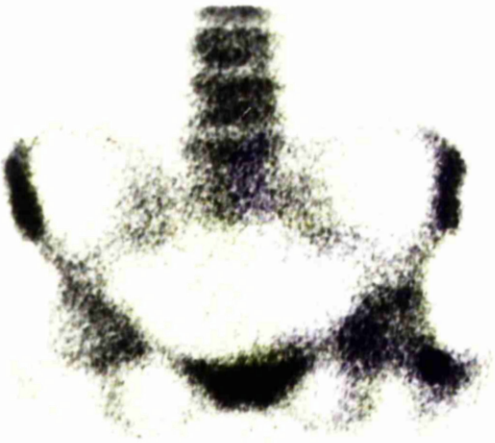
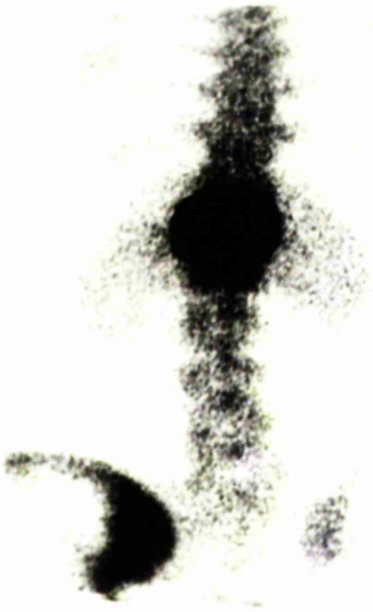


FIGURE 5

Posterior view thoraco-lumbar spine showing Pagetoid involvement of lumbar vertebra 1 and left hemi-pelvis.



References

1. Edelstyn G A et al: Clin Radiol 18, 158, 1967.
2. Francis M D: Calcif Tissue Res 3, 151, 1969.
3. Jones A G et al: Semin Nucl Med 6, 3, 1976.
4. Charkes N D: Radiol Clin N Am 8, 259, 1970.
5. Citrin D L et al: Clin Radiol, 28, 107, 1977.
6. Wahner H W et al: Mayo Clin Proc, 55, 739, 1980
7. Tofe A J et al: J Nucl Med, 16, 986, 1975.
8. Citrin D L and McKillop J H In: Atlas of Technetium Bone Scans. Saunders,Philadelphia, 1978.
9. Corcoran R J et al: Radiology, 121, 663, 1976.
10. Rappaport A M et al: West J Med, 129, 188, 1978.
11. McKillop J H and McDougall I R: Brit Med J, 281, 407, 1980.
12. Khandekar J D: Cancer Treat Rep, 63, 1241, 1979.
13. Front D et al: JAMA 242, 1747, 1979.
14. Galasko C S B: Br J Surg, 56, 757, 1975.
15. McKillop J H et al: Br J Surg, 65, 749, 1978.
16. Haynie T P: Cancer Bull, 30, 127, 1978.
17. Parthasarathy K L et al: Urology, 11, 99, 1978.
18. Katz R D et al: Radiology, 133, 469, 1979.
19. McNeil B J: Semin Nucl Med, 8, 336, 1978.
20. Lisbona R and Rosenthall L: AJR, 132, 77, 1979.
21. Goldman A B et al: Radiology 124, 883, 1975.
22. Goldstein H et al: Radiology 135, 177, 1980
23. McKillop J H et al: Cancer, 48, 1133, 1981.
24. Handmaker H and Leonard R: Semin Nucl Med 6, 95, 1976.
25. Lisbona R and Rosenthall L: Radiology, 123, 123, 1977.

26. Ash J M and Gilday D L: J Nucl Med 21, 417, 1980.

27. Gilday D L et al: Radiology, 117, 331, 1975.

28. Rosenthall L and Lisbona R: In: Nuclear Medicine Annual 1980, eds Freeman L M and Weissmann H S. Raven Press, New York, 1980.

29. Probst S L et al: Clin Nucl Med 5, 559, 1980.

30. Williamson B R J et al: Radiology, 133, 723, 1979.

31. Sy W M and Mittal A K: Br J Radiol 48, 878, 1975.

32. Fogelman I et al: J Nucl Med 19, 245, 1978.

33. Fogelman I et al: Eur J Nucl Med 4, 287, 1979.

34. Fogelman I et al: J Nucl Med 18, 1236, 1977

35. Olgaard K et al: Nephron 17, 325, 1976.

36. Sy W M: J Nucl Med 15, 1089, 1974.

37. Weigmann T et al: J Nucl Med 18, 231, 1977.

38. Fogelman I and Carr D: Clin Radiol 31, 321, 1980.

39. Matin P: J Nucl Med 20, 1227, 1979.

40. Levine S B et al: Clin Nucl Med 2, 318, 1977.

41. Serafini A N: Semin Nucl Med 6, 47, 1976.

42. Shirazi P H et al: CRC Crit Rev Clin Radiol Nucl Med, 5, 523, 1974.

43. Fogelman I and Carr D: Eur J Nucl Med 5, 417, 1980.

44. Beckerman C et al: Radiology 118, 653, 1975.

45. Rosenthall L and Hawkins D: Semin Arthr Rheum 7, 49, 1977,

46. Weissberg D L et al: Am J Roentgenol 131, 665, 1978.

47. Hoffer P B and Genant H K: Semin Nucl Med 6,, 121, 1976.

48. Lentle B C et al: J Nucl Med 18, 524, 1977.

49. Namey T C et al: Arthritis Rheum 20, 1058, 1977.

50. Lentle B C et al: J Nucl Med 18, 529, 1977.

51. Thomas R H et al: Radiology 116, 585, 1975.

52. Roub L W et al: Radiology 132, 431, 1979.

53. Haase G M et al: J Trauma, 20, 873, 1980.

Comment

This paper having been recently written, post-dates the studies described in the thesis but is included because I believe it clearly indicates the extent to which the bone scan is now accepted as a diagnostic procedure in many clinical settings.

As regards the use of bone scanning in metabolic bone disease De Nardo et al (1972) after ten years of experience stated that "while the scan provides a sensitive method for detecting diseases that elicit a localised reparative reaction of the skeleton, the scan is not helpful in the evaluation of diseases that diffusely affect the skeleton". Part of the work in this thesis shows this to have been an over pessimistic assessment and indeed current books and review articles on bone scanning will inevitably include sections on metabolic bone disease (Citrin and McKillop, 1978; McDougall 1979; Sy 1981).

CHAPTER 2

RECOGNITION OF METABOLIC FEATURES AND QUANTITATION OF SKELETAL UPTAKE OF TRACER FROM THE BONE SCAN IMAGE

In this chapter, four papers (3-6) are presented which deal with bone scan appearances, and methods of quantitating skeletal uptake of tracer from the scan image in metabolic bone disease.

Paper 3. The role of bone scanning in osteomalacia (1978)
Journal of Nuclear Medicine 19: 245-248
I Fogelman, J H McKillop, R G Bessent, I T Boyle, J G Turner, W R Greig

Purpose of Investigation

At the time this investigation was conceived there were relatively few reports of bone scanning in metabolic bone disease. It was, however, apparent to me from previous studies that the pattern of abnormality seen on the scan in both primary hyperparathyroidism and renal osteodystrophy were very similar. While there had been no formal study describing the bone scan appearances in osteomalacia, I wondered whether here too the appearances would conform to the same overall pattern which perhaps was typical of metabolic bone disease in general. In addition, I wondered whether such scan appearances could be utilised to differentiate patients with metabolic bone disease from control subjects. Accordingly, bone scans were obtained in patients with osteomalacia, and these together with normal scans and scans from patients with metastatic disease, were evaluated without any knowledge of the clinical information.

The Role of Bone Scanning in Osteomalacia

Ignac Fogelman, James H. McKillop, Rodney G. Bessent, Iain T. Boyle, John G. Turner, and William R. Greig

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The presence of eight "metabolic features" was assessed on the bone scintigrams of ten patients with osteomalacia. In all of these bone images, sufficient features were present to strongly suggest a metabolic disorder. These scintiphotos were included in a controlled blind study using 30 normal bone scans and 20 scans of metastatic disease. Nine of the ten metabolic bone images were correctly identified by two independent observers. Skeletal uptake of radiotracer, expressed as bone-to-soft-tissue ratio, was significantly higher in the osteomalacic patients than in a group of 80 controls.

J Nucl Med 19: 245–248, 1978

Bone scanning is now established as a highly sensitive means of detecting bone metastases, and its superiority over radiographic detection is well recognized (*1,2*). Nevertheless, its use in metabolic bone disease has been limited, although several workers have suggested that it may have a useful role to play in these disorders (*3–7*). Using Tc-99m HEDP, we have obtained bone images in ten patients with osteomalacia, and this communication describes our findings.

METHODS

The study group consists of ten patients complaining of bone and muscle pain and with histologically proven osteomalacia from various causes (Table 1). In each patient multiple views of the skeleton were recorded on Polaroid film from a gamma camera fitted with a high-resolution medium-sensitivity collimator. Spinal views were obtained with 300,000 counts, and all other views with a minimum of 100,000 counts. Bone images were obtained 4 hr after the i.v. injection of 15 mCi of Tc-99m HEDP. The scintiphotos were evaluated for the presence of the following features, which although not necessarily specific have been reported in various metabolic bone diseases: (a) a subjective impression of increased tracer uptake by the axial skeleton (*4,8*), by the long bones (*3–5*), and by the wrists (*5*); (b) prominent calvarium and mandible (*3,7*); (c) beading of the costochondral junctions (*4,5*); and (d) faint kidney images (*4*). In addition, two other features—focal abnormalities representing pseudofractures (Fig. 1) (*9,10*) and a "tie" sternum (Fig. 2), which we have observed in osteomalacic patients —were also included. All of these "metabolic features" were scored either as absent, probably present, or definitely present. The ten sets of images were also included in a controlled blind study using 50 additional, randomly selected sets of bone scans: 30 normal studies and 20 showing metastatic disease. Two observers evaluated the 60 sets of bone images independently without knowledge of patient identification. Each image was recorded as normal, metastatic, or metabolic (Table 3).

In addition to the Polaroid prints, all images were recorded and stored on a minicomputer by means of an analog-to-digital interface. The pictures were stored on computer magnetic tape for later retrieval and processing, and were displayed on a color TV screen. Bone-to-soft-tissue ratios were measured by using the computer to define regions of interest around the L2 vertebra and an area just below the kidney on the TV image. In each area the ratio of the counts per unit area from the former region to the latter was calculated from the teletype printout of the total counts. Similarly, these ratios were calculated for a control group of 80 females with breast

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TABLE 1. CLINICAL AND BIOCHEMICAL DATA FROM OSTEOMALACIC PATIENTS

Patient No., age, and sex	Diagnosis	Serum calcium (normal 2.2–2.6 mmol/l)	Serum phosphate (normal 0.8–1.4 mmol/l)	Serum alkaline phosphatase (normal 80–280 u/l)	Albumin (normal 35–55 g/l)
1. 34 M	Vitamin-D deficiency osteomalacia	1.8	1.5	1,501	38
2. 74 F	Vitamin-D deficiency osteomalacia	2.15	1.0	576	36
3. 68 F	Postgastrectomy osteomalacia	2.05	0.85	679	34
4. 23 F	Vitamin-D deficiency osteomalacia	2.0	1.3	990	33
5. 20 M	Crohn's disease osteomalacia	1.9	0.7	933	25
6. 30 F	Vitamin-D deficiency osteomalacia	2.1	0.75	1,195	40
7. 67 F	Postgastrectomy osteomalacia	1.8	1.2	1,004	41
8. 15 M	Vitamin-D deficiency osteomalacia	1.6	1.35	2,218	45
9. 33 M	Coeliac disease osteomalacia	1.9	0.8	1,391	45
10. 79 F	Anticonvulsant-induced osteomalacia	1.7	1.1	927	34

carcinoma (age range 32–84 yr) without either clinical or scintigraphic suspicion of bone metastases.

RESULTS

The relevant clinical and biochemical details of the osteomalacic patients are shown in Table 1.

Table 2 summarizes the qualitative and quantitative results of the scintigraphic studies in the osteomalacic patients. The mean bone-to-soft-tissue uptake ratio for the osteomalacic group was 6.57 ± 1.43 (s.d.), whereas that in the 80 control patients was 4.05 ± 0.69. Using the Wilcoxon rank sum test, the uptake in the osteomalacic group was significantly higher ($p < 0.001$).

The results of the controlled blind study of the 60 bone images are shown in Table 3. Both observers correctly identified all 30 normal studies and all 20 metastatic studies. Each observer also correctly identified nine of the ten images from the osteomalacic patients.

DISCUSSION

The bone-to-soft-tissue ratio is usually found to be normal in patients with primary hyperparathyroidism (*6,11*). Seven of our osteomalacic patients had elevated ratios compared to our control group; this suggests increased tracer uptake by the axial skeleton, but it was not always apparent from the Polaroid images (Table 2). An elevated bone-to-soft-tissue ratio, when present, however, will support a presumptive diagnosis of osteomalacia.

The most consistent subjective "abnormalities"

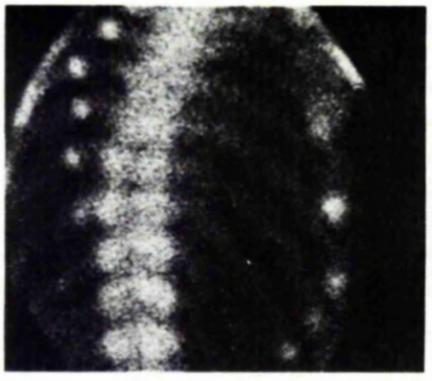

FIG. 1. Dorsolumbar spine. Multiple hot spots in ribs. Radiographs confirmed pseudofractures at these sites.

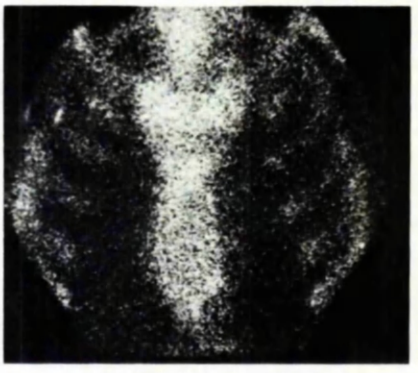

FIG. 2. Anterior view of chest with marked increased uptake of tracer by sternum, especially at its margins—so-called "tie sternum".

TABLE 2. BONE-TO-SOFT-TISSUE (B/ST) RATIOS AND SUBJECTIVE ASSESSMENT* OF SCAN IMAGES

Patient No.	Increased uptake of radiopharmaceutical by: Axial skeleton	Long bones	Wrists	Beading costochondral junction	"Tie sternum"	Hot spots (pseudofractures)	Prominent mandible and calvarium	Faint kidney images	B/ST ratio
1	+	+	++	++	++	++	++	+	4.7
2	+	++	++	+	++	++	++	++	7.8
3	+	++	++	—	—	++	+	++	5.0
4	++	++	not recorded	++	++	++	++	++	7.6
5	++	++	++	+	—	++	++	+	6.9
6	++	++	++	+	—	++	++	++	9.0
7	++	+	++	+	++	++	—	+	4.9
8	++	++	++	++	+	—	++	++	7.2
9	+	++	++	++	+	++	++	+	6.8
10	+	++	+	—	+	++	+	+	5.8

* Absent —; Probably present +; Definitely present ++.

TABLE 3. CONTROLLED BLIND ASSESSMENT OF BONE SCINTIGRAMS

	Metabolic	Metastatic	Normal
Number	10	20	30
Observer J.G.T.	9	21	30
Observer J.H.McK.	9	21	30

noted on the bone images were increased uptake of radiopharmaceutical by the long bones and wrists, with apparent prominence of the calvarium and mandible (Table 2). However, these appearances are nonspecific and are found in other metabolic conditions such as hyperparathyroidism (*4*). Other useful indications of a metabolic disorder—although seen less often in our cases—were the presence of beading of the costochondral junctions, and the "tie sternum." Again, these features may be nonspecific in that they can be seen in patients with renal osteodystrophy, although there is often a significant degree of osteomalacia in such patients.

Although the kidneys were visualized in all patients, in five the kidneys were faint, perhaps reflecting reduced excretion of tracer by the kidneys due to increased skeletal uptake. Pseudofractures were detected in nine patients. In one patient, the previous radiological skeletal survey had been normal, whereas on the scintigram multiple hot spots were seen over the ribs. Subsequent coned radiographs of the areas of abnormality confirmed the presence of several pseudofractures, although these were still not seen in some of the areas indicated by the bone study. In the other patients, routine radiographs identified pseudofractures at the sites of abnormality seen on the bone image. In two patients, however, pelvic pseudofractures shown unequivocally by conventional radiology were not detected on initial scan interpretation. On review of the bone images it was apparent that in one patient there were scintigraphic abnormalities attributable to the pseudofractures, but these had been missed because of their symmetrical nature. In the second patient, no pelvic abnormality was detectable, even on review.

Although the bone images in osteomalacia appear to be nonspecific, we considered that in all our patients, the scintigrams strongly suggested a metabolic disorder. These images were therefore included in a controlled blind study with 50 sets of normal and metastatic bone scintigrams. Table 3 shows that nine of the ten sets of metabolic scans were diagnosed as such by two independent observers. There was complete agreement on all the normal and metastatic images, and on eight of the metabolic ones. No normal or metastatic scan was recorded as metabolic. Each observer considered one osteomalacic scan to be metastatic, and these scans had multiple focal abnormalities representing pseudofractures. Thus an awareness of "metabolic features" on a bone image may alert one to the presence of a metabolic disorder, often with high probability. However, the bone-scan appearances are nonspecific and it is important that adequate clinical information be available during the reading of such scans, since the presence of focal abnormalities, for example, can be mistaken for other conditions, such as metastatic disease.

The bone scintigram, therefore, has a role to play in the detection of osteomalacia, since a combination of several "metabolic features," together with a raised bone-to-soft-tissue ratio, support this diag-

nosis. Multiple focal defects in such an image suggest the presence of pseudofractures, although other conditions cannot be excluded. Roentgenographs of such lesions are mandatory.

REFERENCES

1. CHARKES MD: Bone scanning: Principles, technique and interpretation. *Radiol Clin N Am* 8: 259–270, 1970

2. VERDON TA, YANO Y, ANGER HO: The use of radionuclides in the detection of bone metastases. *J Surg Oncol* 3: 665–672, 1975

3. SY.MW: Bone scan in primary hyperparathyroidism. *J Nucl Med* 15: 1089–1091, 1974

4. SY WM, MITTAL AK: Bone scan in chronic dialysis patients with evidence of secondary hyperparathyroidism and renal osteodystrophy. *Br J Radiol* 48: 878–884, 1975

5. ROSENTHALL L, KAYE M: Technetium-99m-pyrophosphate kinetics and imaging in metabolic bone disease. *J Nucl Med* 16: 33–39, 1975

6. WIEGMANN T, ROSENTHALL L, KAYE M: Technetium-99m-pyrophosphate bone scans in hyperparathyroidism. *J Nucl Med* 18: 231–235, 1977

7. KRISHNAMURTHY GT, BRICKMAN AS, BLAHD WH: Technetium-99m-Sn-pyrophosphate pharmacokinetics and bone image changes in parathyroid disease. *J Nucl Med* 18: 236–242, 1977

8. FOGELMAN I, MCKILLOP JH, BOYLE IT, et al: Absent kidney sign associated with symmetrical and uniformly increased uptake of radiopharmaceutical by the skeleton. *Eur J Nucl Med*: in press

9. SINGH BN, KESALA BA, MEHTA SP, et al: Osteomalacia on bone scan simulating skeletal metastases. *Clin Nucl Med* 2: 181–183, 1977

10. FOGELMAN I, MCKILLOP JH, GREIG WR, et al: Pseudofractures of the ribs detected by bone scanning. *J Nucl Med* 18: 1236, 1977

11. FOGELMAN I, BESSENT RG, BOYLE IT, et al: Skeletal uptake of Tc-99m HEDP in primary hyperparathyroidism. *J Nucl Med* 18: 1040, 1977

Comment

This paper introduces for the first time the term "metabolic features" and also the important concept of such features being recognisable on bone scans from patients with metabolic bone disease. While all the individual features, with the exception of the "tie" sternum had been previously described in various publications, their general application to metabolic bone disease had not been recognised. This theme is further developed and the wider application of metabolic features illustrated in papers 4 and 5. It should be noted, however, that the presence of focal lesions on the scan cannot be considered a metabolic feature and in retrospect should not have been included as such. Nevertheless when the scan appearances do suggest the presence of a metabolic disorder and focal lesions are present, particularly in the ribs, the possibility of osteomalacia with pseudofractures should be considered in the differential diagnosis.

It has been shown in the present study that by recognition of metabolic features on the bone scan, patients with osteomalacia can be identified in the great majority of cases, and differentiated from both normal subjects and those with metastatic disease. It must, however, be emphasised that the metabolic features described are not specific to osteomalacia and may be seen in a wide variety of metabolic bone disorders or in any situation where there is generalised increased bone turnover.

Paper 4. Semi-quantitative interpretation of the bone scan in metabolic bone disease. Definition and validation of the metabolic index (1979)

European Journal of Nuclear Medicine 4: 287-289

I Fogelman, D L Citrin, J G Turner, I D Hay, R G Bessent, I T Boyle

Purpose of Investigation

Following on from the work described in paper 3, I suggested that metabolic features on the bone scan may be seen in a wide variety of clinical settings. Indeed these features simply demonstrate increased uptake of tracer at various sites in the skeleton and many are normally seen on the adolescent bone scan, reflecting the high avidity of the growing skeleton for bone seeking radiopharmaceuticals. However, I believed that recognition of those features on the adult bone scan might be of value in the identification of patients with increased skeletal metabolism. I considered that simple visual evaluation of the bone scan was too subjective for this purpose and suggested that a semi-quantitative scoring system be derived from the scan image.

Quantitation of skeletal uptake of tracer is theoretically attractive for if generalised increased bone turnover exists, there will also be increased skeletal avidity for bone seeking radiopharmaceuticals (Neuman and Neuman, 1953).

However, in the absence of focal lesions on the bone scan image an awareness of abnormality depends upon a subjective impression of increased tracer uptake by the skeleton, and this is not always apparent. Accurate quantitation of tracer uptake by the skeleton may provide a sensitive means of evaluating altered skeletal metabolism.

In the present study three independent observers numerically graded seven metabolic features on the bone scan images from 50 control subjects and 100 patients with various metabolic bone disorders, the total score for an individual subject being defined as the metabolic index. The purpose of the study was to evaluate whether this metabolic index allowed differentiation between control subjects and those with metabolic bone disease.

Eur. J. Nucl. Med. 4, 287–289 (1979)

European Journal of Nuclear Medicine

Semi-Quantitative Interpretation of the Bone Scan in Metabolic Bone Disease

Definition and Validation of the Metabolic Index

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Abstract. Certain easily recognisable features are commonly seen in the bone scans of patients with metabolic bone disorders. Seven such features have been numerically graded by three independent observers in the scans of 100 patients with metabolic bone disease and of 50 control subjects. The total score for each patient is defined as the metabolic index. The mean metabolic index for each group of patients with metabolic bone disease is significantly greater than that for the control group ($P < 0.001$).

Introduction

The bone scan is of value in the diagnosis and assessment of patients with benign skeletal disease (Marty et al., 1976). In metabolic bone disease certain patterns of bone scan abnormality are common and we have previously described several scan features which are characteristic of these disorders (Fogelman et al., 1978a). Other workers have suggested techniques for numerical assessment of scan features in parathyroid disease, (Olgaard et al., 1976; Sy and Mittal, 1975; Krishnamurthy et al., 1977) but inter-group correlation and comparison with a control group have not been reported. In this study we describe a semi-quantitative diagnostic index for metabolic bone disease derived from the bone scan.

Materials and Methods

One hundred patients with metabolic bone disease (29 patients with renal osteodystrophy, 14 with osteomalacia, 15 with osteoporosis, 13 with primary hyperparathyroidism, 9 with thyrotoxicosis, 20 with acromegaly) and 50 control subjects were studied. In each patient the diagnosis was confirmed by relevant biochemical and radiological studies. In addition bone biopsies were obtained in all patients with osteoporosis, osteomalacia and primary hyperparathyroidism. The control group was composed of 50 female patients with primary breast cancer who had been referred to our Department of Nuclear Medicine for bone scanning as part of their initial evaluation or routine post mastectomy follow-up. There was no clinical suspicion of skeletal metastases in these patients and in all cases the bone scans were reported as showing no focal abnormality by three independent observers. By these criteria, the patients were considered to be suitable "normal" controls and their scans were re-analysed for the presence of metabolic features as described below.

In all patients the bone scan was obtained 4 hours after the intravenous injection of 15 mCi of ^{99m}Tc-hydroxyethylidene diphosphonate (H.E.D.P.). Multiple views of the skeleton were recorded on Polaroid film using an Ohio Nuclear Series 100 gamma camera fitted with a high resolution medium sensitivity collimator. Views of the spine were obtained with 300,000 counts, of pelvis, shoulder and sternum with 150,000 counts, of skull with 100,000 counts, and of limbs with 30,000 counts.

The scan images of patients and controls were independently evaluated in a random order by three observers who were unaware of the clinical diagnosis. Each bone scan was inspected for seven metabolic features (listed in Table 1) which we have previously shown to be common in metabolic bone disease, (Fogelman et al., 1978a). These features were independently scored by each observer: 0 - Normal; 1 - Abnormal; or 2 - Markedly abnormal (e.g. Figs. 1–3). The sum of the scores for each metabolic feature was defined as the Metabolic Index for that patient.

Table 1. Metabolic features

1. Increased activity in axial skeleton
2. Increased activity in long bones
3. Increased activity in periarticular area (wrist)
4. Prominent calvarium and mandible
5. Beading of the costo-chrondral junctions
6. "Tie" sternum
7. Faint or absent kidney images

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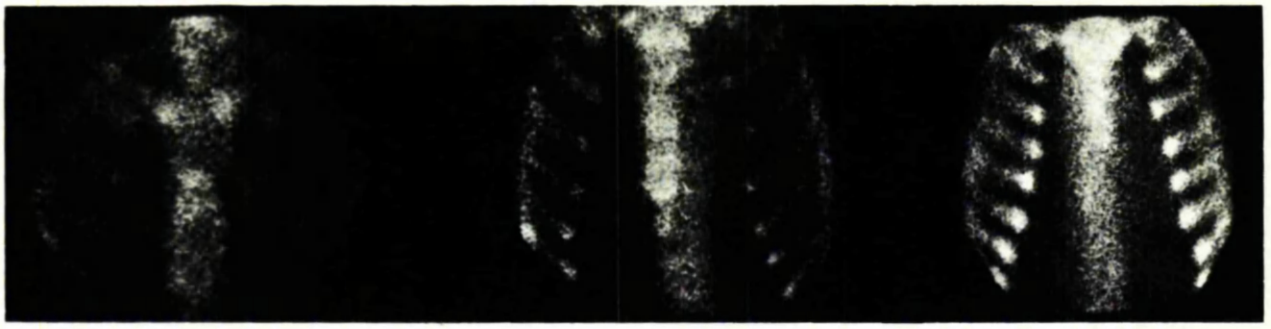

Fig. 1. Bone scans of anterior thorax. Normal, with 2 examples of beading of the costo-chondral junctions. (These and images shown in Figs. 2 and 3 are graded 0, 1 and 2 respectively)

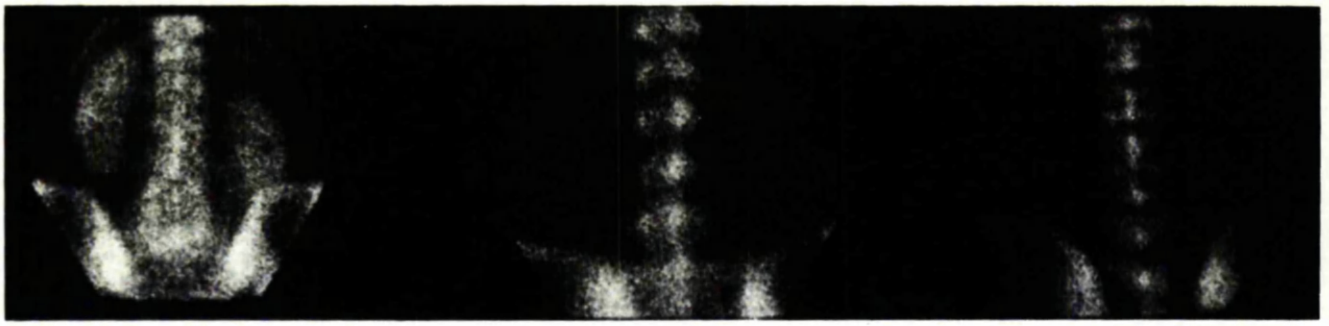

Fig. 2. Posterior views of lumbosacral spine demonstrating normal, faint and absent kidney images

Results

The mean scores obtained for the metabolic index by each of the 3 observers for the different study groups are shown in Table 2. There was good concordance between individual observers. The last 2 columns of Table 2 show the mean of the 3 observers' results and the absolute range for each group.

The metabolic index of each patient group was significantly higher than that of the control group ($P < 0.001$, using the Wilcoxon Rank Sum Test). There was, however, overlap between individual patient results and normal controls. This was not seen in patients with renal osteodystrophy and osteomalacia, where each individual patient's result lay outside the normal range. The mean metabolic index of the renal osteodystrophy and osteomalacia groups was significantly higher than the other patient groups ($P < 0.02$). In addition, the mean metabolic index of the thyrotoxic group was significantly higher than that of the osteoporotic group ($P < 0.005$).

The distribution of individual results of the metabolic index (mean of 3 observers) is shown in Fig. 4.

Table 2. Results of metabolic index[a]; mean and range of 3 observers

	No.	Observers			Mean	Absolute range
		1	2	3		
Controls	50	0.6	0.8	0.7	0.7	0 – 2.3
Osteoporosis	15	2.1	1.7	2.2	2.0	0.3– 5.0
Acromegaly	20	4.0	4.0	5.1	4.4	0 –10.7
Primary Hyperparathyroidism	13	5.3	5.0	5.0	5.1	0.3–12.3
Thyrotoxicosis	9	5.1	6.0	5.2	5.4	0 – 9.0
Renal Osteodystrophy	29	9.5	8.5	8.5	8.8	3.3–14.0
Osteomalacia	14	9.3	7.9	10.2	9.1	4.3–12.3

[a] Metabolic Index in an individual patient is a whole number without decimals

Discussion

In contrast to metastatic disease where focal abnormalities are characteristically seen, the bone scan diagnosis of metabolic bone disease depends upon recognition of generalised increased bone uptake of radiopharmaceutical. This may be difficult to assess on visual interpretation and simple quantitation of the bone scan image as measured by bone to soft tissue ratios may also be unreliable, (Fogelman et al., 1978b). We have previously described scan features which are commonly seen in metabolic bone disease and found that these features differentiated between

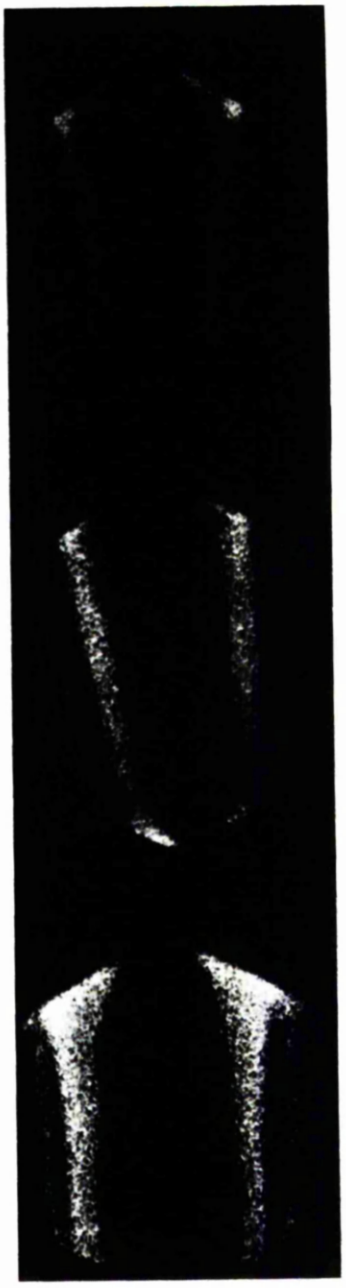

Fig. 3. Normal appearance of lower limbs with 2 examples of increased tracer uptake. Note fibulae have become visible

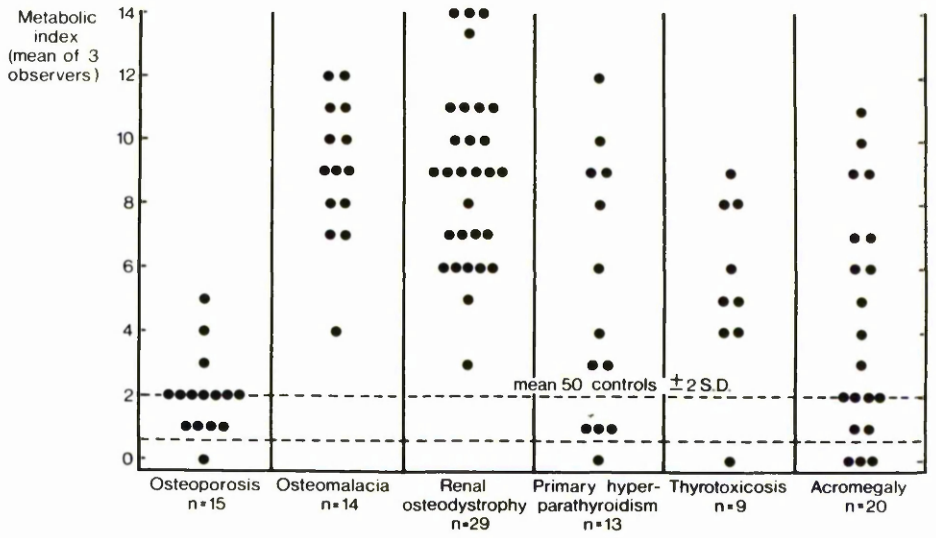

Fig. 4. Distribution of individual results for metabolic index. (Mean of three observers)

osteomalacia, metastatic disease and control subjects, (Fogelman et al., 1978b). In the present study these metabolic features were given a numerical score and the total score for each patient defined as the metabolic index. This derived value was found to differentiate well between each disease group and the control group. In addition, there was no overlap between individual results in the osteomalacia or renal osteodystrophy groups and the control group (Fig. 4). However, in the other patient groups there was overlap with the control range rendering a normal result in an individual patient of limited value.

The metabolic index provides a reproducible semiquantitative diagnostic index for metabolic bone disease. It focuses attention on specific metabolic features of the bone scan, and an elevated value may alert an observer to the presence of a metabolic bone disorder which requires further investigation.

References

Fogelman, I., Bessent, R.G., Turner, J.G., Citrin, D.L., Boyle, I.T., Greig, W.R.: The use of whole body retention of 99m-Tc-Diphosphonate in the diagnosis of metabolic bone disease. J. Nucl. Med. **19**, 270–275 (1978b)

Fogelman, I., McKillop, J.H., Bessent, R.G., Boyle, I.T., Turner, J.G., Greig, W.R.: The role of bone scanning in osteomalacia. J. Nucl. Med. **19**, 245–248 (1978a)

Krishnamurthy, G.T., Brickman, A.S., Blahd, W.H.: Technetium-99m-Sn-pyrophosphate pharmacokinetics and bone image changes in parathyroid disease. J. Nucl. Med. **18**, 236–242 (1977)

Marty, R., Denney, J.D., McKamey, M.R., Rowley, M.J.: Bone trauma and related benign disease: Assessment by bone scanning. Sem. Nucl. Med. **6**, 107–120 (1976)

Olgaard, K., Heerfordt, J., Madsen, S.: Scintigraphic skeletal changes in uraemic patients on regular haemodialysis. Nephron **17**, 325–334 (1976)

Sy, W.M., Mittal, A.K.: Bone scan in chronic dialysis patients with evidence of secondary hyperparathyroidism and renal osteodystrophy. Br. J. Radiol. **48**, 878–884 (1975)

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Comment

This study illustrates that a numerical score reflecting skeletal avidity for tracer can be obtained from a bone scan image by visually evaluating several metabolic features. This metabolic index has been shown to allow differentiation of groups of patients with various metabolic bone disorders from control subjects. Nevertheless, the overlap in most groups, between patients and controls, limits its value in individual patients.

However, the metabolic index score is extremely simple and quick to obtain, and can thus provide a convenient semi-quantitative means of evaluating a bone scan image. Indeed it has been used in this way in a recent study by Alberts et al (1981) where bone scans from patients with symptomatic renal osteodystrophy were evaluated for severity of disease. The metabolic index may also be of some value where sequential studies are being performed on an individual patient to document change, either improvement or deterioration, over a period of time. At its simplest the metabolic index will focus an observer's attention as to the presence or otherwise of metabolic features on the bone scan.

Nevertheless, even the above statements as to the limited usefulness of the metabolic index in metabolic

bone disease may need review in the light of current bone scanning practice. When this study and indeed all the bone scan imaging described in this thesis were carried out, Tc-99m hydroxyethylidene diphosphonate (HEDP) was the radiopharmaceutical used. Currently Tc-99m methylene diphosphonate (MDP) is the most widely used bone scanning agent and this has significantly higher skeletal uptake than HEDP (see paper 14). From personal experience I believe that the presence of metabolic features on the bone scan is less obvious when higher bone uptake is routinely obtained in normal subjects, and the metabolic index is thus likely to prove less discriminating with MDP scans. A comparison of the available diphosphonate bone scanning agents and the clinical implications of their use is discussed in chapter 5.

Paper 5. Semi-quantitative analysis of the bone scan in acromegaly: Correlation with human growth hormone values (1980)

British Journal of Radiology 53: 874-877

I Fogelman, I D Hay, D L Citrin, G H Beastall, J G Turner, R G Bessent.

Purpose of Investigation

The purpose of this investigation was to evaluate bone scan images in patients with acromegaly, and correlate the metabolic index, reflecting skeletal avidity for a bone-seeking radiopharmaceutical, with serum growth hormone values, a biochemical measure of disease activity.

1980, *British Journal of Radiology*, *53*, 874–877

Semi-quantitative analysis of the bone scan in acromegaly: correlation with human growth hormone values

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ABSTRACT

$^{99}Tc^{m}$-HEDP bone scans were obtained in 20 acromegalic patients. Twelve patients had active disease with elevated basal serum human growth hormone (HGH) levels. Eight patients were in clinical and biochemical remission.

The bone scans, assessed independently by three observers, showed features characteristic of metabolic bone disease in patients with active acromegaly. The metabolic index derived from the scan correlated well with serum HGH levels ($R=0.71$, $p<0.002$).

The bone scan may accurately reflect oversecretion of HGH and is of potential value in the assessment of patients with acromegaly.

Radioisotope bone scans are widely used in the diagnosis of metastatic and metabolic bone disease. In active acromegaly bone formation is significantly increased (Riggs *et al.*, 1972) but no clinical study of bone scanning in this disorder has been described. We have obtained $^{99}Tc^{m}$ diphosphonate bone scans in a group of 20 acromegalic patients and correlated the results with clinical status and biochemical evidence of anterior pituitary overactivity.

PATIENTS AND METHODS

Clinical data

Twenty acromegalic patients were studied (13 female, seven male). Their mean age was 48 years (range 16–68 years). Eighteen of the patients were treated for acromegaly between 15 months and 16 years prior to the study. Two of the patients had received no treatment at the time of study but subsequently transsphenoidal microsurgery was performed. Details of previous treatment are shown in Table I.

TABLE I

MODE OF PREVIOUS TREATMENT

Transsphenoidal microsurgery	6
Transsphenoidal cryosurgery	6
Transfrontal craniotomy	5
External irradiation	1
Untreated	2
	20

The diagnosis of acromegaly was based on clinical criteria and confirmed in all cases by non-suppressibility of human growth hormone (HGH) by an oral 50 g glucose load. Histological evidence of an anterior pituitary adenoma was obtained in 19 patients at the time of hypophysectomy. The remaining patient was treated with external irradiation and tissue confirmation was not obtained.

Bone scans

In each patient a bone scan was obtained four hours after the intravenous injection of 555 MBq (15 mCi) of $^{99}Tc^{m}$-hydroxyethylidene diphosphonate (HEDP). Multiple views of the skeleton were recorded on polaroid film from an Ohio Nuclear Series 100 gamma camera fitted with a high resolution medium sensitivity collimator. Views of the spine were obtained with 300000 counts, of pelvis, shoulder and sternum with 150000 counts, of skull with 100000 counts and of limbs with 30000 counts. The scan images were independently evaluated by three observers (I.F., D.L.C., J.G.T.) for the following features which are characteristic of metabolic bone disease: a subjective impression of increased radiopharmaceutical uptake by the axial skeleton, by the long bones and by the wrists, prominent calvarium and mandible, beading of the costochondral junctions, "tie" sternum and faint kidney images (Figs. 1–3), (Fogelman *et al.*, 1978). These scan features were numerically graded: 0—normal; 1—abnormal; 2—markedly abnormal. The total score for each patient was defined as the "metabolic index", which has been previously shown to differentiate between control subjects and patients with metabolic bone disease (Fogelman *et al.*, 1979).

Biochemical investigations

The HGH status of each patient was assessed by measurement of a diurnal HGH profile because of the known marked fluctuation in HGH levels and the unreliability of a single fasting HGH sample

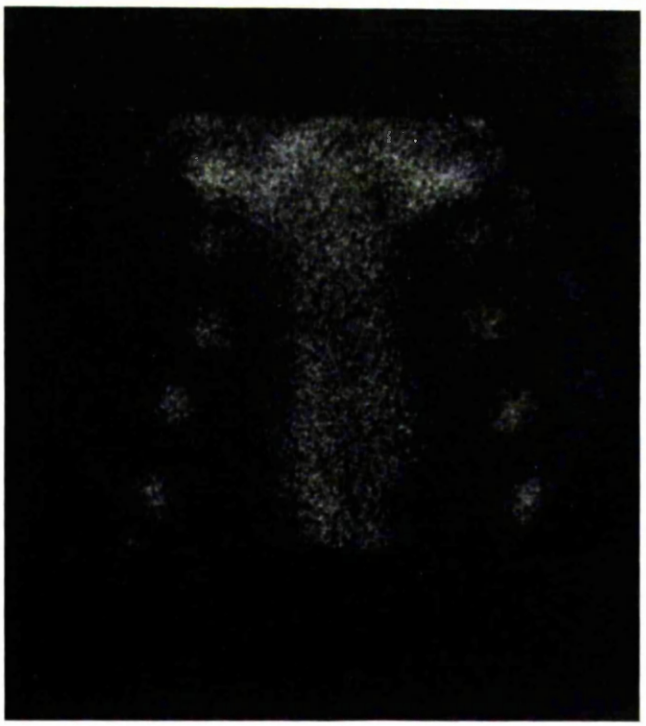

FIG. 1.

Anterior view of thorax on bone scan from acromegalic patient showing increased tracer uptake by costochondral junction ("beading") and a "tie" sternum.

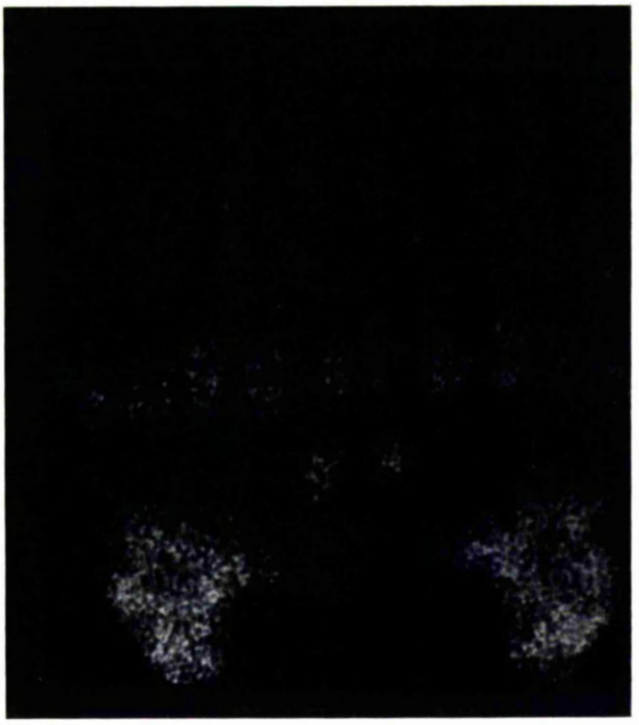

FIG. 3.

Views of wrists and hands showing increased tracer uptake by periarticular areas—in the wrists and small joints of the hand.

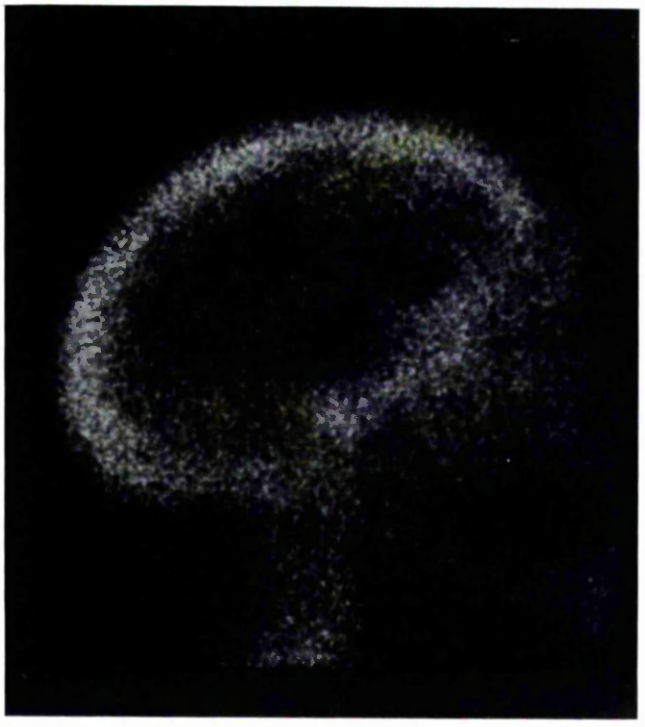

FIG. 2.

Lateral view of skull showing increased uptake by calvarium and mandible. Prognathism is apparent.

(Cryer and Daughaday, 1969). Blood samples were taken through an indwelling venous catheter at two-hourly intervals between 08.00 and 20.00 hours during one day. Serum HGH levels were measured using a radioimmunoassay modified from the method of Hunter and Greenwood (1964), and the mean HGH level calculated for each patient from the seven samples of the diurnal profile and the fasting basal sample of the glucose tolerance test.

A patient was considered biochemically "active" if his mean HGH level was above 10 mU/l. By this criterion 12 patients were active while the other eight were inactive (Table II).

Serum calcium, inorganic phosphate and alkaline phosphatase were estimated in all patients using standard techniques as employed by the Department of Clinical Biochemistry in the Royal Infirmary, Glasgow.

The values for the mean metabolic index and HGH levels were correlated using the Spearman rank correlation coefficient. Comparison of the results for the metabolic index from the three observers was performed using a paired Wilcoxon rank sum test.

TABLE II

A. ACROMEGALIC PATIENTS SHOWING BIOCHEMICAL ACTIVITY

HGH level		Number of patients
Mild	< 50 mU/l	6
Moderate	50–150 mU/l	3
Severe	> 150 mU/l	3
		12

B. ACROMEGALIC PATIENTS WITH BIOCHEMICAL INACTIVITY

HGH level	Number of patients
0–5 mU/l	5
5–10 mU/l	3
	8

TABLE III

RESULTS OF METABOLIC INDEX AND HGH LEVELS

Pt	Metabolic index				HGH mU/l
	Obs. 1	Obs. 2	Obs. 3	Mean	
1	10	10	12	10.7	4955
2	11	9	11	10	491
3	7	9	10	8.7	420
4	4	7	9	6.7	141
5	6	7	8	7	111
6	5	6	8	6.3	50
7	8	9	9	8.7	27
8	5	2	3	3.3	24
9	2	2	2	2	17
10	0	2	2	1.3	13
11	0	0	1	0.3	12
12	5	3	4	4	11
13	0	0	0	0	10
14	5	6	6	5.7	7
15	5	3	6	4.7	6
16	0	0	2	0.7	4
17	0	0	1	0.3	1.5
18	2	2	3	2.3	1.4
19	2	1	2	1.7	1
20	2	2	3	2.3	1

RESULTS

There was no significant difference between the three observers' results for the metabolic index. The Spearman rank correlation coefficient between observers 1 and 2, 1 and 3, and 2 and 3 was 0.88, 0.91 and 0.95 respectively ($p < 0.001$, in all cases). The mean metabolic index for the acromegalic group as a whole was 4.4, significantly higher than previously described for a control group (0.7, $p < 0.001$) (Fogelman *et al.*, 1979). The mean metabolic index for patients with active disease was 5.8 and for inactive patients 2.3 ($p < 0.001$). In individual patients there was good correlation between the mean metabolic index and mean serum HGH level ($R = 0.71$, $p < 0.002$) (Table III).

Serum calcium was normal in all patients. Serum inorganic phosphate was elevated (> 1.4 mmol/l) in five patients (25%) and alkaline phosphatase (> 280 U/l) in three patients (15%). These abnormalities were only found in patients with active disease.

DISCUSSION

Routine skeletal radiology plays an important role in the diagnosis of acromegaly but is an insensitive means of assessing the current metabolic activity of the condition (Steinbach *et al.*, 1959; Puckette and Seymour, 1967). The present study has shown that, in patients with active acromegaly, the bone scan will often display features characteristic of a metabolic bone disorder. Other features noted on the bone scan were prognathism with enlarged frontal sinuses and focal abnormalities representing degenerative changes.

The metabolic index derived from the bone scan has previously been shown to provide a sensitive means of identifying the presence of metabolic bone disease (Fogelman *et al.*, 1979) and in the present study was found to correlate well with biochemical activity as measured by HGH. We have decided empirically to interpret a metabolic index of over four (*i.e.*, five or above) as abnormal (*i.e.*, strongly suggestive of a metabolic bone disorder) and by this criterion there were five false negative and two false positive results. However, these patients all had HGH levels of between 6 and 24 mU/l and although we have found a correlation between the metabolic index and HGH levels it seems that this test is not sensitive enough to predict accurately whether an individual patient is active or inactive, particularly when HGH levels are only moderately elevated or else high normal. As expected, serum alkaline phosphatase and inorganic phosphate levels were of little diagnostic value (Hall *et al.*, 1975).

The bone scan and derived metabolic index provides a numerical score for assessing current metabolic activity in acromegalic patients. It is thus possible to obtain a semi-quantitative measure of the peripheral effect of HGH and this may be of value in assessing patients where there is a discrepancy between the apparent clinical severity of the disease and the absolute HGH level (Nabarro, 1977). This technique may also be of value in monitoring the duration of abnormal skeletal metabolism in patients following neurosurgical treatment.

Radionuclide imaging draws attention to the high incidence of skeletal disease in acromegaly and it is concluded that the bone scan and derived metabolic index may provide useful clinical information in patients with known or suspected hypersecretion of HGH.

REFERENCES

CRYER, P. E. and DAUGHADAY, W. H., 1969. Regulation of growth hormone secretion in acromegaly. *Journal of Clinical Endocrinology and Metabolism, 29*, 386–393.

FOGELMAN, I., CITRIN, D. L., TURNER, J. G., HAY, I. D., BESSENT, R. G. and BOYLE, I. T., 1979. Semiquantitative interpretation of the bone scan in metabolic bone disease: definition and validation of the metabolic index. *European Journal of Nuclear Medicine, 4*, 287–289.

FOGELMAN, I., MCKILLOP, J. H., BESSENT, R. G., BOYLE, I. T., TURNER, J. G. and GREIG, W. R., 1978. The role of bone scanning in osteomalacia. *Journal of Nuclear Medicine, 19*, 245–248.

HALL, R., ANDERSON, J., SMART, G. A. and BESSER, M., 1975. In: *Fundamentals of Clinical Endocrinology* (Pitman, London), p. 7.

HUNTER, W. M. and GREENWOOD, F. C., 1964. Radio-immunoelectrophoretic assay for human growth hormone. *Biochemical Journal, 91*, 43–56.

NABARRO, J. D. N., 1977. Management of acromegaly. *Journal of Clinical Pathology, 30*, 62–67 Suppl.

PUCKETTE, S. E., Jr. and SEYMOUR, E. Q., 1967. Fallibility of the heel-pad thickness in the diagnosis of acromegaly. *Radiology, 88*, 982–983.

RIGGS, B. L., RANDALL, R. V., WAHNER, H. W., JOWSEY, J., KELLY, P. J. and SINGH, M., 1972. The nature of the metabolic bone disorder in acromegaly. *Journal of Clinical Endocrinology and Metabolism, 34*, 911–918.

STEINBACH, H. L., FELDMAN, R. and GOLDBERG, M. B., 1959. Acromegaly. *Radiology, 72*, 535–549.

Comment

While acromegaly is not generally considered to be a metabolic bone disorder, it is recognised that growth hormone is a potent stimulator of osteoblastic activity (Riggs et al, 1972) and that periosteal bone formation and cortical hypertrophy occur in this condition (Frohman 1981). Routine radiology may play a supportive role in the diagnosis of acromegaly but is extremely insensitive in assessing the current metabolic activity of disease.

The present study attracted me for two reasons. Firstly there was no previous report on the use of bone scanning in acromegaly and this study provided an opportunity to determine whether metabolic features would be recognisable on the scan images in a condition where new bone formation was known to occur. Secondly in this prospective study which included patients with disease activity ranging from inactive to severe, metabolic indices could be derived from the bone scans and correlated with serum growth hormone levels, an independent biochemical marker reflecting disease activity. While calcium kinetic studies in acromegaly had previously shown increased bone uptake of tracer (Eisenberg and Gordon, 1961; Nadarajah et al, 1968), this was not correlated with disease activity.

In the present study it was found that the metabolic index correlated well with growth hormone levels suggesting that the degree of altered skeletal metabolism is directly dependent on the activity of acromegaly.

As can be seen the metabolic features described previously in other metabolic bone disorders were observed in patients with active acromegaly, thus confirming that such features may be seen outwith the narrow confines of a few specific conditions. However, in acromegaly prognathism can often be recognised on the scan image and this may allow differentiation. Although not the purpose of the study, degenerative changes were frequently noted, and the bone scan provides a convenient means of evaluating the extent of osteoarthritis in acromegaly, should this be required.

Paper 6. A critical assessment of bone scan quantitation (bone to soft tissue ratios) in the diagnosis of metabolic bone disease (1981)

European Journal of Nuclear Medicine 6: 93-97

I Fogelman, R G Bessent, D Gordon

Purpose of Investigation

As stated previously, it would be highly desirable to be able to quantitate accurately skeletal uptake of radiopharmaceutical to provide a more sensitive means of detecting increased bone turnover. Several groups had suggested that measurement of bone to soft-tissue (B/ST) ratios from the bone scan image may provide a satisfactory method for quantitating bone uptake of tracer (Wiegmann et al, 1976; 1977; Holmes 1978; Lien et al, 1976). Utilising a computer programme , bone to soft-tissue ratios are measured by selecting regions of interest over both bone and adjacent soft-tissue on the television display. The bone and soft-tissue count densities in these areas are then obtained. The B/ST ratio is thus easily measured, and theoretically should reflect skeletal avidity for tracer.

It was my belief, however, that B/ST ratios were likely to be of limited value in the identification of

patients with metabolic bone disease because of the small area of bone that was selected to reflect total skeletal metabolism. Nevertheless, critical studies of the technique had not been performed. The present study reports B/ST ratio measurements in a large series of patients with metabolic bone disease and control subjects. The reproducibility of B/ST measurements and the inter- and intra-observer variation of the contributing procedures were also evaluated.

Eur J Nucl Med (1981) 6:93–97

European Journal of Nuclear Medicine

A Critical Assessment of Bone Scan Quantitation (Bone to Soft Tissue Ratios) in the Diagnosis of Metabolic Bone Disease

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Abstract. Accurate quantitation from the bone scan image of skeletal uptake of radiopharmaceutical would be of value in the assessment of patients with metabolic bone disease. Repeat measurements of bone to soft tissue (B/ST) ratios on the one set of images were made for 103 subjects, a) by the same observer using lumbar vertebra 2 for the area of bone; b) by the same observer using lumbar vertebra 2 then lumbar vertebra 4; c) by two observers both using lumbar vertebra 2. The median difference between repeat measurements by the same observer was well under 1% but the 5–95 percentile range was −13 to +14%. Between the two observers there was a median difference of 10.6% with a 5–95 percentile range of −11 to +44%.

We also measured B/ST ratios in 150 control subjects and 139 patients with various metabolic bone disorders. While statistically significant differences for B/ST ratios were found between the osteomalacia, renal osteodystrophy, Paget's groups, and the control population ($P < 0.001$ in all cases), there was appreciable overlap between individual patient results and the control range.

It is concluded, therefore, that measurement of B/ST ratios for the individual is of limited value in clinical practice.

Introduction

In contrast to metastatic disease where the characteristic feature of the bone scan is the irregularity of the image with focal abnormalities present, in metabolic bone disease typically there is diffusely increased skeletal activity. Recognition of abnormalities in such cases depends upon a subjective impression of generally increased skeletal uptake of tracer and errors in interpretation are likely, particularly in milder examples of disease. Accurate quantitation of skeletal uptake of tracer may thus be helpful in the diagnosis of metabolic bone disease. Measurement of bone to soft tissue (B/ST) ratios from the bone scan image has been proposed as a useful index (Weigmann et al. 1976; Weigmann et al. 1977; Holmes 1978; Lien et al. 1976), but there is doubt as to the value of this technique (Fogelman et al. 1978a; Fogelman et al. 1978b). In view of the number of variables contributing to a B/ST measurement we considered it important to investigate in detail the reproducibility of the technique and the inter- and intra-observer variability of the contributing procedures. To these ends we have measured B/ST ratios in a large series of both patients with metabolic bone disease and control subjects and have asked the following questions on the technique:

1. Is the B/ST measurement by a single observer reproducible for an individual subject?
2. Does the exact area of soft tissue selected affect the result?
3. Does the exact area of bone selected affect the result?
4. What is the inter-observer variability?

We also wished to assess the usefulness of an optimum B/ST measurement in diagnosing metabolic bone disease when carried out under carefully controlled conditions by one observer. We therefore went on to ask these further questions:

5. Does the bone to soft tissue ratio alter with advancing age?
6. What is the diagnostic value of the B/ST ratio in metabolic bone disease?

Patients and Methods

The control group consisted of 150 females with breast carcinoma, but without either clinical or radiological suspicion of bone metastases, who had been referred to our department for routine bone

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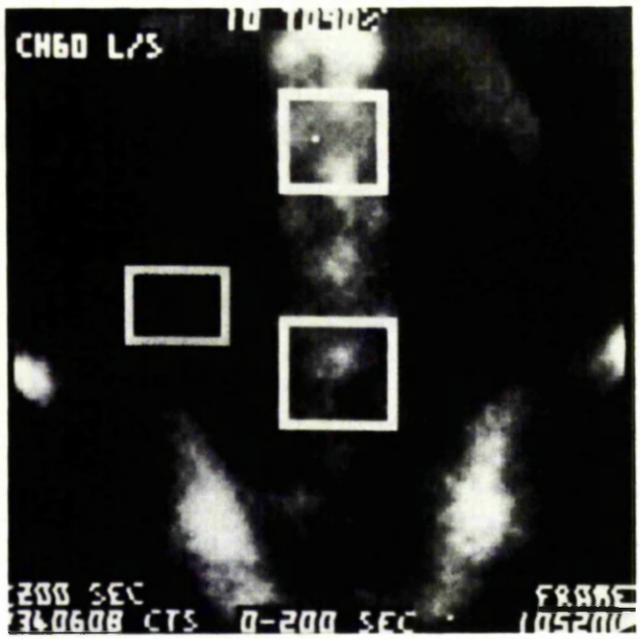

Fig. 1. Monochrome representation of colour television image of lumbosacral spine showing areas defined for bone and soft tissue measurements

Table 1. Percentage differences between 2 measurements of bone to soft tissue ratio on each lumbar image

Method	Number of subjects	Median % difference between repeat measurements	5–95 percentile range of difference (%)
One observer using lumbar vertebra 2 on 2 separate occasions	103	0.73	−13.1 to +14.4
One observer using lumbar vertebra 2 and lumbar vertebra 4 but same soft tissue area	93	0.34	−12.4 to +14.0
Two observers using lumbar vertebra 2	93	10.60	−10.6 to +43.8

scanning and had been found to have a negative scan. The study group consisted of 139 patients with various metabolic bone disorders (Table 4). Bone scans were performed on all subjects 4 h after intravenous injection of 15 mCi of technetium-99m hydroxyethylidine diphosphonate (HEDP) using a 25 cm gamma camera with a high resolution, low energy, parallel collimator. All images were recorded by computer on magnetic tape for later retrieval and processing, and displayed on a colour television set. Bone to soft tissue ratios were measured by drawing a region of interest (ROI) around the second lumbar vertebra (or, in the case of Paget's disease, an involved vertebra) and an area just below the kidney and clear of the spine and pelvis on the television image (Fig. 1). The bone and soft tissue count densities in these areas and their ratio, which we define as the bone to soft tissue ratio, were calculated from the teletype print out of the total count and areas. One hundred and three subjects (47 controls and 56 of the study group) had B/ST ratios calculated on 2 separate occasions from the one image by the same observer using lumbar vertebra 2. In 93 of these cases (47 controls, 46 of study group) B/ST ratios were also calculated on the same occasion by the same observer using 2 different areas of bone (lumbar vertebrae 2 and 4) but the same soft tissue area, to assess any variation in ratios from altering the area of bone selected. In addition B/ST ratios were calculated for these 93 subjects from the same images by another observer, using lumbar vertebra 2 only, to assess inter-observer variation.

Finally, in 26 control subjects multiple regions of interest (17 on average) were selected across the area of soft tissue (avoiding kidney) to assess any variation attributable to altering the precise area selected for soft tissue measurement.

All repeat measurements of B/ST ratios and count densities were compared by calculating the median percentage difference between the pairs of results, with the 5–95 percentile range of percentage difference giving a measure of the variability of individual results.

The variability due to moving the soft tissue area was quantified for each subject by calculating the percentage difference between each measurement and the mean count density for that patient.

The effects of age and metabolic bone disease on the measured B/ST ratio were examined using the results from the one observer who made measurements on all 150 controls and 139 patients. Using the Wilcoxon rank sum test, statistical comparisons were made between the various age decades within the control group, and also between the total control group and the various metabolic disease groups.

Results and Discussion

A. Technique of B/ST Measurement

Results for the variation between repeat measurements of B/ST ratio on the same images under different condition are given in Table 1.

1. One Observer on 2 Occasions. Using lumbar vertebra 2 on both occasions the median difference between repeat measurements for the whole group of 103 subjects was very small at only 0.7%. However, this conceals the wide range of variation between individual repeated results, the 5–95 percentile range being −13.1 to +14.4% difference.

To localise more clearly the major source of variation, the bone and soft tissue count densities from this study were examined separately (Table 2). Both components of the B/ST ratio gave a low median percentage difference between the pairs of measurements. However, the 5–95 percentile range of difference of the soft tissue count density was over twice that of the bone count density. This is probably to be expected since the vertebra is a well defined part

Table 2. Percentage differences between 2 measurements of bone count density and soft tissue count density on each image

Measurement	Median % difference between repeat measurements	5–95 percentile range of difference (%)
Bone count density (lumbar vertebra 2)	0.0	− 4.2 to + 8.7
Soft tissue count density	−1.63	−12.7 to +13.8

Table 3. Bone to soft tissue ratios in control group, measured by one observer

Age range	Number	Median B/ST ratio	Full range
Whole group	150	4.03	2.44–6.00
30–40	15	3.90	2.08–5.40
41–50	51	4.10	2.70–5.80
51–60	43	4.30	3.20–6.00
61–70	34	3.90	2.40–5.90
71–80	7	3.70	3.10–4.00

of the image, easy to outline on the television screen, in contrast to the possible range of selection of a suitable soft tissue area which does not include pelvic or renal activity.

2. Variation of Soft Tissue Count Density with Position of Selected Area. For 26 of the control subjects a total of 439 measurements of soft tissue count density were made from the 26 lumbar/sacral images. The median difference between separate measurements and the mean for each subject was 0.8% indicating a symmetrical distribution. The 5–95 percentile range of difference was from −13.7% to +14.9%, demonstrating a distribution very similar to that obtained from the duplicate measurements of soft sissue count density on the much larger total group of controls and patients (Table 2).

3. One Observer Using Lumbar Vertebrae 2 and 4. When measurements were made using the 2 vertebrae on the same image the median difference between pairs of results was also very low at 0.34% (Table 1) with a 5–95 percentile range of −12.4 to +14.0% difference. Since the same soft tissue area was used for each ratio this range indicates the variability of bone count density alone between lumbar vertebrae 2 and 4. The range of differences is about twice that for repeat measurements of bone density on a single vertebra (Table 2) and indicates that the precise area of bone selected can have a significant effect on the measured B/ST ratio, similar in importance to that of choosing a slightly different soft tissue area.

4. Two Observers Using the Same Vertebra. Returning to lumbar vertebra 2 only, but with two observers using the same image, gave a median difference this time of 10.6% (Table 1) showing a systematic difference in their technique. Furthermore the 5–95 percentile range of difference for individual subjects was large at −10.6 to +43.8%, being nearly double the range for repeated measurements by one observer, and 3 of the individual percentage differences were greater than 60%.

Table 4. Bone to soft tissue ratios in various patient groups measured by one observer

Group	Number	Median B/ST ratio	Full range
Control	150	4.03	2.44–6.00
Osteoporosis	24	4.06	2.90–5.50
Thyrotoxicosis	8	4.35	2.80–8.50
Osteomalacia	16	6.75	2.60–9.50
Primary hyperparathyroidism	21	4.17	3.00–9.90
Renal osteodystrophy	26	5.99	3.30–9.60
Paget's	23	9.10	5.70–29.0
Acromegaly	21	4.41	2.50–5.90

B. Effect of Age and Disease on B/ST Ratio

The results on technique suggest that while individual results are subject to wide variation it may be that average group results for B/ST ratio are clinically meaningful. Measurements should be made by the same observer, being careful in selection of soft tissue, bone area, and following a constant study protocol. Adhering to these conditions we found as follows:

5. Age Variation of Normal B/ST Ratio. Table 3 shows the results for B/ST ratios measured by one observer in the control group as a whole and also for each decade between 30 and 80 years. When the various decades were compared, the only statistically significant differences were between the 51–60 years group and the 61–70 and 71–80 years group ($P<0.01$ in each case). It is perhaps not surprising that the B/ST ratio is somewhat lower in patients over 60 years old as they have reduced bone mass and there is also histological evidence that osteoblastic activity is reduced as one grows older (Merz and Schenk 1970; Avioli 1976).

6. Bone to Soft Tissue Ratio in Metabolic Bone Disease. Table 4 shows the values for median B/ST ratios measured by one observer in the various patient groups studied and the distribution of individual results is shown in Fig. 2. The osteomalacia, renal os-

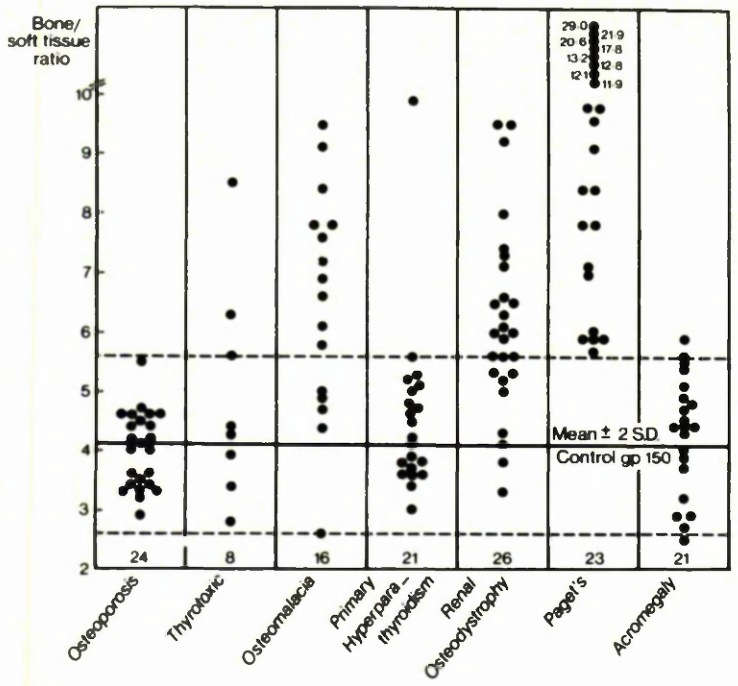

Fig. 2. Distribution of individual bone to soft tissue ratios in various groups of metabolic bone disorders

teodystrophy and Paget's group were all significantly different from the control group ($P<0.001$ in all cases). The Paget's group was also significantly different from all other groups ($P<0.005$ for the osteomalacia group, $P<0.001$ for the rest) and the renal osteodystrophy group was significantly different from all except the thyrotoxicosis, and osteomalacia groups ($P<0.001$).

All individual patient results for B/ST ratio measurements in the Paget's group lay outside the control range (Fig. 2) but this finding is somewhat artificial in that the area of bone selected in these cases was an involved vertebra. Also this finding is of limited clinical value as patients with Paget's disease usually have characteristic bone scan appearances (Serafini 1976).

In the osteomalacia and renal osteodystrophy groups there was appreciable overlap of individual patient results and the control range (Fig. 2). In the osteoporosis, primary hyperparathyroidism and acromegaly groups, virtually all individual results lay within the control range (Fig. 2) and these groups were indistinguishable from the control population. For primary hyperparathyroidism these results are in keeping with other workers (Weigmann et al. 1977) and our own previous experience (Fogelman et al. 1978a; Fogelman et al. 1977). However, while radiologic examination is generally negative in this condition, it has been shown histologically that there is skeletal involvement in approximately 90% of cases of patients with primary hyperparathyroidism (Holmes 1977), and in this situation measurement of B/ST ratios seems particularly disappointing. While acromegaly is generally not considered to be a metabolic bone disorder, it has been shown histologically that bone formation is significantly increased in this condition (Riggs et al. 1972) and one might have expected to find increased values for B/ST ratios. The median value for B/ST ratios in the osteoporotic group, was not significantly different from the control population (Table 4).

In the thyrotoxicosis group there was a wide range of individual results overlapping the control range (Fig. 2). This group was not distinguishable from any other group (except the Paget's group) but since it contained only 8 subjects no firm conclusions can be drawn.

Conclusions

The overall conclusions from the studies on the technique of B/ST measurement are that the fiarly large groups of subjects used produce low average differences between repeat results when studied by one observer using the same or different vertebrae. However, there is a significant systematic difference between our two observers but more important is the wide range of individual differences found in all cases. It should be remembered that these were repeat measurements on the same image from a single study. When the differences due to variation of patient positioning, obesity, water loading and radiopharmaceutical quality in interpatient comparisons are considered the lack of clear differentiation between disease groups is not unexpected (Table 4).

The comparisons of B/ST ratio measurements in control and disease groups illustrated in Fig. 2 and Table 4 were based upon measurements by one observer. It is likely, therefore that measurements on individual patients by different observers would lead to wider spreads in the various groups and poorer discrimination between groups. Furthermore at 4 h the soft tissue activity is still changing to some extent (Citrin et al. 1975) so the precise time of measurement will affect the B/ST ratio obtained. Because of the considerable overlap of individual patient results with the control range, (except for the rather artificially measured group with Paget's disease) a positively elevated value for B/ST ratio may be of some help in confirming increased skeletal uptake of radiopharmaceutical, but a normal value does not exclude this.

It is concluded, therefore, that on the grounds of variability of individual results together with failure to distinguish clearly between disease patients and controls, attempts to quantitate skeletal uptake of radiopharmaceutical by measurement of a bone to soft tissue ratio are of limited value in clinical practice.

Acknowledgement. We are grateful to Mrs. G.F. Cuthbert, Senior Technician of the Department of Nuclear Medicine, for bringing together selected digital bone scan images from the past 3 years to facilitate the analyses reported.

References

Avioli LV (1976) Senile and postmenopausal osteoporosis. Adv Intern Med 21:391–415

Citrin DL, Bessent RG, McGinlay E, Gordon D (1975) Dynamic studies with 99mTc-HEDP in normal subjects and in patients with bone tumours. J Nucl Med 16:886–890

Fogelman I, Greig WR, Bessent RG, Boyle IT (1977) Skeletal uptake of 99mTc-HEDP in primary hyperparathyroidism. J Nucl Med 18:1040–1041

Fogelman I, Bessent RG, Turner JG, Citrin DL, Boyle IT, Greig WR (1978a) The use of whole body retention of 99mTc-diphosphonate in the diagnosis of metabolic bone disease. J Nucl Med 19:270–275

Fogelman I, McKillop JH, Bessent RG, Boyle IT, Turner JG, Greig WR (1978b) The role of bone scanning in osteomalacia. J Nucl Med 19:245–248

Holmes RA (1977) 99mTc-pyrophosphate in demonstrating bone disease of parathyroid dysfunction. J Nucl Med 18:309–310

Holmes RA (1978) Quantitation of skeletal Tc-99m labelled phosphates to detect metabolic bone disease. J Nucl Med 19:330–331

Lien JWK, Wiegmann T, Rosenthall L, Kaye M (1976) Abnormal ^{99m}Technetium-tin-pyrophosphate bone scans in chronic renal failure. Clin Nephrol 6:509–512

Merz WA, Schenk RK (1970) A quantitative histological study on bone formation in human cancellous bone. Acta Anat (Basel) 76:1–15

Riggs BL, Randall RV, Wahner HW, Jowsey J, Kelly PJ, Singh M (1972) The nature of the metabolic bone disorder in acromegaly. J Clin Endocr Metab 34:911–918

Serafini AN (1976) Paget's disease of bone. Semin Nucl Med 6:47–58

Wiegmann T, Kirsh J, Rosenthall L, Kaye M (1976) Relationship between bone uptake of 99mTc-pyrophosphate and hydroxyproline in bone and urine. J Nucl Med 17:711–714

Wiegmann T, Rosenthall L, Kaye M (1977) Technetium-99m-pyrophosphate bone scans in hyperparathyroidism. J Nucl Med 18:231–235

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Comment

It is seen that if repeat bone to soft-tissue (B/ST) ratio measurements are obtained, by a single observer, in large groups of patients then average differences between results are low. An increased error was, however, introduced when the area of soft-tissue selected was varied, and a wide range of individual patient results obtained when two observers independently measured B/ST ratios.

However for comparison of B/ST ratio values in patients with metabolic bone disease and control subjects, all measurements were performed by myself. Thus even when B/ST ratios were obtained by a single observer, a huge overlap of individual results was found in all patient groups and with the control group. Although an elevated B/ST result may support the presence of increased bone turnover, a normal result certainly does not exclude it. It is probable that if different observers were to measure B/ST ratios this would lead to even greater uncertainty as to the significance of any differences shown between results.

It is, therefore, concluded from these studies that B/ST ratio measurements are of very limited value in the diagnosis of metabolic bone disease. This is not surprising as the measurement is obtained by selecting a very small area of bone in the hope of being able to detect relatively small but significant alterations in total skeletal metabolism. In addition there is the demonstrated

uncertainty introduced by the variability of counts obtained in selecting the soft-tissue region. Perhaps the ratio of total skeletal counts to total soft-tissue counts would provide a more sensitive measure of skeletal metabolism, but there is no convenient means of obtaining this, and in practice any measurements would be extremely laborious with great uncertainties and errors introduced by attempting to separate bone and soft-tissue in areas such as the ribs.

It is, however, possible that B/ST ratio measurements performed on sequential bone scan studies may be of some value in an individual patient to document improvement or deterioration in their condition. There is indirect evidence to support this as Espinasse et al (1981) have suggested that quantitative scintigraphic parameters are suitable for the assessment of therapy in Paget's disease. However, in Paget's disease focal lesions with extremely high tracer uptake are seen and easily identified on the bone scan and Espinasse was able to analyse ratios of activity of involved Pagetic sites to activity of symmetrical non-involved bone areas. It has still to be established whether B/ST ratio measurements are of value in monitoring the effect of therapy in sequential bone scan studies where a generalised alteration in skeletal metabolism exists.

SUMMARY

CHAPTER 2

RECOGNITION OF METABOLIC FEATURES AND QUANTITATION OF SKELETAL UPTAKE OF TRACER FROM THE BONE SCAN IMAGE

In this chapter several studies are described evaluating bone scan images, both visually and with quantitative techniques, as a means of identifying the presence of metabolic bone disease. In paper 3 the original concept of recognisable metabolic features being present on the bone scan is introduced and it is suggested that such features may be characteristic of the metabolic bone disorders in general. In this first report of bone scanning in osteomalacia, it is shown that patients with osteomalacia can easily be differentiated from both normal subjects and patients with metastatic disease on the basis of recognisable metabolic features on the bone scan.

It is, however, argued that often when increased skeletal uptake of tracer is present, simple visual evaluation of the bone scan may prove too subjective to detect this and hence quantitation of tracer uptake is desirable to provide a more sensitive measure of increased bone turnover.

Paper 4 develops the theme that metabolic features may be seen in various metabolic bone disorders and other conditions where there is generalised increased bone turnover. Seven characteristic bone scan features are selected and a semi-quantitative scoring system is described whereby a numerical scoring system is applied to each

feature, the total score being defined as the metabolic index. It is shown that the metabolic index allows clear differentiation of various groups of metabolic patients from control subjects but an appreciable overlap with individual patient results is seen. Paper 5 provides the first report of bone scanning in acromegaly. In this study it was of interest that metabolic features were frequently noted on the bone scans of acromegalic subjects and it was found that metabolic indices correlated well with serum growth hormone levels. However, while this study validates the metabolic index as a measure of skeletal involvement in this systemic disorder, it was nevertheless found that the test was not sensitive enough to differentiate individual subjects with active disease from those with inactive disease.

Several groups had previously suggested that measurement of bone to soft-tissue (B/ST) ratios from the bone scan image may provide a valuable means of quantitating skeletal uptake of tracer. Paper 6 describes a critical evaluation of this technique and its application to a large group of patients with various metabolic bone disorders. It was concluded that B/ST ratio measurements would be of very limited value in clinical practice, once again because of the large overlap of individual patient results with the control group.

It is thus seen that in individual patients, neither visual evaluation of the bone scan nor quantitative techniques derived from the scan image provide a sensitive measure of altered skeletal metabolism.

CHAPTER 3

A COMPARISON OF SKELETAL SCINTIGRAPHY AND RADIOLOGY IN METABOLIC BONE DISEASE

In this chapter, following an initial review of the different principles and mechanisms by which radiology and scintigraphy each image the skeleton, two papers (7 and 8) are presented comparing these techniques in metabolic bone disease.

PRINCIPLES OF SKELETAL SCINTIGRAPHY COMPARED TO RADIOLOGY

While it is now recognised that the bone scan is more sensitive than radiology in detecting skeletal abnormality, it is important to be aware that each of these investigations assesses different parameters in relation to bone. X-ray absorption indicates bone mineral content and shows the net result of bone destruction and repair. The bone scan, however, depends upon osteoblastic activity and to a lesser extent skeletal vascularity for uptake of tracer (Davis and Jones, 1976) (see chapter 1). In the context of disease the scan indicates the dynamic response of bone to whatever insult is present, be it traumatic, inflammatory or neoplastic.

If involvement of the skeleton by malignancy is chosen as a specific example of disease, then when tumour cells invade bone they produce two basic effects: bone destruction, and an osteoblastic reaction which represents attempts by the surrounding bone to repair the destructive effects (Milch and Changus, 1956). Radiographs demonstrate both processes - bone destruction is seen as radiolucencies (osteolytic areas) and bone repair as radiodensities (osteosclerotic areas). Bone destruction, however, must be advanced before an abnormality is seen on the radiograph,

and it has been suggested that a lesion in trabecular bone must be greater than 1-1.5 cm in diameter, with loss of approximately 50% of bone mineral before radiolucencies will be apparent on a conventional radiograph (Edelstyn et al, 1967). Early in bone repair, insufficient mineral has been laid down to be visualised radiographically as radiodensities. For these reasons the radiograph is normal during the early phase of tumour involvement, and several studies have confirmed that histologically proven metastases may not be detected by radiology (Borak 1942; Shackman and Harrison, 1948). The bone scan is based on an entirely different principle. Tracer uptake is not directly dependent on bone destruction, but reflects the functional reaction of the bone to tumour invasion. There is an increase in new bone formation with increased skeletal blood flow following tumour invasion and this is demonstrated by high uptake of a bone seeking radiopharmaceutical. It is important to note that the increased concentration of tracer is not due to or directly dependent on the metabolism of the tumour cells themselves, but is directly related to the local changes in bone metabolism consequent upon tumour invasion.

Thus, early in bone invasion by tumour, a positive bone scan may be associated with normal radiology. As the tumour progresses, the bone destruction it causes will become

visible on the radiograph as an osteolytic lesion. In these circumstances bone reaction is considerable, and the bone scan is also strongly positive. If the tumour does not progress calcium will be laid down during the healing process in such quantities that sclerotic areas will be visible on the radiograph. At this stage both investigations are positive. Eventually, if the lesion heals completely, there will be extensive calcification producing a dense appearance on the radiograph. At this stage the bone scan may appear normal.

As the bone scan depends on the metabolic reaction of the bone, it is clear that if there is absent or little bone reaction to tumour invasion, the scan may be normal or near normal despite radiological evidence of bone destruction. This occurs infrequently but is more likely to be found in some cases of myeloma (Leonard et al, 1981), in some cases of rapidly growing anaplastic carcinoma or conversely in cases of indolent tumours such as thyroid cancer (Charkes 1970). If bone destruction is extensive (Goergen et al, 1974), or if bone metabolism is modified by radiotherapy (Cox 1974) a "cold" area may be seen, corresponding to the area of diminished bone activity.

Similarly, in the metabolic bone disorders a considerable change in bone calcium may occur without detectable change on the radiograph. If there is net balance between bone formation and bone resorption, albeit if both are increased, then these changes may

theoretically never be revealed by radiology (De Nardo 1966). Radioactive tracer techniques may circumvent these difficulties since they depend only upon increased bone turnover regardless of the net calcium balance.

It is clear, however, that the techniques of skeletal radiology and scintigraphy are in many instances complementary and maximum diagnostic information can be obtained by performing both studies.

Paper 7. A comparison of bone scanning and radiology in the evaluation of patients with metabolic bone disease (1980)

Clinical Radiology 31: 321-326

I Fogelman, D Carr

Purpose of Investigation

The purpose of this study was to compare the relative sensitivity of bone scanning and radiology in the diagnosis of metabolic bone disease. Eighty patients with metabolic bone disorders were studied, and the bone scans and radiographs were each read independently without the observers being aware of the specific clinical diagnoses.

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A Comparison of Bone Scanning and Radiology in the Evaluation of Patients with Metabolic Bone Disease

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Bone scans and radiographs were evaluated in 80 patients with metabolic bone disease (27 with osteoporosis, 14 with primary hyperparathyroidism, 24 with renal osteodystrophy and 15 with osteomalacia). The bone scan did not suggest a metabolic bone disorder in any of 27 patients with histologically proven osteoporosis. In 22 (81%) patients radiographs were reported as showing osteoporosis. In 19 (70%) vertebral fractures were seen on X-ray while these were noted in 11 (41%) patients on the bone scan. Vertebral fractures were usually visualised on the bone scan when these had occurred less than one year previously. In primary hyperparathyroidism the bone scan was suggestive of a metabolic bone disorder in 7 of 14 (50%) patients, while radiographs were reported as showing evidence of hyperparathyroidism in three (21%) cases. The bone scan suggested the presence of a metabolic bone disorder in all 24 patients with renal osteodystrophy and 15 patients with osteomalacia while the correct diagnosis was obtained in 14 (58%) and nine (60%) of these patients on X-ray. It is concluded that the bone scan is the more sensitive investigation in patients with osteomalacia, primary hyperparathyroidism and renal osteodystrophy. For osteoporosis radiology is the investigation of choice but the bone scan may be of value in assessing the duration of vertebral collapse.

Bone scanning is now established as a sensitive means of detecting skeletal metastases and its superiority over radiology is well recognised (Citrin *et al.*, 1977). Recently there has been considerable interest in the use of bone scanning in metabolic bone disease (Sy, 1974; Sy and Mittal, 1975; Rosenthal and Kaye, 1975; Weigmann *et al.*, 1977; Krishnamurthy *et al.*, 1977; Fogelman *et al.*, 1977a, 1978, 1979. Fogelman and Citrin, 1980) and although focal abnormalities may not be seen, certain recognisable patterns of bone scan abnormality are becoming apparent in these conditions (Fogelman *et al.*, 1977a, 1979). However, there is only limited information available as to the value of radioisotopic imaging compared with routine radiology in the various metabolic bone disorders. In this study 80 patients with metabolic bone disease had a gamma-camera bone scan performed using a standard technique, and a conventional radiological skeletal survey was also obtained. The bone scans and radiographs were assessed independently and in a random order by two observers (scans, I.F.; radiographs, D.C.) who were unaware of the clinical diagnoses.

METHODS

Eighty patients (27 with osteoporosis, 14 with primary hyperparathyroidism, 24 with renal osteodystrophy, and 15 with osteomalacia) were studied. The diagnosis of primary hyperparathyroidism was established in all patients by the finding of elevated serum calcium levels with elevated or inappropriate plasma parathyroid hormone levels. In addition, 11 of the 14 patients had parathyroid tumours removed. In the osteoporosis, osteomalacia and renal osteodystrophy groups, the diagnosis was established by routine biochemistry and radiology and, in addition, transilial bone biopsies were performed in all 80 patients to obtain histological confirmation of the diagnoses.

Bone Scan

Each patient was scanned 4 h after the intravenous injection of 15 mCi of technetium-99 m hydroxyethylidene-diphosphonate (HEDP). Details of the technique employed have been described elsewhere (Fogelman *et al.*, 1978).

Radiological Skeletal Survey

In all patients the radiographic skeletal survey comprised antero-posterior and lateral views of skull, antero-posterior and lateral views of the cervical, dorsal and lumbar spine. A postero-anterior radiograph of chest, antero-posterior views of the pelvis and views of the long bones and hands were also obtained.

RESULTS

The scan and radiograph were read independently without any knowledge of the clinical diagnosis although both observers were aware that the study group consisted of patients with metabolic bone disease. The studies were reported and a diagnosis was suggested if it was felt that this was indicated. In addition, any abnormalities observed were charted on skeletal maps.

The bone scans were assessed for the presence of seven metabolic features that have previously been shown to be characteristic of metabolic bone disorders. These features are (a) increased tracer uptake by the axial skeleton, (b) by the long bones, (c) by the wrists, (d) prominence of the calvarium and mandible (Fig. 1), (e) beading of the costochondral junctions (Fig. 2), (f) a 'tie' sternum, and (g) faint or absent kidney images.

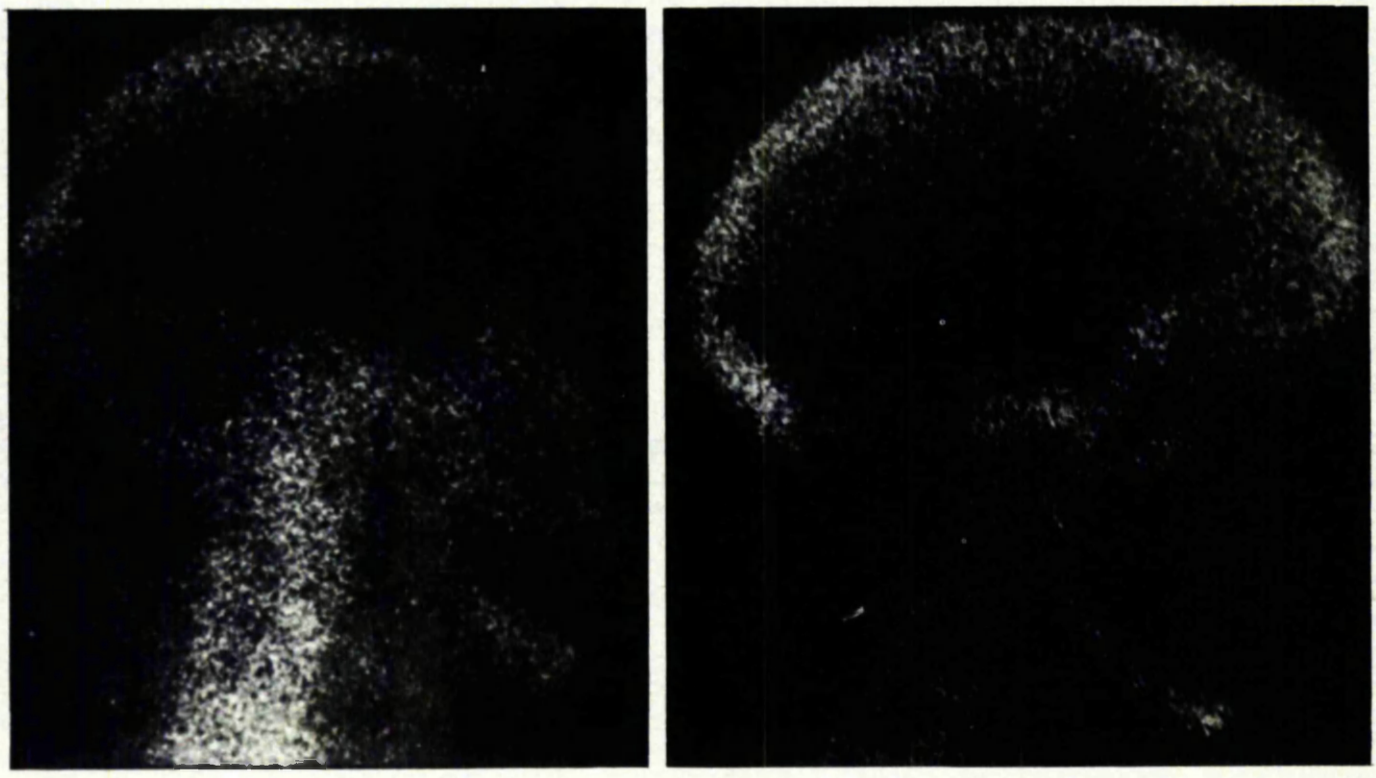
Each of these features was scored in the following way: 0, normal; 1, abnormal, and 2, strikingly abnormal, and the metabolic index (total score for the seven features) for each patient was calculated (Fogelman *et al.*, 1979). For the purpose of this study a metabolic index of over 4, i.e. 5 or above, was taken as abnormal. The skeletal surveys were assessed for the standard radiological features associated with metabolic bone disease (Hodson, 1975).

The results of the two investigations were compared and related to the clinical status of the patient where relevant.

The results for the various patient groups will be presented separately. We have accepted the radiograph as the standard skeletal investigation as it is the universally available technique against which any new development must be judged and also the radiograph may allow a specific diagnosis to be made due to the anatomical details displayed. In contrast the bone scan presents a non-specific abnormality, namely increased tracer uptake which may be seen with virtually all bone pathology. Therefore, while radiology often suggests a specific diagnosis, in interpreting the bone scan we can often only say that the appearances are suggestive of a metabolic bone disorder.

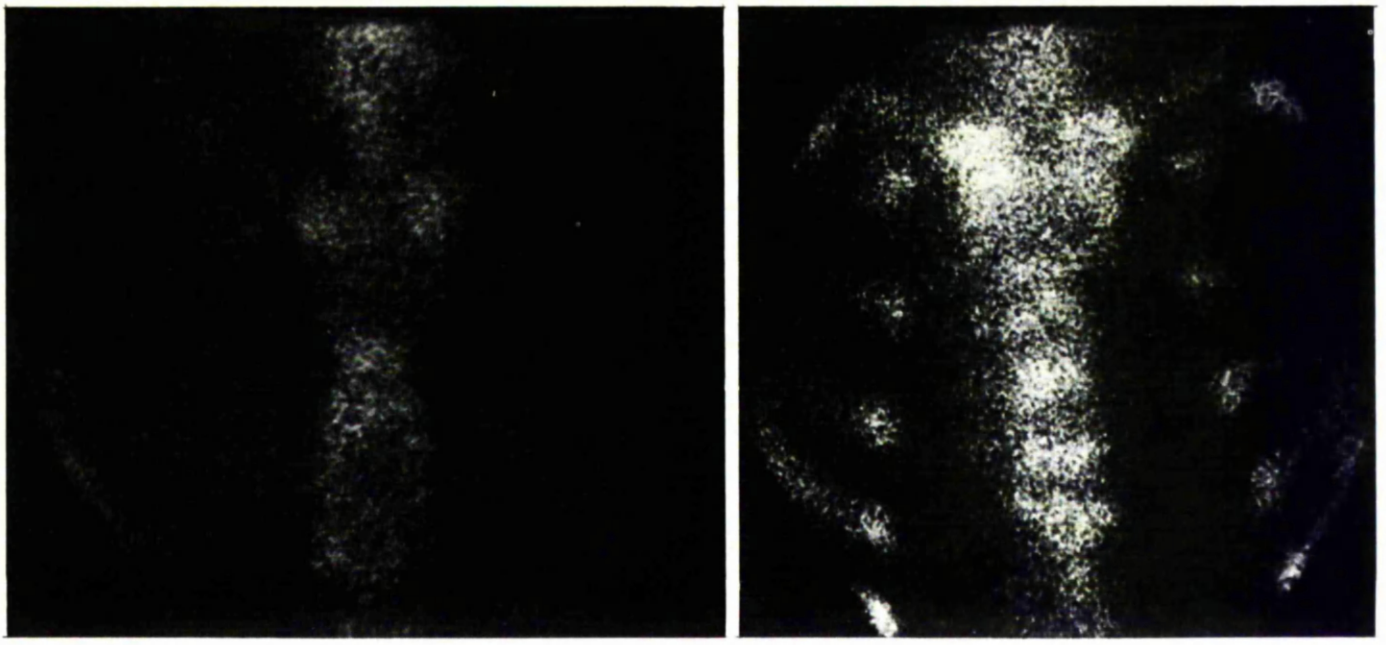
Osteoporosis

The bone scan was not suggestive of a metabolic bone disorder in any of the 27 patients with histologically proven osteoporosis. In 22 (81%) cases the radiographs were reported as showing osteoporosis. In 19 (70%) patients vertebral fractures were seen on X-ray while these were noted in 11 (41%) patients on the bone scan. In eight (30%) cases the bone scan underestimated the extent of vertebral collapse which



(*a*) (*b*)

Fig. 1 – Lateral view of skull on bone scan – (*a*) normal, (*b*) showing increased tracer uptake by calvarium with prominent mandible in patient with primary hyperparathyroidism.



(*a*) (*b*)

Fig. 2 – Anterior views of thorax – (*a*) normal, (*b*) showing 'beading' of costochondral junctions in patient with osteomalacia.

was seen on X-ray. The relationship of scan evidence of vertebral fracture to the history of the most recent severe episode of acute back pain is shown in Table 1. Generally vertebral fractures were visualised on the bone scan when less than one year from the time of fracture although this was not always the case. Renal images were seen in all patients on the bone scans.

Primary Hyperparathyroidism

The bone scan was suggestive of a metabolic bone disorder in 7 of 14 (50%) patients with primary hyperparathyroidism while radiographs were reported as showing evidence of hyperparathyroidism in three (21%) cases. In only one patient were the renal images not visualised on the bone scan.

Renal Osteodystrophy

The bone scan was suggestive of a metabolic bone disorder in all 24 patients with renal osteodystrophy while radiographs were reported as showing hyperparathyroidism or renal osteodystrophy in 14 (58%) cases. The renal images were not visualised in 20 (83%) patients on the bone scan.

Osteomalacia

The bone scan was suggestive of a metabolic bone disorder in all 15 patients with osteomalacia while radiographs were reported as showing osteomalacia in nine (60%) cases. Ten patients had pseudo-fractures present and there were 24 sites involved in these patients. Nineteen (79%) sites were detected on the bone scan while 14 (58%) were seen on X-ray. The ribs were the most frequently involved site (90%), then femur (70%), pelvis (40%), scapula (20%) and fibula and forearm (10%). Absent kidney images on the bone scan were noted in two patients, and both of these cases had multiple hot spots present which were interpreted as pseudo-fractures.

DISCUSSION

Bone scanning provides a highly sensitive means of detecting skeletal pathology but abnormalities tend to be non-specific. The bone scan in Paget's disease or if skeletal metastases are present shows focal abnormalities but in osteomalacia, primary hyperparathyroidism and renal osteodystrophy where the whole skeleton is involved by a metabolic process, these may not be seen. However, recognisable patterns of abnormality may be apparent and by giving a numerical score to seven metabolic features on the bone scan we have derived a metabolic index for metabolic bone diseases (Fogelman *et al.*, 1979). An abnormal value suggests that a metabolic bone disorder may be present but seldom can allow a definite diagnosis. In osteoporosis there is usually only a very gradual change in bone volume that occurs over many years and in keeping with this the bone scan appearances are usually normal. However, when bones become so abnormally brittle that pathological fracture with vertebral collapse occurs then this

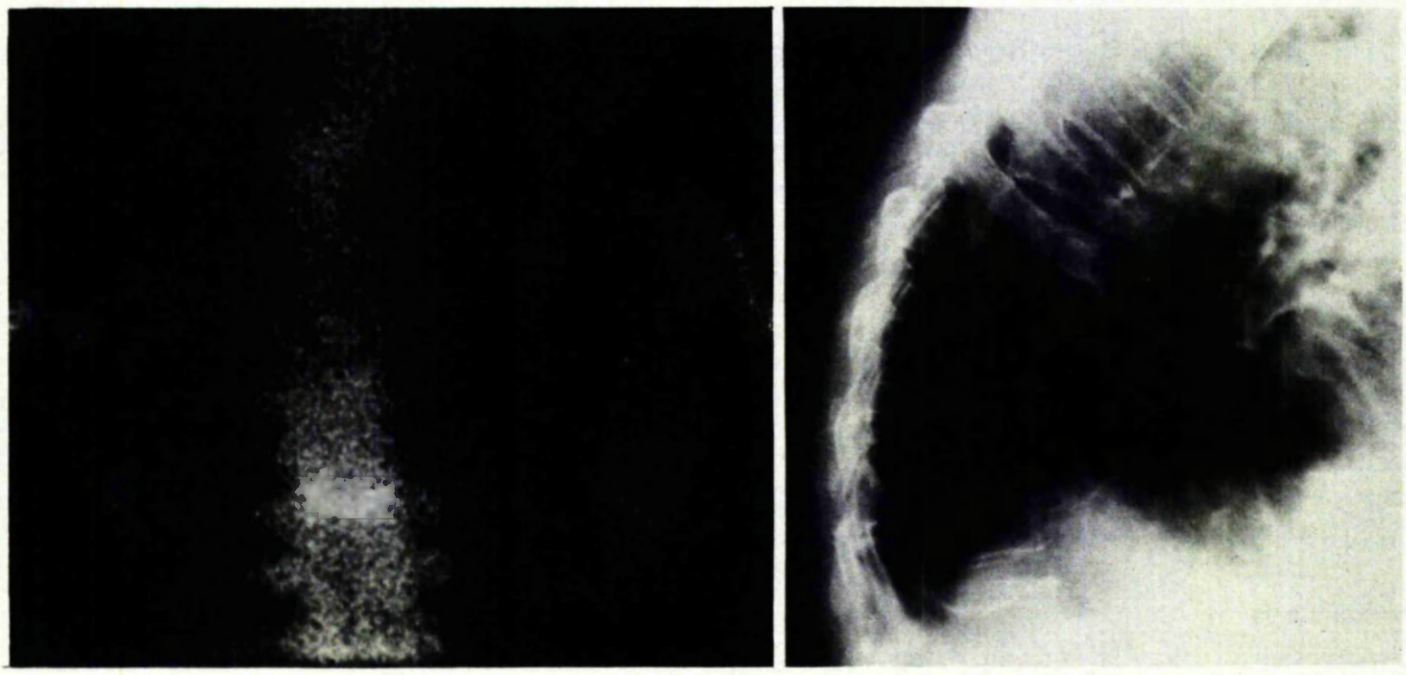
Table 1 – Osteoporotic patients with radiological evidence of vertebral collapse

Patient		*History (duration since acute episode of severe back pain)*
(a)	Scan +ve	
	1	Eight months
	2	Three months
	3	Chronic pain only
	4	Chronic pain only
	5	Four months
	6	One month
	7	14 months
	8	Four months
	9	No back pain
	10	Chronic pain only
	11	12 months
(b)	Scan –ve	
	1	14 months
	2	Chronic pain only
	3	Chronic pain only
	4	Chronic pain – seven years since acute episode
	5	Chronic pain – 2½ years since acute episode
	6	Chronic pain only
	7	12 months – long history of chronic pain previously
	8	Three months – long history of chronic pain previously

appears on the bone scan as a focal area of increased tracer uptake and the scan appearances are characteristic (Fogelman and Citrin, 1980).

In the present study the bone scan did not suggest the presence of a metabolic bone disorder in any of the 27 patients with histologically proven osteoporosis. Radiographs were reported as showing osteoporosis in 22 (81%) patients. In 19 (70%) patients vertebral fractures were seen on X-ray while these were noted in 11 (41%) patients on the bone scan. In addition, the bone scan underestimated the extent of vertebral collapse in eight patients (Fig. 3). Generally vertebral fractures were visualised on the bone scan when an acute episode of severe back pain had occurred less than one year previously although this was not always the case (Table 1). One patient who gave a history of an acute episode of severe back pain three months prior to scanning had a negative bone scan but this patient also gave a history of long-standing chronic back pain prior to the acute episode. It may be that the 'acute' episode represented an exacerbation of her chronic condition rather than further vertebral collapse.

The bone scan was suggestive of a metabolic bone disorder in seven of 14 (50%) patients with primary hyperparathyroidism while X-rays were reported as showing evidence of hyperparathyroidism in three (21%) cases. The renal images were not visualised in one case and in this instance the scan appearances could have been misinterpreted as those of renal osteodystrophy (see later). With the availability of parathyroid hormone assays the diagnosis of primary hyperparathyroidism is being made more frequently and, indeed, much earlier than previously. In the majority of cases there will be no radiological or



(*a*) (*b*)

Fig. 3 – (*a*) Bone scan image of posterior thoracic spine showing a single area of linearly increased tracer uptake in mid-spine in keeping with history of an acute episode of back pain four months previously. Lateral X-ray of spine (*b*) shows several collapsed vertebrae.

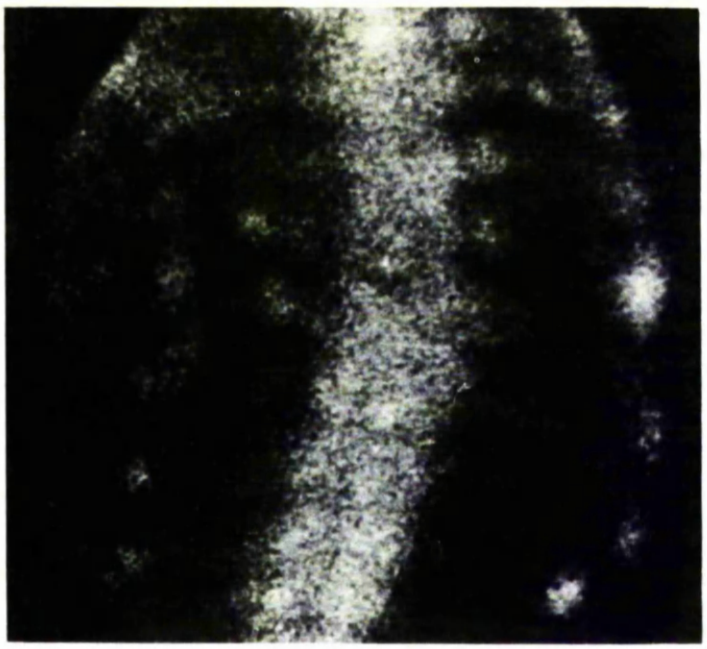


Fig. 4 – Multiple hot spots in ribs (representing pseudo-fractures) in patient with osteomalacia. These were not seen on routine radiology although two pseudo-fractures in the pelvis were detected.

biochemical evidence of skeletal involvement and there may be little evidence of skeletal disease even when bone biopsies are performed. It is, therefore, to be expected that the bone scan will be normal in many cases of primary hyperparathyroidism but this test still provides a more sensitive indicator of metabolic bone disease than routine radiology (Sy, 1974; Krishnamurthy *et al.*, 1977).

The bone scan was suggestive of a metabolic bone disorder in all 24 patients with renal osteodystrophy while radiographs were reported as showing hyperparathyroidism or renal osteodystrophy in 14 (58%) cases. Renal images were not visualised in 20 (83%) patients. Sy and Mittal (1975) graded seven areas on the bone scans of 14 chronic dialysis patients on a scale 0–4+ and found that the bone scan was abnormal in 13 (93%) patients; however, only four (29%) of these patients showed resorptive changes on radiographs. Olgaard *et al.* (1976) studied 30 patients on haemodialysis and classified their bone scans into four groups according to the degree of increased tracer uptake in the lower limbs. They found 90% of the bone scans but only 33% of X-rays abnormal. Cavalli *et al.* (1976) studied 43 patients with chronic renal disease (34 on dialysis, nine on maintenance therapy) and found that the bone scans indicated that 88% had skeletal disease, while radiographs were abnormal in 56%. De Graaf *et al.* (1977) studied 30 dialysis patients and found that the bone scan was positive in 80% while radiographs showed skeletal disease in 14%. It therefore seems that the bone scan provides a sensitive means of detecting skeletal involvement in patients with chronic renal failure.

The bone scan was suggestive of a metabolic bone disorder in all 15 patients with osteomalacia while X-rays were reported as osteomalacia in 19 (60%) cases. Absent kidney images were noted in the bone scans in two patients and both of these had multiple hot spots on the bone scans which were interpreted as pseudo-fractures. Ten patients had pseudo-fractures present and there were 24 sites involved. Nineteen (79%) of these were detected on the bone scan while 14 (58%) were seen on X-ray. The most frequently involved sites were ribs (90%), femur (70%), pelvis (40%), and scapula (20%). Pseudo-fractures of the ribs were clearly seen on the bone scan (Fig. 4) but were often not seen on an initial chest X-ray although many but not all were later decided if selected rib views were obtained. Generally the bone scan provides the superior test for detecting pseudo-fractures (Fogelman *et al.*, 1977b; Macfarlane *et al.*, 1977); however, we found that these were missed on one occasion in the pelvis due to the symmetry of the lesions in the pubic rami and on another occasion were mised due to poor technique where overlapping views of the skeleton did not include the upper femora. In two further patients pseudo-fractures of the upper femora although present were not initially recognised on the bone scan because of the symmetry of the lesions. There is also the theoretical possibility of bladder activity obscuring lesions in the pelvis.

In the present study many of the patients with renal osteodystrophy and osteomalacia were severe examples of disease and one would not expect the bone scan to be abnormal in 100% of cases when 'milder' disease was studied. However, in this selected population the bone scan undoubtedly proved superior to conventional radiology. The scan appearances in osteomalacia, primary hyperparathyroidism and renal osteodystrophy are often non-specific although an elevated metabolic index together with absent kidney images is strongly suggestive of renal osteodystrophy and focal abnormalities (particularly when predominantly in the ribs) on a 'metabolic' scan raise the probability of osteomalacia.

The relative sensitivities of bone scanning and radiology in the various patient groups are shown in Table 2. It should be noted that while an assessment of the metabolic features on the bone scan did not suggest the presence of a metabolic bone disorder in any of the patients studied with osteoporosis, if the non-metabolic feature of linearly increased tracer uptake in the spine, representing vertebral collapse, is included (which would suggest the presence of osteoporosis) then the sensitivity rises to 41%. In the evaluation of patients with hyperparathyroidism

Table 2 – Comparison of X-ray and scan sensitivity

Disease	*X-ray (%)*	*Scan (%)*
Osteoporosis	81	0 (41)*
Primary hyperparathyroidism	21	50
Renal osteodystrophy	58	100
Osteomalacia	60	100

*If the non-metabolic bone scan feature of vertebral collapse (which would suggest the presence of osteoporosis) is included then sensitivity rises to 41%.

magnification radiographs of the hands, either by optical magnification (Meema, 1977) or using direct radiographic magnification (Carr *et al.*, 1980) may increase the radiological sensitivity but these techniques are not yet widely available.

It is concluded that the bone scan is the more sensitive investigation in patients with osteomalacia, renal osteodystrophy and primary hyperparathyroidism and should be performed prior to X-ray. In osteoporosis radiology is the investigation of choice but the bone scan may be of value in assessing the duration of vertebral collapse and perhaps alerting an observer to the presence of an underlying condition which is responsible for accelerated bone loss, e.g. primary hyperparathyroidism or thyrotoxicosis.

REFERENCES

Carr, D., Davidson, J. K., McMillan, M. & Davison, M. (1980). Renal osteodystrophy – an underdiagnosed condition. *Clinical Radiology*, **1**, 55–59.

Cavalli, P. L., Camuzzini, G. F., Ghezzi, P., Palanca, R., Rovere, A. & Tortore, P. (1976). Total body gammagraphy in uraemic patients. *Minerva Nefrologica*, **23**, 142–148.

Citrin, D. L., Bessent, R. G. & Greig, W. R. (1977). A comparison of the sensitivity and accuracy of the ^{99m}Tc-phosphate bone scan and skeletal radiograph in the diagnosis of bone metastases. *Clinical Radiology*, **28**, 107–117.

Fogelman, I. & Citrin, D. L. (1980). Bone scanning in metabolic bone disease: a review. *Applied Radiology*, in press.

Fogelman, I., Citrin, D. L., Turner, J. G., Hay, I. D., Bessent, R. G. & Boyle, I. T. (1979). Semi-quantitative interpretation of the bone scan in metabolic bone disease: definition and validation of the metabolic index. *European Journal of Nuclear Medicine*, **4**, 287–289.

Fogelman, I., McKillop, J. H., Bessent, R. G., Boyle, I. T., Turner, J. G. & Greig, W. R. (1978). The role of bone scanning in osteomalacia. *Journal of Nuclear Medicine*, **19**, 245–248.

Fogelman, I., McKillop, J. H., Boyle, I. T. & Greig, W. R. (1977a). Absent kidney sign associated with symmetrical and uniformily increased uptake of radiopharmaceutical by the skeleton. *European Journal of Nuclear Medicine*, **2**, 257–259.

Fogelman, I., McKillop, J. H., Greig, W. R. & Boyle, I. T. (1977b). Pseudofractures of the ribs detected by bone scanning. *Journal of Nuclear Medicine*, **18**, 1236–1237.

De Graaf, P., Schicht, I. M., Pauwels, E. K. J. & de Graeff, J. (1977). Bone scintigraphy in renal osteodystrophy. *Journal of Nuclear Medicine*, **18**, 605.

Hodson, C. J. (1975). Endocrine and metabolic bone disease. In *Textbook of Radiology*, ed. Sutton, D., pp. 183–204. Churchill Livingstone, London.

Krishnamurthy, G. T., Brickman, A. S. & Blahd, W. H. (1977). Technetium-99m-Sn-pyrophosphate pharmacokinetics and bone image changes in parathyroid disease. *Journal of Nuclear Medicine*, **18**, 236–242.

Macfarlane, J. D., Lutkin, J. E. & Burwood, R. J. (1977). The demonstration by scintigraphy of fractures in osteomalacia. *British Journal of Radiology*, **50**, 369–371.

Meema, H. E. (1977). Recognition of cortical bone resorption in metabolic bone disease *in vivo*. *Skeletal Radiology*, **2**, 11–19.

Olgaard, K., Heerfordt, J. & Madsen, S. (1976). Scintigraphic skeletal changes in uraemic patients on regular haemodialysis. *Nephron*, **17**, 325–334.

Rosenthal, L. & Kaye, M. (1975). Technetium-99m-pyrophosphate knetics and imaging in metabolic bone disease. *Journal of Nuclear Medicine*, **16**, 33–39.

Sy, W. M. (1974). Bone scan in primary hyperparathyroidism. *Journal of Nuclear Medicine*, **15**, 1089–1091.

Sy, W. M. & Mittal, A. K. (1975). Bone scan in chronic dialysis patients with evidence of secondary hyperparathyroidism and renal osteodystrophy. *British Journal of Radiology*, **48**, 878–884.

Wiegmann, T., Rosenthall, L. & Kaye, M. (1977). Technetium-99m-pyrophosphate bone scans in hyperparathyroidism. *Journal of Nuclear Medicine*, **18**, 231–235.

Comment

This investigation presents the only comparative study of radiographs and bone scans in a group of patients with various metabolic bone diseases. Any previous reports relating to the metabolic bone disorders have simply evaluated radiographs and scans in a single condition, and then only in renal osteodystrophy and primary hyperparathyroidism. In the present study all radiographs and scans were read independently without the observers having any knowledge of the specific diagnoses.

Utilising the presence of metabolic features on the scan image as a means of identifying metabolic bone disease, the bone scan was shown to be superior to radiology in primary hyperparathyroidism, renal osteodystrophy and osteomalacia. However the scan appearances are non-specific and simply allow identification of increased bone turnover, whether related to metabolic bone disease or to other causes. It is clear that radiology can on occasion show specific changes, but on the basis of the present findings it would appear that if the bone scan does not suggest the presence of a metabolic disorder, then radiology will almost certainly be negative. Thus in the initial assessment of the above disorders the bone scan should be the imaging investigation of choice and radiology reserved for obtaining supplementary information when required.

In osteoporosis, however, evaluation of the bone scan for metabolic features is of very little value in the identification of disease, and radiology remains the investigation of choice. Clearly when the appearances of benign vertebral collapse are seen on the scan this suggests a diagnosis of osteoporosis and in these cases there was usually a history of fracture occurring within the previous year. It is thus suggested that the bone scan may be helpful in evaluating the time interval since collapse occurred. In addition, the bone scan may also be of value as a general screening test in those patients with osteoporosis but in whom the clinical picture or biochemical investigations are somewhat atypical. Here the scan may on occasion allow identification of otherwise unsuspected pathology such as malignancy, Paget's disease or osteomalacia.

It is of interest that all the bone scan studies to date in the field of metabolic disease have utilised the "older" bone scanning agents such as Tc-99m polyphosphate, pyrophosphate or hydroxyethylidene diphosphonate. The possibility of metabolic features being less apparent with the newer imaging agents has previously been commented upon in chapter 2 and this topic will be more fully dealt with in chapter 5. Thus there is a clear need for further studies to be carried out in metabolic bone disease comparing radiology with bone scans obtained with the newer diphosphonate scanning agents.

Paper 8. A comparison of bone scanning and radiology in the assessment of patients with symptomatic Paget's disease (1980)

European Journal of Nuclear Medicine 5: 417-421

I Fogelman, D Carr

Purpose of Investigation

This study was designed to compare the relative sensitivities of radiology and bone scanning in the detection of lesions in patients with symptomatic Paget's disease.

Eur. J. Nucl. Med. 5, 417–421 (1980)

European Journal of Nuclear Medicine

A Comparison of Bone Scanning and Radiology in the Assessment of Patients with Symptomatic Paget's Disease

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Abstract. Bone scans and X-rays from 23 subjects with symptomatic Paget's disease were evaluated. One-hundred and twenty-seven sites of Pagetoid involvement were found, of which 120 (94.5%) were recognised on the bone scan as compared to 94 (74%) on X-ray. The anatomical distribution and relationship of lesions on scan and X-ray to the patient's symptoms are also discussed.

It is concluded that the bone scan is more sensitive than radiology in detecting Paget's disease and only rarely will a lesion that is seen on X-ray not be visualised by scanning.

Introduction

Paget's disease affecting the skeleton is common with an incidence of approximately 4% in hospital patients over the age of 40 years (Collins, 1956). The bone scan appearances in this condition are often characteristic (Serafini, 1976) and it is well recognised that the scan is more sensitive than radiographic examination in the detection of metabolically active disease (Serafini, 1976; Shirazi et al., 1974; Khairi et al., 1974; Lavender et al., 1977; Vellenga et al., 1976).

In the present study, Technetium-99m diphosphonate bone scans and radiological skeletal surveys were obtained in 23 patients with symptomatic Paget's disease. The incidence, anatomical distribution and relationship of lesions on scan and X-ray to the patient's symptoms are discussed.

Patients and Methods

Twenty-three patients with symptomatic Paget's disease were studied. Clinical details are shown in Table 1.

Bone Scans. Bone scans were obtained in each patient 4 h after the intravenous injection of 15mCi of Technetium-99m hydroxyethylidene diphosphonate (HEDP). Details of the technique employed have been described elsewhere (Fogelman et al., 1978).

Radiological Skeletal Surveys. In all patients, the radiographic skeletal survey comprised antero-posterior and lateral views of the skull, antero-posterior and lateral views of the cervical, dorsal

Table 1. Paget's disease

Patient	Age and sex	Alkaline phosphatase (normal 80–280 U/l)	Predominant clinical complaints
1. GH	69 F	380 U/l	Pain lumbar spine and pelvis
2. SA	61 F	942 U/l	Pain femur
3. WO	51 M	717 U/l	Pain tibia
4. JC	42 F	626 U/l	Pain lumbar spine, pelvis and femur
5. JMcl	57 M	781 U/l	Pain femur
6. MMcD	60 F	448 U/l	Pain sacrum, pelvis and femur
7. AB	49 M	325 U/l	Pain tibia
8. FMcC	41 M	2,255 U/l	Pain thoracic spine
9. ME	65 F	2,268 U/l	Pain tibia
10. JO'B	62 M	2,967 U/l	Pain tibia
11. JG	55 M	639 U/l	Pain tibia
12. IO	60 F	494 U/l	Pain lumbar spine
13. ET	48 M	3,171 U/l	Pain tibia
14. MR	66 F	786 U/l	Headache
15. DL	56 M	2,012 U/l	Pain in chest
16. JC	73 F	1,506 U/l	Pain thoracic, lumbar spine and femur
17. CF	78 F	2,318 U/l	Pain lumbar spine, pelvis and femur
18. FM	69 F	1,413 U/l	Pain lumbar spine and tibia
19. JM	72 M	2,928 U/l	Pain lumbar spine and sacrum
20. MF	74 F	1,693 U/l	Pain lumbar spine and tibia
21. JD	73 F	1,740 U/l	Pain lumbar spine, pelvis and femur
22. CI	73 F	5,825 U/l	Pain lumbar spine, pelvis and femur
23. JG	70 M	1,187 U/l	Pain lumbar spine, pelvis, tibia and humerus

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Table 2. Comparison of sites of involvement on bone scan and X-ray in Paget's disease

	Skull	Spine[a]				Pelvis[b]	Femur	Tibia	Scapula	Humerus	Miscella-neous	Total
		C	D	L	S							
Lesions seen on X-ray	6	–	7	15	1	27	22	9	–	4	3	94
Lesions seen on bone scan	9	1	12	17	2	25	22	10	7	5	10	120
Lesions seen on X-ray only	–	–	–	–	1	4	2	–	–	–	–	7
Lesions seen on bone scan only	3	1	5	2	2	2	2	1	7	1	7	33
Patients with symptomatic sites	1	–	2	12	2	8	8	9	–	1	3	46

Lesions in the long bones and scapula are counted as two when bilateral

[a] Involvement of any area of spine in a single subject is counted as one lesion while the number of affected vertebrae in that area is not considered

[b] The pelvis is considered as two separate areas, ie. right and left hemi-pelvis

Table 3. Sites of involvement in 23 patients with Paget's disease

Spine	– 18 patients (78.3%)
Cervical	– 1 (4.4%)
Thoracic	– 12 (52.2%)
Lumbar	– 17 (73.9%)
Sacrum	– 3 (13.0%)
Pelvis	– 16 patients (69.6%)
Femur	– 15 patients (65.3%)
Tibia	– 10 patients (43.6%)
Skull	– 9 patients (39.1%)
Scapula	– 6 patients (26.1%)
Humerus	– 4 patients (17.4%)
Clavicle	– 2 patients (8.7%)
Rib	– 2 patients (8.7%)
Metacarpal	– 2 patients (8.7%)
Patella	– 1 patient (4.4%)
Forearm	– 1 patient (4.4%)
Mandible	– 1 patient (4.4%)

and lumbar spine. A postero-anterior radiograph of chest, antero-posterior views of the pelvis, and views of the long bones and hands were also obtained.

Comparison of Results. The bone scans and X-rays from the present study were included with others obtained from patients with various metabolic bone disorders (Fogelman and Carr, 1980). All the studies were assessed independently and in a random order by 2 observers (Scans-IF, X-rays DC) who were unaware of the clinical diagnoses. All abnormalities noted were charted on skeletal maps.

Results

Twenty-three patients with Paget's disease were studied and 127 sites of involvement were found. One-

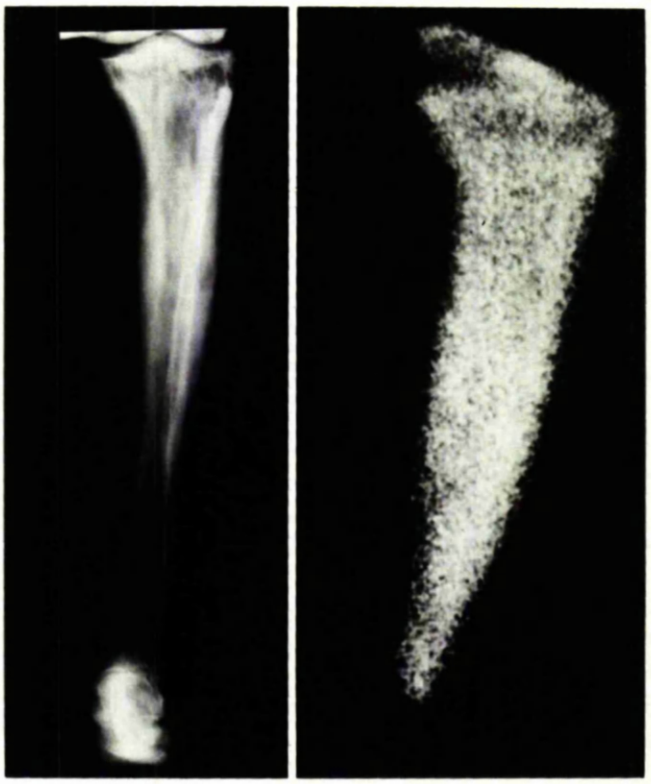


Fig. 1. X-ray (**A**) and bone scan (**B**) showing Pagetoid involement of the left tibia

hundred and twenty (94.5%) sites were recognised on the bone scan as compared to 94 (74%) on X-ray. There was agreement between the bone scan and X-ray in 87 (67.5%) sites. Four (17.4%) patients had monostotic Paget's disease, in 2 cases affecting the tibia, in 1 the femur and in 1 the skull.

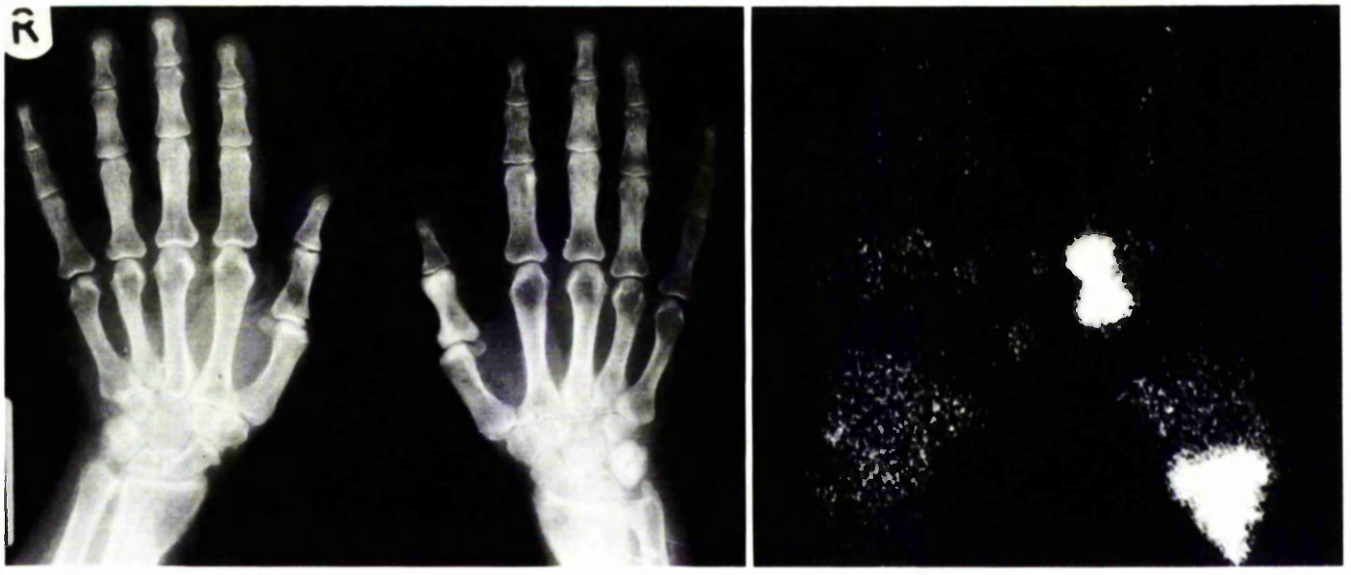


Fig. 2. X-ray (**A**) and scan (**B**) showing Pagetoid involvement of the left 1st proximal phalynx and distal radius

The comparison of the distribution of sites of Pagetoid involvement seen on bone scan and X-ray is shown in Table 2, while the relative incidence of sites affected in individual patients in shown in Table 3.

Discussion

The main feature on the bone scan in Paget's disease is markedly increased uptake of tracer, which is usually uniformly distributed throughout most or all of the affected bone. Distortion or expansion of the bone is commonly seen (Figs. 1, 2). When polyostotic Paget's disease is present, there is seldom any doubt as to the correct diagnosis, so much so that it is often possible to differentiate co-existing Paget's disease and metastatic disease (Citrin and McKillop, 1978). When monostotic Paget's disease is present it may be difficult to differentiate this from other pathology and particularly from a sclerotic lesion in the spine, eg. from carcinoma of the prostate, but usually even the appearance of a single lesion is so characteristic as to be highly suggestive of Paget's disease (Fig. 3).

In Paget's disease it has been shown that bone scanning is more sensitive than radiology in the detection of lesions (Shirazi et al., 1974; Khairi et al., 1974) and our study confirms these findings. In 23 patients with symptomatic disease we have found 127 sites of Pagetoid involvement and 12 (94.5%) of these sites were detected by the bone scan whereas 94 (74%) were seen on X-ray. In addition, in 6 patients the extent of disease affecting a long bone was underestimated by radiology. Although 33 sites were not present on X-ray (Table 2), approximately one-third of these involved areas which are difficult to evaluate with standard radiographic views, eg. scapulae, ribs (Fig. 4) and sternum (Milstein et al., 1974) and the bone scan was particularly valuable in detecting such

Fig. 3. Bone scan showing Pagetoid involvement of a single mid-thoracic vertebrae. Note the uniform distribution of tracer throughout the whole of the affected vertebrae and that the spinous process is clearly seen

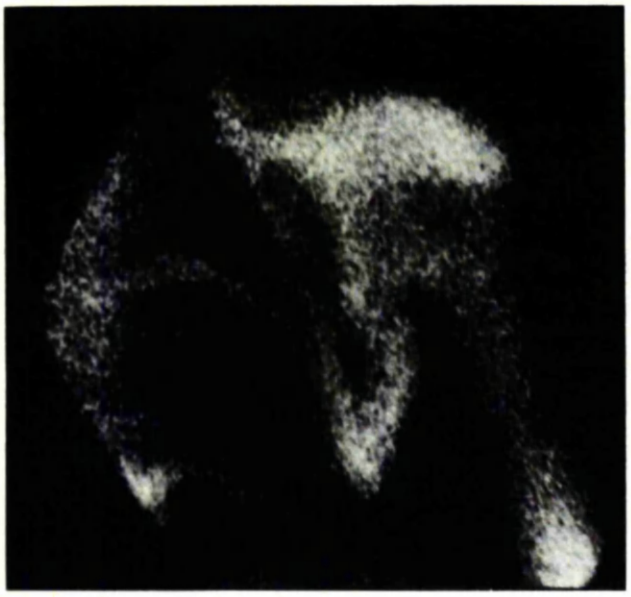
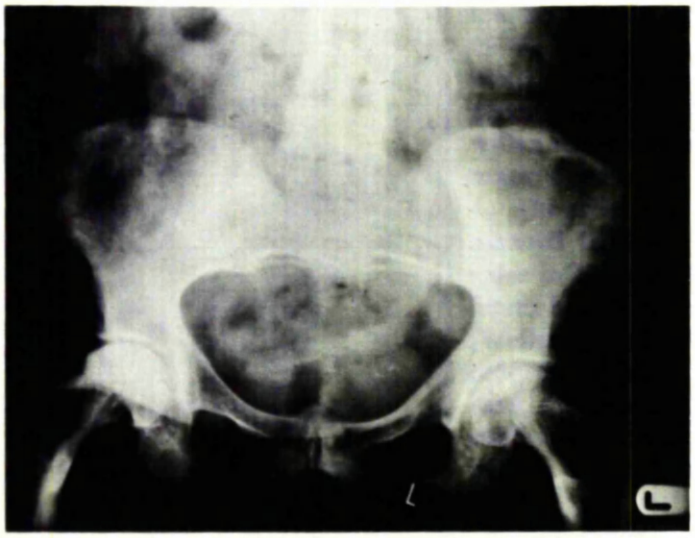


Fig. 4. Bone scan view of posterior right shoulder showing Pagetoid involvement of scapula and two ribs



lesions. Other X-ray negative sites included the spine, pelvis, femur, tibia and humerus.

It is often difficult to classify Paget's disease into lytic, blastic and sclerotic phases by radiology as has been suggested by other workers (Khairi et al., 1973) as there is usually a mixed picture present in any patient and occasionally this is the case even in the same bone. While we did not initially classify the radiological features, we did revise those X-rays from patients where lesions were missed on the bone scan and in all cases, sclerotic changes were found (Fig. 5).

The sites of Pagetoid involvement are shown in Table 3. The relative incidence is similar to that reported in other series (Shirazi et al., 1974; Vellenga et al., 1976) but we have found the spine rather than pelvis to be the most commonly involved site. We were somewhat surprised at the frequency of involvement of the scapula (26%) but this finding is in agreement with other reported series (Shirazi et al., 1974; Wellman et al., 1977). We believe that the incidence of scapular involvement remains largely unrecognised because this area is seldom symptomatic and will often be missed on routine radiology (Miller et al., 1974). Monostotic Paget's disease was found in 4 patients (17.4%) but this may not accurately reflect the general incidence in the population as we are dealing with a selected series of patients referred with symptomatic disease.

The areas of symptomatic Paget's disease are summarised in Table 2. The most common sites were spine in 13 patients, tibia in 9 patients and pelvis and femur both 8 patients, i.e. in the weight bearing areas (Wellman et al., 1977). Although headaches have been reported to be a characteristic feature of Paget's disease (Ibbertson et al., 1979) of the 9 patients with skull involvement, only one specifically complained of this. Overall there was good accordance between

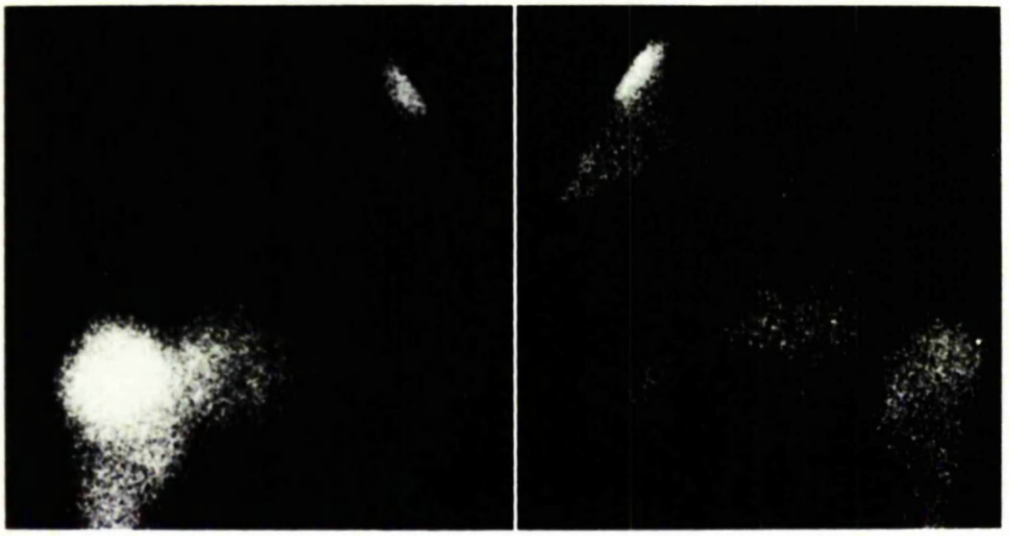


Fig. 5. X-ray (**A**) and scan (**B**) of anterior pelvis. There is striking Pagetoid involvement which is apparent on X-ray but not seen on scan

the sites of patients' pain and X-ray and scan findings, although in 4 of the 23 patients no correlation was found. There seems to be general agreement that symptomatic lesions usually appear strongly positive on the bone scan (Shirazi et al., 1974; Khairi et al., 1973) but only 36% of the lesions seen in the present study were found to be symptomatic. We have found that all 4 sites visualised on one study only (33 on the bone scan, 7 on X-ray), were asymptomatic. However, Khairi studied 27 patients with Paget's disease and found that all 19 lesions visualised on X-ray but not on the bone scan were asymptomatic but that 15 of the 21 lesions seen on the scan and not on X-ray were symptomatic (Khairi et al., 1974).

In conclusion, we have shown that the bone scan is more sensitive than radiology in detecting Paget's disease and only rarely will a lesion that is seen on X-ray not be visualised on scanning. This phenomenon was limited to the sclerotic lesion in agreement with other groups (Shirazi et al., 1974; Khairi et al., 1973). In addition to its sensitivity, the bone scan provides adequate visualisation of the whole skeleton and is easier to perform and interpret than a radiological skeletal survey.

References

Citrin, D.L., McKillop, J.H.: Paget's disease. In: Atlas of Technetium bone scans, p. 126. Philadelphia: W.B. Saunders 1978

Collins, D.H.: Paget's disease of bone. Incidence and subclinical forms. Lancet **2**, 51–57 (1956)

Fogelman, I., Carr, D.: A comparison of bone scanning and radiology in the evaluation of patients with metabolic bone disease. Clin. Radiol. **31**, 321–326 (1980)

Fogelman, I., McKillop, J.H., Bessent, R.G., Boyle, I.T., Turner, J.G., Greig, W.R.: The role of bone scanning in osteomalacia. J. Nucl. Med. **19**, 245–248 (1978)

Ibbertson, H.K., Henley, J.W., Fraser, T.R., Tait, B., Stephens, E.J., Scot, D.J.: Paget's disease of bone - Clinical evaluation and treatment with diphosphonate. Aust. N.Z.J. Med. **9**, 31–35 (1979)

Khairi, M.R., Rob, J.A., Wellman, H.N., Johnston, C.C. Jr.: Radiographs and scans in diagnosing symptomatic lesions of Paget's disease of bone (osteitis deformans). Geriatrics **29**, 49–54 (1974)

Khairi, M.R., Wellman, H.N., Robb, J.A., Johnston, C.C. Jr.: Paget's disease of bone (osteitis deformans): symptomatic lesions and bone scan. Ann. Int. Med. **79**, 348–351 (1973)

Lavender, J.P., Evans, I.M., Arnot, R., Bowring, S., Doyle, F.H., Joplin, C.F., MacIntyre, I.: A comparison of radiography and radioisotope scanning in the detection of Paget's disease and in the assessment of response to human calcitonin. Br. J. Radiol. **50**, 243–250 (1977)

Miller, S.W., Castronovo, F.P.Jr., Pendergrass, H.R., Potsaid, M.S.: Technetium 99m labelled diphosphonate bone scanning in Paget's disease. Am. J. Roentgenol. **121**, 177–183 (1974)

Milstein, D., Nusynowitz, M.L., Lull, R.J.: Radionuclide diagnosis in chest disease resulting from trauma. Semin. Nucl. Med. **4**, 339–355 (1974)

Serafini, A.N.: Paget's disease of bone. Semin. Nucl. Med. **6**, 47–58 (1976)

Shirazi, P.H., Ryan, W.G., Fordham, E.W.: Bone scanning in evaluation of Paget's disease of bone. CRC Crit. Rev. Clin. Radiol. Nucl. Med. **5**, 523–558 (1974)

Vellenga, C.J., Pauwels, E.K., Bijvoet, O.L., Hosking, D.J.: Evaluation of scintigraphic and roentgenologic studies in Paget's disease under treatment. Radiol. Clin. (Basel) **45**, 292–301 (1976)

Wellman, H.N., Schauwecker, D., Robb, J.A., Khairi, M.R., Johnston, C.C.: Skeletal scintimaging and radiography in the diagnosis and management of Paget's disease. Clin. Orthop. **127**, 55–62 (1977)

Received December 7, 1979

Comment

This study essentially confirms previous reports that the bone scan will identify many more sites of Pagetoid involvement than routine radiology. It is suggested that this is due to the combination of greater sensitivity for disease and the improved visualisation of the total skeleton obtained with bone scanning. It is extremely uncommon for any lesion seen on a radiograph not to be detected on a scan, and this is limited to the sclerotic metabolically inactive lesion. Symptomatic lesions appear strongly positive on the bone scan but it was found that only 36% of all lesions detected by the bone scan were symptomatic.

SUMMARY

CHAPTER 3.

A COMPARISON OF SKELETAL SCINTIGRAPHY AND RADIOLOGY IN METABOLIC BONE DISEASE

This chapter deals with comparisons of bone scanning and radiology in metabolic bone disease and Paget's disease. Initially the different principles and mechanisms relating to lesion detection with both radiology and bone scan are discussed.

Paper 7 describes the only investigation to date comparing radiology and bone scanning in metabolic bone disorders. All radiographs and scans were independently evaluated without prior knowledge of the specific diagnoses and it was found that the scan was more sensitive in identifying patients with primary hyperparathyroidism, renal osteodystrophy and osteomalacia. In osteoporosis radiology remains the investigation of choice although it was found that the bone scan may be of some value in indicating the time interval since vertebral collapse, as the intense tracer uptake at the site of collapse gradually disappears over a 1-2 year period.

Paper 8 presents the results of a study comparing radiology and bone scanning in patients with symptomatic Paget's disease. The findings confirm previous reports that the bone scan is more sensitive than radiology for detecting sites of Pagetoid involvement.

It is noted that all bone scan studies to date in metabolic bone disease have used 'older' bone scanning agents, and it is possible that with the new diphosphonates which have higher skeletal affinity, metabolic features may be less apparent. It is clear that further comparative studies between bone scanning and radiology require to be carried out. This is not the case in Paget's disease for here focal pathology is present and this is easily identified on the scan image, regardless of which radiopharmaceutical is used.

CHAPTER 4.

QUANTITATION OF 24-HOUR WHOLE-BODY RETENTION OF TECHNETIUM-99m DIPHOSPHONATE - A TRACER TECHNIQUE FOR THE ASSESSMENT OF SKELETAL METABOLISM

Following a review of the use and limitations of established radioactive tracer techniques, four papers (9-12) are presented which deal with the development and validation of a new test, 24-hour whole-body retention of technetium-99m diphosphonate, for the measurement of skeletal metabolism.

THE HISTORY OF RADIONUCLIDE TRACER TECHNIQUES IN THE EVALUATION OF SKELETAL METABOLISM

The earliest indication that radionuclides could accumulate in the skeleton originated from observations in painters of luminous watch dials who developed bone necrosis, osteomyelitis and bone tumours following chronic exposure to radium (Blum 1924, Hoffman 1924). It was initially thought that this radionuclide was taken up by reticuloendothelial cells, until autoradiography of human post mortem material revealed that the bone itself was radioactive (Martland 1926). Nevertheless, it was widely believed that bone was metabolically inactive until Chiewitz and Hevesy (1935) demonstrated incorporation of P-32 phosphate into the skeleton of adult rats. This was the first use of an artificially produced radionuclide in the study of skeletal metabolism, and in addition to finding deposition of P-32 in bone, its distribution in other organs and excretion in both urine and faeces were studied.

Walke (1940) described the physical characteristics of Ca-45 and suggested its use as a tracer in biological studies. The first animal experiments using Ca-45 were reported by Campbell and Greenberg (1940) who measured its absorption and excretion in a rat. The first report,

however, of the use of Ca-45 in humans was from Bellin and Laszlo (1953) who administered Ca-45 intravenously to patients with malignancy and measured its blood clearance and excretion. They suggested that such studies might yield useful information on skeletal metabolism. This paper has been followed by a great many others (Anderson et al, 1956; Krane et al, 1956; Bronner et al, 1956; Fink and Laszlo, 1957; Comar et al, 1957; Spencer et al, 1957; 1960; Mazzuoli et al, 1958; Dow and Stanbury, 1960) which have simply expanded these original observations, with the same or different radionuclides, without however adding any theoretical basis as to how one might obtain an accurate measurement of skeletal metabolism.

While bone crystals are extremely small, they have a huge total surface area and yet this surface appears to have such little contact with body fluids that the vast bulk of skeletal mineral has to be considered separate from and effectively non-exchangeable with the calcium of the body fluids (Neuman and Neuman, 1953; 1957). It has been suggested that in normal adults injected tracer mixes with only 1% or less of the estimated total body calcium (Heaney 1963). Although several early papers proposed that processes other than exchange were required to explain observed bone tracer behaviour (Norris and Kisieleski, 1948) it was Carlsson (1951) who first provided the conceptual basis on which most subsequent calcium kinetic data is based. He suggested that the tracer content of bone

represented two distinct and essentially independent components: (a) an exchangeable calcium fraction in which tracer concentration, by definition, must change in parallel with that of the body fluids, and (b) that associated with bone accretion, in which tracer is removed from body fluids and deposited irreversibly in the skeleton during new bone formation.

ASSESSMENT OF SKELETAL METABOLISM WITH RADIOCALCIUM

Bone Remodelling

While growth ceases with skeletal maturity, the skeleton remains a metabolically active organ with remodelling of bone continuing throughout life. By this means both the mass and architecture of bone can be altered. Essentially remodelling is the term used to describe the sequential occurrence of a wave of cellular activity which is initiated by osteoclastic bone resorption, then osteoblasts refill the resorbed area with osteoid and this is subsequently mineralised (Frost 1963). Remodelling is not a generalised process, and takes place at localised sites. Why this should be so is not known, nor is the stimulus which may commence the sequence recognised. However it is likely that remodelling is necessary to repair damaged tissue such as sites of micro-fracture (Frost 1973), and may have a role to play in altering bony trabeculae in response to mechanical stress (Doyle et al, 1970;

Aloia et al, 1978). Certainly at any one time there are many active sites throughout the skeleton and it has been suggested that a healthy adult remodels approximately 10% of the skeleton annually (Aaron 1976).

Clearly if a subject is in calcium balance the rate of bone resorption and formation must be equal, but if one is losing bone then the rate of resorption must exceed that of formation. While alterations in skeletal metabolism occur in many diseases it has been observed that the rates of bone resorption and formation change in the same direction, although not necessarily to the same degree (Harris and Heaney, 1969).

Calcium Metabolism

Calcium is found in the body in bone, extracellular fluids and soft tissues. From the body fluids calcium may enter the skeleton in two ways; either by exchanging with other calcium ions on exposed surfaces of bone crystals or by deposition into new bone crystals as these are formed. The first or exchange process occurs rapidly and extensively and this has been confirmed in studies with bone labelled in vitro (Amprino 1952; Lacroix 1952) and in bone cell culture studies (Lengemann 1957). The exchange process, however, is clearly not the only one for new bone is constantly being formed to keep pace with resorption. In addition, autoradiographic studies have shown that

injected radionuclides are initially deposited widely throughout an animal's skeleton, but later remain where deposited in deeper bone (Tutt et al, 1952; Jowsey et al, 1953; Bauer 1954). Bauer and Carlsson (1955) injected both P-32 and Ca-45 into rats, and over the next five days obtained serial measurements of each in plasma and bone. From these results they computed the rate of deposition of calcium and phosphorus in various parts of the skeleton. Good agreement was obtained between the two sets of data. It was found that for the first 24-48 hours after injection, tracer uptake by bone was rapid, presumably due to the summation of exchange and deposition; but thereafter mixing or exchange with surface bone was evidently completed, and the rate remained steady, reflecting the rate of incorporation of tracer into deeper bone. Such findings suggest that surface bone and body fluids are in equilibrium and these two fractions of body calcium may thus be regarded as comprising a single pool or mass of exchangeable calcium.

It is convenient to consider the body's calcium as existing in two main pools, the exchangeable calcium pool and deep bone. The exchangeable pool receives calcium from intestinal absorption and bone resorption, while calcium is lost from it by urinary and faecal excretion, as well as by deposition into deep bone.

Calcium Kinetic Measurements

One method of measuring skeletal metabolism, and perhaps the only generally accepted one available at the present time is to label the calcium atoms entering bone with radiocalcium and so distinguish them from the calcium atoms coming out. There are several ways in which this can be accomplished but most methods are variations of the same theme. Essentially an injection of radiocalcium (Ca-47 or Ca-45) is given intravenously and plasma decay curves and whole-body retention of tracer estimated over a period of time, usually in the order of two weeks. The plasma decay curve is obtained from radioactivity measurements at various time intervals following injection and the retention curve either by collecting excreta or by counting the retention of tracer in a whole-body counter. Several mathematical approaches based on these primary sets of data are then possible and have been reviewed by Heaney (1963), Marshall (1964) and Wendeberg (1965). A relatively simple and straightforward calculation may be obtained from the postulate of Bauer et al (1961) that the amount of activity in the skeleton at any given time is the sum of the amount deposited by new bone mineralisation and the amount that has entered by exchange. From this the basic equation $R = E + A$ is derived, where R = activity retained, E is activity in the exchangeable pool and A is activity deposited by accretion

(bone mineralisation). As there are two unknowns (E and A), two equations can be written at different time intervals following administration of the dose to determine the two unknowns. The times chosen are of great importance since during much of the first week or so after injection the fall of activity of tracer in plasma is relatively rapid, almost certainly due to exchange processes, and any calculation of mineralisation rates would tend to over-estimate the true value until these processes have reached equilibrium. To avoid this, measurement should be made as late as possible, but if too late other problems arise. Firstly the rapid decay of Ca-47 may make it impossible to measure activity, and secondly and in practical terms much more important, if resorption of labelled bone were to occur, this would release tracer into the exchangeable pool and render the whole measurement meaningless. Nordin (1967) has suggested that measurements should be made at 7 or 11, and 14 days after injection, but much controversy exists (Heaney 1963) and the optimal times remain speculative. Alternative procedures for the calculation of bone mineral-isation rate from the isotopic data include drawing a line through the most linear part of the plasma decay curve, extrapolating back to zero time and calculating the exchangeable calcium pool size from the reciprocal of the intercept. Total turnover is calculated from the rate of fall of plasma specific activity multiplied by this pool and if urinary

calcium and endogenous faecal calcium are subtracted from the turnover, this yields the bone mineralisation rate (Nordin 1967).

Limitations of Calcium Kinetic Measurements

The conceptual basis for calcium kinetic studies is complex and Heaney (1963) has suggested that the extreme simplifications necessary for diagnostic purposes may negate the value of these techniques. He also stated that the field of calcium kinetics is sufficiently complex that with very little effort it could be made totally incomprehensible. The accretion rate and exchangeable calcium pool size have both been defined on a mathematical or kinetic basis and while it is argued that such measurements are of great importance in the overall understanding of the metabolic bone diseases, nevertheless their physiological significance is not immediately apparent and measurements have little direct clinical significance (Dymling 1971). Values for accretion rate in patients with metabolic bone disease, for example, tend to show large overlap with values from control subjects (Dymling 1962; Nordin et al, 1976).

Calcium kinetic techniques have further practical disadvantages, for they are laborious to perform, are expensive, and utilise significant amounts of radioactivity.

Furthermore when balance techniques are used, collection of excreta is necessary, and it is recognised that many additional sources of error may be introduced (Reifenstein et al, 1945; Isaksson and Sjogren, 1967). In addition, prolonged periods of in-patient hospitalisation are required for calcium kinetic studies and for these reasons such tests have been less often performed in recent years.

OTHER TRACER TECHNIQUES FOR ASSESSMENT OF SKELETAL METABOLISM

A. Continuous Infusion of Calcium-45

In view of the complexity and other problems related to the calcium kinetic techniques, Rich et al (1961) investigated the possibility of using the distribution of radiocalcium delivered by constant intravenous infusion as a means of reflecting skeletal metabolism in metabolic bone disease. Each infusion was delivered over a period of 1.7 to 3.3 hours and during this time the specific activity of plasma calcium was found to increase at a constant rate, which made it possible to calculate the amount of calcium with which the administered Ca-45 appeared to mix. It was suggested that this test principally reflected alterations in bone formation which made available a larger area of bone surface for exchange reactions. The results of the Ca-45

infusion test were found to be similar in all normal subjects and appeared to vary characteristically in states of altered skeletal metabolism such as Paget's disease, primary hyperparathyroidism and osteomalacia. However, unexpectedly high results for available calcium were found in three patients with senile osteoporosis and this finding could not be adequately explained.

Haymovitz and Horwith (1964) evaluated the Ca-45 infusion technique in a larger group of patients with metabolic bone disease. They obtained similar results to Rich et al (1961) but found that the majority of patients with osteoporosis had normal values for the test. They suggested that the technique may be useful in elucidating the pathogenesis of bone disease.

The radiocalcium infusion technique, while relatively simple to carry out, was not however shown to provide a sensitive measure of altered skeletal metabolism in individual patients and this test is no longer performed.

B. Tracer Techniques using non-radioactive substances

(i) Stable Strontium

Fraser et al (1960) and Eisenberg and Gordon (1961) described techniques for estimating the rate of skeletal deposition of calcium using stable strontium as a tracer.

After an intravenous dose of strontium, its concentration in serum and urine was measured over the next six days. From the rate of decline of these concentrations it was possible to calculate the rate of movement of strontium out of the body fluids into urine and bone. It was suggested that this technique provided a sensitive means of identifying patients with increased bone turnover and that it may be of particular value as an aid to the diagnosis of primary hyperparathyroidism or osteomalacia (Fraser et al, 1960). However to carry out this test patients were required to take fixed calcium diets for three or more days prior to the commencement of the study (Fraser et al, 1960) and multiple blood and urine samples (with inevitable uncertainties as to whether the urine collections were complete) were obtained over the six day period. A small but significant amount of strontium (approximately 8-16%) is excreted by the faeces and this was not corrected for.

A similar test using stable strontium, which measures the 24-hour strontium space, has also been suggested as a valuable index of exchangeable calcium (Nadarajah et al, 1968; Thalassinos et al, 1970). Here the strontium space result is expressed in plasma units, and this calculation requires the assumption that plasma is 5% of body weight expressed in kilograms. To carry out the above studies

facilites for measuring strontium are required and in practice these tests are no longer performed.

(ii) Calcium Infusion Tests

The use of calcium infusions in the diagnosis of metabolic bone disease was first suggested by Schilling and Laszlo (1951) who argued that the amount of calcium appearing in the urine after a standard infusion should be inversely related to the avidity of the skeleton for calcium. Since that time many groups have published data on various aspects of calcium infusions with only limited success in clinical practice (McCance and Widdowson, 1939; Baylor et al, 1950; Howard et al, 1953; Kyle et al, 1954; Spencer et al, 1954; Goldman and Bassett, 1954). However Nordin and Fraser (1956) described a standard procedure utilising a four hour calcium infusion and they considered this test to be of diagnostic value for osteomalacia. Essentially the net output of calcium following infusion is expressed as a percentage of the administered dose after deduction of a basal excretion figure calculated from the previous 24 hours' urinary output of calcium.

This test is inconvenient to perform as it requires the patient to take a low calcium diet for three days prior to study, with urine collections over the following 48 hours. There is the further disadvantage that calcium infusions are not without risk in patients with hypercalcaemia and

the usefulness of this test in clinical practic has not been substantiated (Bhandarkar and Nordin, 1962).

ADVANTAGES OF TECHNETIUM-99m DIPHOSPHONATE UPTAKE AS A MEASURE OF SKELETAL METABOLISM

The vast bulk of skeletal mineral has such little contact with body fluids that it is effectively unavailable for exchange reactions, and surface phenomena dominate the chemical behaviour of bone due to the enormous surface area of the bone crystals (Neuman and Neuman, 1953). It is believed that alterations in the bone surface available for exchange reactions are directly proportional to the level of skeletal metabolism (Fraser et al, 1960). Bone that is actively remodelling thus appears to be more accessible than resting bone for exchange with calcium (or bone seeking radiopharmaceuticals) in the circulating body fluids (Heaney 1976). A means of quantitating such alterations in skeletal affinity for tracer may therefore provide a valuable measure of skeletal metabolism in clinical practice.

Tc-99m diphosphonate is an avid bone seeking compound which has been shown to adsorb onto the surface of bone crystals (Francis 1969) (see chapter 1). Tc-99m diphosphonate is rapidly cleared from the soft tissues and excreted via the urinary tract, and because of this it is possible to measure skeletal retention of tracer at

relatively early times following injection. A direct measure of skeletal avidity for this bone seeking radiopharmaceutical can thus be obtained. This is not possible with radiocalcium because of excreted activity in the bowel and all the values obtained relating to skeletal avidity of tracer, such as mineralisation rates, are derived from indirect data. While quantitation of skeletal uptake of Tc-99m diphosphonate is not strictly comparable with the other more elaborate calcium kinetic techniques, the magnitude of bone remodelling is nevertheless clearly reflected. In addition quantitation of Tc-99m diphosphonate requires no patient preparation, is simple and quick to perform, is inexpensive and uses extremely small amounts of radioactivity.

Paper 9. The use of whole-body retention of Tc-99m diphosphonate in the diagnosis of metabolic bone disease (1978)

Journal of Nuclear Medicine 19: 270-275

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Purpose of Investigation

In chapter 2 it was emphasised that quantitation of skeletal uptake of radiopharmaceutical may provide a sensitive measure of accelerated bone turnover. A semi-quantitative scoring system based on the presence of metabolic features on the bone scan image and the technique of measuring bone to soft-tissue ratios from the scan were described and critically evaluated. It was apparent, however, that these techniques did not provide a sensitive means of identifying altered skeletal metabolism in individual subjects, and a large degree of overlap was found between results from patients with metabolic bone disease and control subjects.

The present study arose from my desire to obtain a more accurate means of quantitating total skeletal uptake of radiopharmaceutical. Utilising a standard shadow-shield whole-body monitor, sequential measurements of whole-body retention of Tc-99m hydroxyethylidene diphosphonate (WBR) were obtained over 24 hours in 4 patients with osteoporosis,

11 with renal osteodystrophy, 7 with osteomalacia, 5 with primary hyperparathyroidism, 10 with Paget's disease and 12 healthy volunteer subjects.

It is recognised that diphosphonate is either largely taken up by the skeleton or else excreted via the urinary tract. Normally, approximately 70% of an intravenous dose of Tc-99m hydroxyethylidene diphosphonate will be excreted via the urinary tract within 4-6 hours of injection. I therefore suggested that if the majority of the non-skeletal activity were excreted then a whole-body count would effectively provide a skeletal count. The purpose of this study was to assess whether WBR measurements could provide a sensitive measure of skeletal metabolism.

The Use of Whole-Body Retention of Tc-99m Diphosphonate in the Diagnosis of Metabolic Bone Disease

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The limited role of bone scanning in the diagnosis of metabolic bone disease might be considerably improved by accurate quantification of skeletal uptake of the radiopharmaceutical. Using a standard shadow-shield whole-body monitor, we have measured whole-body retention (WBR) of Tc-99m HEDP up to 24 hr in 11 patients with renal osteodystrophy (mean WBR 88.6% at 24 hr); in ten patients with Paget's disease (mean 56.9%); in seven patients with osteomalacia (mean 40.7%); in five patients with primary hyperparathyroidism (mean 50.7%); in four patients with osteoporosis (mean 21.2%); and in 12 normals (mean 19.2%). The osteoporotic group could not be differentiated from the normal group, but the other groups were significantly different from the normal group at 24 hr ($p < 0.002$), and each individual result for the 24-hr WBR of Tc-99m HEDP in these groups lay outside our normal range. This test may, therefore, provide a sensitive means of detecting conditions with increased bone turnover. We obtained measurements of plasma activity of Tc-99m HEDP in these patients up to 24 hr, and 4-hr bone to soft-tissue ratios from bone-scan images, but little additional information resulted.

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There has been recent interest in the use of bone scanning in metabolic bone disease, and there emerge certain patterns of abnormality that may aid in the diagnosis of these disorders (*1–5*). Nevertheless, the scan appearances are often nonspecific and are of limited use in those cases that present the most difficulties in clinical practice. Because of the great affinity of bone for the phosphate and phosphonate tracers, quantification of their skeletal uptake may have a useful role in the detection of metabolic disorders. Simple quantification of the bone scan has been performed by measuring the bone to soft-tissue ratio (*3*), but this is a relatively crude method as the small area of bone selected may not reflect a small yet significant change in the total skeletal uptake of radiopharmaceutical. There is also the problem of standardizing the "soft tissue," since counts per unit area vary with vascularity and muscle bulk.

In an attempt to quantify total skeletal uptake of radiopharmaceuticals, we have measured the whole-body retention (WBR) of Tc-99m hydroxyethylidene diphosphonate (HEDP) sequentially over 24 hr in patients with Paget's disease and other metabolic bone disorders. We also measured bone to soft-tissue ratios from the bone scans in these patients,

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gallium-67 and scintigraphic imaging. *J Infect Dis* 130: 125–131, 1974

5. KUMAR B, COLEMAN RE, ALDERSON PO: Gallium citrate (^{67}Ga) imaging in patients with suspected inflammatory processes. *Arch Surg* 110: 1237–1242, 1975

6. HOPKINS GB, MENDE CW: Gallium-67 and subphrenic abscesses, is delayed scintigraphy necessary? *J Nucl Med* 16: 609–611, 1975

7. HAAGA JR, ALFIDA RJ, HAVRILLA TR, et al: CT detection and aspiration of abdominal abscesses. *Am J Roentgenol* 128: 465–474, 1977

8. HOFFER PB, SCHOR R, ASHBY D, et al: Comparison of Ga-67 citrate images obtained with rectilinear scanner and large-field Anger camera. *J Nucl Med* 18: 538–541, 1977

and this communication describes our findings (Table 2).

Each patient was given 50 μCi of Tc99m HEDP by i.v. injection and the whole-body count was measured at 5 min, and at 2, 4, 6, 8, and 24 hr, using a standard shadow-shield whole-body monitor (*6*). Whole-body retention of radiopharmaceutical was calculated, after appropriate background subtraction, by taking the 5-min count as 100% and correcting thereafter for radioactive decay. In addition, 10-ml blood samples (20-ml at 24 hr) were collected by venepuncture at the time of each whole-body count and plasma radioactivity was measured in an automatic gamma counter. Results were expressed as a percentage of injected activity per litre plasma, using a fraction of the injected material as a standard.

The above measurements were made in: (a) ten patients with Paget's disease (age range 47–78 yr, symptomatic, and with extensive radiologic and bone-scan evidence of disease); (b) four with osteoporosis (age range 51–72 yr, symptomatic, and with vertebral crush fractures); (c) five with primary hyperparathyroidism (age range 51–80 yr, three having parathyroid adenomas, subsequently removed, and two having hypercalcaemia with elevated parathormone levels); (d) seven with osteomalacia (age range 15–68 yr, all having bone and muscle pain and having had bone-biopsy evidence of osteomalacia); (e) 11 with renal osteodystrophy (age range 15–55 yr, creatinine clearance range 5–35 ml/min, all with biochemical and bone-biopsy evidence of renal osteodystrophy); and (f) 12 healthy volunteers with no evidence of bone disease (age range 19–31 yr).

Bone scintigrams were performed with Tc-99m HEDP in all patients, using a gamma camera with high-resolution, medium-sensitivity collimator. In addition, all images were recorded and stored in a minicomputer. The pictures were stored for later retrievel and processing on computer magnetic tape. Bone to soft-tissue ratios were measured by using the computer to define regions of interest around the L2 vertebra or, in the case of Paget's disease, an involved vertebra. An adjacent soft-tissue area clear of bone and renal activity was similarly defined (Fig. 1). The computer was used to derive mean counts per unit area for each region, and the simple ratio of these two results is defined as the bone to soft-tissue ratio.

In 35 patients bone to soft-tissue ratios were measured but in two patients (one with Paget's disease and one with primary hyperparathyroidism) the stored images were "lost." Bone to soft-tissue ratios were also measured in a control group of 80 women with breast carcinoma without clinical suspicion of bone metastases, and with bone scans considered completely normal.

Differences between groups for any parameter were tested using the Wilcoxon rank-sum test which —unlike the Student t-test—makes no assumptions about the distribution of values for the populations being compared.

RESULTS AND DISCUSSION

Table 1 shows the mean values for plasma Tc-99m activity at each sampling time for the various groups of patients. The renal osteodystrophy group was significantly higher than the normal and Paget's groups at all times, but with greatest significance at 24 hr ($p < 0.01$ and $p < 0.002$, respectively). The primary hyperparathyroidism group also differed significantly from the normal and Paget's groups up to 8 hr ($p < 0.01$), but there was no significant difference at 24 hr. The osteomalacia group was significantly different from the normal group at 24 hr only ($p < 0.02$). At 4 and 6 hr there was marginal significance ($p < 0.05$) in the difference between the osteomalacia and primary hyperparathyroidism groups. There was also marginal significance in the difference between the osteoporotic and normal groups at 24 hr ($p < 0.05$). Although these differences exist between the various group averages, there is marked overlap of individual plasma results

TABLE 1. MEAN VALUES FOR PLASMA ACTIVITY OF Tc-99m HEDP (% INJECTED ACTIVITY/LITRE PLASMA ± 1 s.d.)

	5 min	2 hr	4 hr	6 hr	8 hr	24 hr
Osteoporosis (N = 4)	20.0 ± 4.48	3.78 ± 0.84	1.99 ± 0.48	1.33 ± 0.32	0.96 ± 0.25	0.43 ± 0.12
Renal osteodystrophy (N = 11)	16.38 ± 3.98	4.01 ± 1.57	2.6 ± 1.11	1.83 ± 0.91	1.78 ± 0.78	0.64 ± 0.42
Paget's disease (N = 10)	16.35 ± 4.09	2.23 ± 0.93	1.2 ± 0.51	0.79 ± 0.27	0.58 ± 0.13	0.25 ± 0.05
Osteomalacia (N = 7)	20.44 ± 3.48	2.89 ± 0.84	1.54 ± 0.54	1.03 ± 0.42	0.94 ± 0.35	0.49 ± 0.16
Primary hyperparathyroidism (N = 7)	21.6 ± 5.56	5.21 ± 1.62	2.89 ± 1.13	1.86 ± 0.82	1.44 ± 0.67	0.52 ± 0.24
Normals (N = 10)	15.24 ± 2.68	2.78 ± 0.65	1.46 ± 0.4	0.98 ± 0.29	0.73 ± 0.23	0.29 ± 0.07

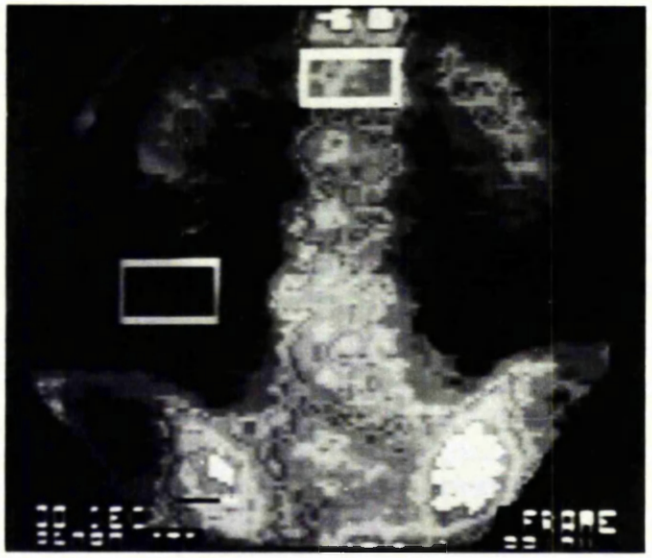

FIG. 1. Monochrome representation of color TV image of lumbo-sacral spine, showing regions defined for "bone" and "soft-tissue" activity measurements.

between all groups; accordingly—with the possible exception of the osteoporotic group—measurement of plasma activity does not provide diagnostic information beyond that derived from the measurement of 24-hr WBR of Tc-99m HEDP (discussed later).

The distribution of the bone to soft-tissue ratios is shown in Fig. 2. The primary hyperparathyroidism patients are indistinguishable from the normal group, as previous workers have found (*3*). The osteomalacic and renal osteodystrophy groups are both significantly different from the normal group ($p < 0.001$). However, there is an appreciable overlap between each of these groups and the normal range, rendering a normal result in an individual patient of no value. The bone to soft-tissue ratios for the Paget's group all lie above the normal range. In all these patients, however, the diagnosis was obvious from the bone-scan appearance [patients with Paget's disease usually have characteristic bone-scans (*7*)] and the area of bone for the bone to soft-tissue ratio was deliberately chosen as an affected area. Note further that our bone to soft-tissue ratios are of no value in those situations that often provide the greatest difficulty clinically—namely, primary hyperparathyroidism and osteoporosis.

The measurement of the bone to soft-tissue ratio is a crude means of quantifying skeletal uptake of a tracer, and although elevated values confirm increased skeletal uptake, normal values do not exclude this.

Figure 3 plots the mean whole-body retention against time for the different groups, up to the end of our study at 24 hr. The continuous curves were derived from a least-squares fit of the data to a double exponential function, using an iterative procedure. Intergroup differences are most striking at 24 hr (Fig. 3), but the osteoporosis curve lies close to the normal. The 24-hr value for whole-body retention of Tc-99m HEDP is a more convenient measurement than the 8-hr value. Also, the 24-hr value is not subject to error from failure to empty the bladder, which may cause artificially high values in the earlier hours of study. The technetium either is taken up by the skeleton or is almost totally excreted by the kidneys (*8*); in fact, almost 70% of an i.v. dose of Tc-99m HEDP is normally excreted through the urinary tract within 6 hr of injection (*9*). Therefore, by 24 hr the body burden of Tc-99m HEDP represents almost entirely skeletal uptake.

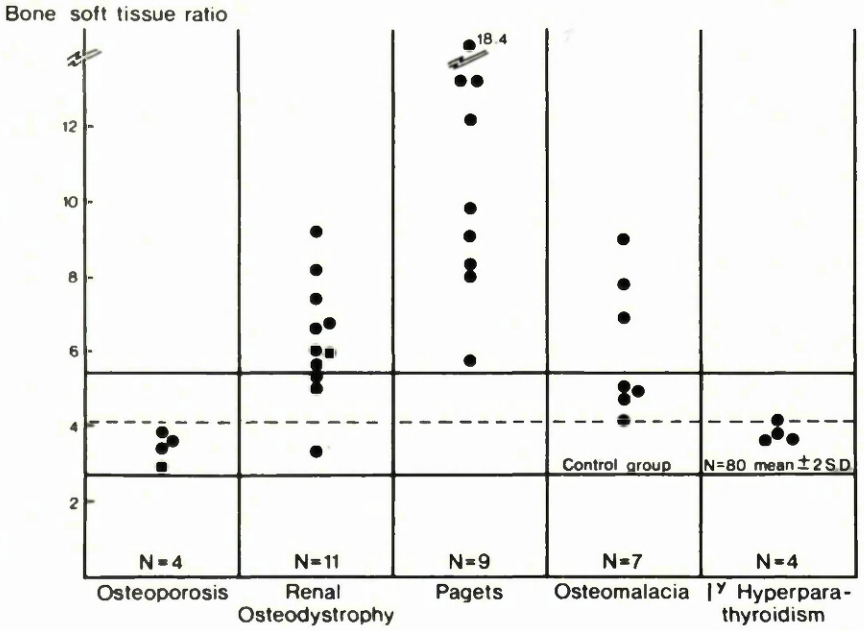

FIG. 2. Distribution of 4-hr bone/soft-tissue ratios.

TABLE 2. MEAN VALUES FOR 24-HR WBR OF Tc-99m HEDP (% INJECTED ACTIVITY ± 1 s.d.), AND 4-HR BONE TO SOFT-TISSUE RATIOS ± 1 s.d.

	No.	Mean 24-hr WBR ± 1 s.d.	Difference from normal group	Mean 4-hr bone to soft-tissue ratio ± 1 s.d.
Osteoporosis	4	21.2 ± 1.7	Not significant	3.43 ± 0.39
Renal osteodystrophy	11	88.6 ± 10.5	$p < 0.002$	6.29 ± 1.6
Paget's	10	56.9 ± 13.1	$p < 0.002$	10.87 ± 3.79
Osteomalacia	7	40.7 ± 8.0	$p < 0.002$	6.06 ± 1.85
Primary hyperparathyroidism	5	50.7 ± 14.6	$p < 0.002$	3.76 ± 0.26
Normals	12	19.2 ± 1.7	—	4.05 ± 0.69

The control group had a mean 24-hr whole-body Tc-99m HEDP of 19.18% ± 1.73 (1 s.d.), this being significantly different from the groups with Paget's disease, osteomalacia, primary hyperparathyroidism, and renal osteodystrophy (Table 2).

Figure 4 shows that in these groups all results for 24-hr WBR of Tc-99m HEDP in individual patients lay outside our normal range. The osteoporotic group could not be differentiated from the controls, but since there were only four patients in this group, it requires further study.

The 24-hr whole-body retention of Tc-99m HEDP in the renal osteodystrophy group (mean 88.6% ± 10.5) was much higher than in all other groups ($p < 0.002$). Although very high values for WBR of Tc-99m HEDP can be expected in any patient unable to excrete the tracer due to severe renal impairment (e.g., in acute renal failure, obstructive uropathy, or end-stage chronic renal failure), we find that in our patients with renal osteodystrophy the high retentions were largely due to increased skeletal uptake of the tracer. This was shown by elevated bone to soft-tissue ratios (Fig. 2) and the high-contrast scintigrams (Fig. 5). On the other hand, two patients with acute renal failure, who previously had normal renal function, had low bone to soft-tissue ratios (2.0 and 2.6 against the normal of 4.05 ± 0.69) and their bone images were of poor quality due to high soft-tissue background (Fig. 5). These patients with previously normal bones were anuric, and their WBR of Tc-99m HEDP (although not measured) must have been 100%. Although increased soft-tissue retention no doubt made some contribution to the high WBR in our patients with renal osteodystrophy, the increased skeletal uptake appears to be the dominant factor.

A high WBR of Tc-99m HEDP cannot differentiate between uraemic patients with significant renal osteodystrophy and those with other forms of severe renal impairment, but the bone scintigram clearly shows the high bone uptake and low soft-tissue background typical of renal osteodystrophy.

Whereas the 24-hr whole-body retention of Tc-99m HEDP in the Paget's group showed marginal significance in its difference from the primary hyperparathyroidism group ($p < 0.05$), neither group differed significantly from the group with osteomalacia. Moreover, the scatter of individual results in

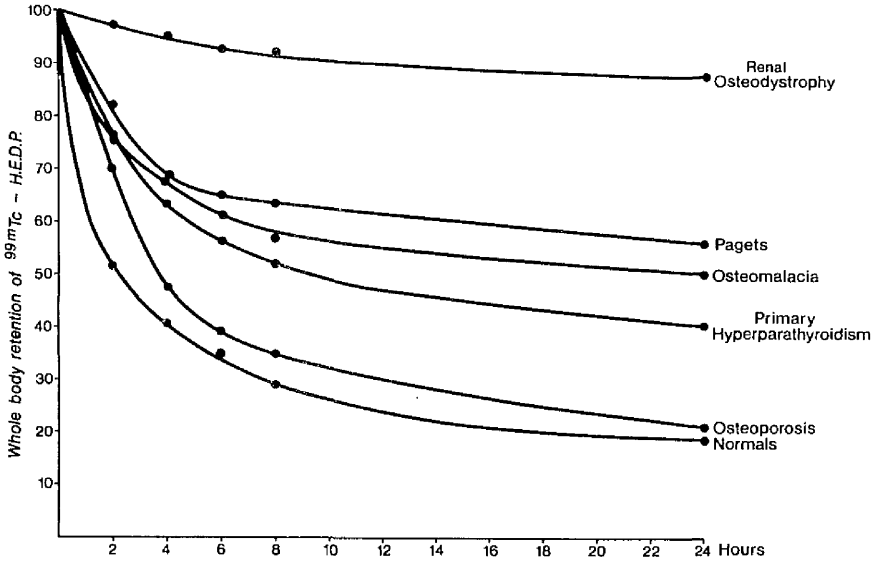

FIG. 3. Mean whole-body retentions of Tc-99m HEDP up to 24 hr.

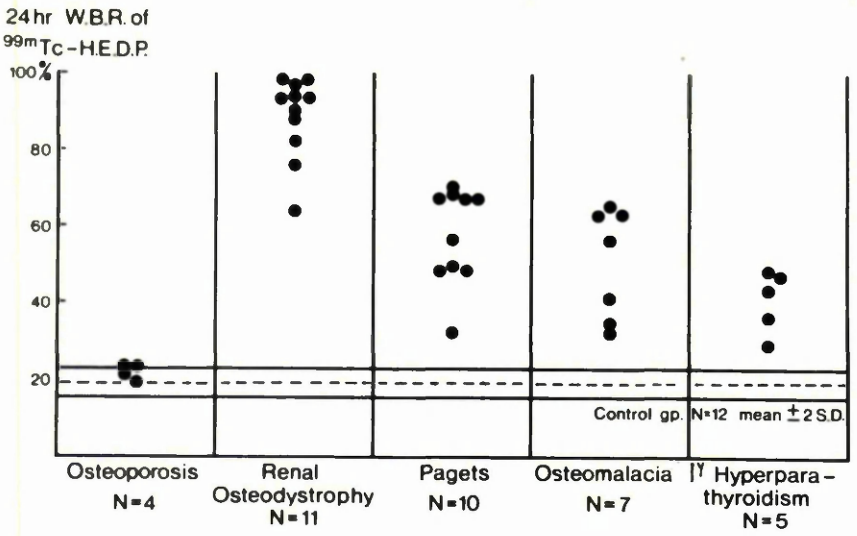

FIG. 4. Distribution of individual 24-hr whole-body retentions of Tc-99m HEDP.

these groups was such that no diagnostic value could be attached to them. However, they show clear demarcation between normal and abnormal, and when the diagnosis is already established or strongly suspected (as is often the case), the knowledge that the result is either higher or lower than the group mean may provide additional information as to the severity of the disease.

Elevated values for 24-hr whole-body retention of Tc-99m HEDP have also been found in two patients in whom primary hyperparathyroidism was suspected, but definite confirmation of diagnosis has not yet been obtained. In each case transileal bone biopsies were abnormal, showing increased bone resorption in keeping with hyperparathyroidism. Therefore, in every case where we have found an elevated value for 24-hr whole-body retention of Tc-99m HEDP this could be correlated with conditions known to cause increased bone turnover (Table 2) or else there was histological evidence of increased bone turnover. The measurement of whole-body Tc-99m HEDP may therefore provide a sensitive means of detecting conditions with rapid bone turnover. It can be used as a screening test for various metabolic bone disorders, and in particular for primary hyperparathyroidism, which at times can present a considerable diagnostic problem (*10*). Although patients with osteoporosis seem to have results in the normal range, this test may help to differentiate those cases where rapid bone loss is due to an underlying condition such as thyrotoxicosis. Also, it may be that plasma activity of Tc-99m HEDP at 24 hr may be of some help in diagnosing osteoporosis, since a marginally significant difference ($p < 0.05$) has been found between this group and the normals, and an elevated plasma result would tend to support the diagnosis of osteoporosis.

As indicated in the discussion on renal osteodystrophy, a knowledge of renal status is essential when one is interpreting the WBR of Tc-99m HEDP. All patients in the present study, except those with renal osteodystrophy, had normal renal function.

The use of a whole-body monitor to calculate the 24-hr whole-body retention of Tc-99m HEDP provides an overall measurement of skeletal retention of radiopharmaceutical as contrasted with measurement of the bone to soft-tissue ratio, which uses only a small and perhaps nonrepresentative area of bone. Measurement of whole-body retention is a simple noninvasive test that provides accurate and reproducible results (*11*). It can be performed as an outpatient investigation. Very small amounts of radioactivity are used and this test can therefore be repeated safely. This may be of use when one is following the progression of disease or monitoring the effect of treatment.

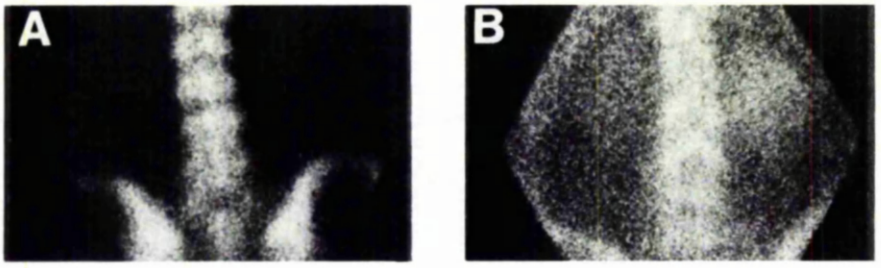

FIG. 5. Bone scintiphotos of lumbosacral spine, posterior view. (A) Chronic renal failure. Note high skeletal uptake of tracer. Kidney images are not seen. (B) Acute renal failure. Poor-quality image due to high tissue background.

ACKNOWLEDGMENTS

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REFERENCES

1. SY WM: Bone scan in primary hyperparathyroidism. *J Nucl Med* 15: 1089–1091, 1974

2. SY WM, MITTAL AK: Bone scan in chronic dialysis patients with evidence of secondary hyperparathyroidism and renal osteodystrophy. *Br J Radiol* 48: 878–884, 1975

3. ROSENTHALL L, KAYE M: Technetium-99m-pyrophosphate kinetics and imaging in metabolic bone disease. *J Nucl Med* 16: 33–39, 1975

4. WIEGMANN T, ROSENTHALL L, KAYE M: Technetium-99m-pyrophosphate bone scans in hyperparathyroidism. *J Nucl Med* 18: 231–235, 1977

5. KRISHNAMURTHY GT, BRICKMAN AS, BLAHD WH: Technetium-99m-Sn-pyrophosphate pharmacokinetics and bone image changes in parathyroid disease. *J Nucl Med* 18: 236–242, 1977

6. WARNER GT, OLIVER R: A whole-body counter for clinical measurements utilizing the "shadow-shield" technique. *Phys Med Biol* 11: 83, 1966

7. SERAFINI AN: Paget's disease of bone. *Sem Nucl Med* 6: 47–58, 1976

8. MCDOUGALL IR, CITRIN DL: Bone scanning: The current position. *Scot Med J* 20: 149–151, 1975

9. CITRIN DL, BESSENT RG, MCGINLAY E, et al: Dynamic studies with ^{99m}Tc H.E.D.P. in normal subjects and in patients with bone tumours. *J Nucl Med* 16: 886–890, 1975

10. DRAGO JR, ROHNER TJ JR, SANFORD EJ, et al: Diagnosis of hyperparathyroidism. *Urology* 7: 4–6, 1976

11. ANDREWS GA, GIBBS WD, MORRIS AC JR, et al: Whole-body counting. *Sem Nucl Med* 3: 367–388, 1973

Fatty Acid Accumulation and Abnormal Lipid Deposition in Peripheral and Border Zones of Experimental Myocardial Infarcts

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Twenty-eight dogs with acute anterior myocardial infarcts due to proximal occlusion of the left anterior descending coronary artery (LAD) were studied at various periods following the occlusion to determine: (a) the time course and location of abnormal lipid accumulation after infarction, (b) the degree of muscle-cell injury associated with increased lipid deposition, and (c) whether uptake of fatty acid from the circulating fat pool contributes to lipid accumulation in certain myocardial regions. The findings show that myocardial lipid accumulation begins as early as 6 hr after proximal LAD occlusion. The increased lipid deposition occurs as nonmembrane-bound lipid droplets in muscle cells with and without ultrastructural evidence of irreversible injury. Analysis of tissue uptake of intravenously injected [^{14}C] oleic acid conjugated with albumin revealed relatively selective concentration of label in the peripheral and border regions of the infarct, but occasionally even the central subendocardial portion of the infarct concentrated the fatty acid. Thin-layer chromotography showed that most of the label was associated with the triglyceride fraction when the radiolabeled fatty acid was injected 6 or 24 hr after LAD occlusion. These myocardial cellular and topographical alterations will have to be considered when labeled fatty acids are used for imaging acute myocardial infarcts and/or if attempts are made to identify myocardial fat-laden cells scintigraphically.

J Nucl Med 19: 276–283, 1978

During our studies of experimental myocardial infarction, we have observed, in border-zone regions of canine myocardial infarcts, the presence of prominent, fine vacuolization of muscle cells, suggesting the accumulation of lipid droplets in these cells (*1*). These findings are consistent with the observations made over 20 years ago by Wartman and associates, who demonstrated that neutral lipid droplets, stained with oil-red-O, were present in "viable" myocardial fibers within and around an area of experimental myocardial infarction (*2*). They believed that this material accumulated only in reversibly damaged myocardial cells and were uncertain as to whether the "fat" came from circulating plasma lipids or from the internal metabolism of these cells (*2*). Since that time fatty acids have been implicated in the genesis of cardiac arrhythmias and myocardial depression in patients and experimental animals with acute myocardial infarcts (*3–5*). It has also been suggested that decreased fatty acid uptake occurs in regions of acutely ischemic myocardium, and efforts

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Comment

This paper describes what I believe to be an important new, and sensitive test for the assessment of skeletal metabolism. At the time of publication the Journal of Nuclear Medicine invited Dr R A Holmes to write a teaching editorial "Quantification of skeletal Tc-99m labelled phosphates to detect metabolic bone disease" (Holmes 1978) discussing this paper.

In the present study it was found that patients with osteomalacia, primary hyperparathyroidism, renal osteodystrophy and Paget's disease, could be clearly differentiated from a control population. In addition it was found that each individual patient's result in these groups lay outside the control range. While blood samples were taken for Tc-99m counting at the time of each WBR measurement, these results did not provide any additional diagnostic information.

The results of WBR from patients with renal osteodystrophy are difficult to interpret because of the severe renal impairment present in these cases. Although these patients had severe bone disease it is nevertheless impossible to separate that proportion of the total WBR due to bone uptake from that due to soft-tissue retention. These

findings, however, emphasise the point that one must always be aware of renal function when interpreting WBR results. The use of WBR in Paget's disease may also appear questionable - as this diagnosis is usually simply made on the basis of clinical, biochemical and scintigraphic or radiological evidence. However, if a screening test were required to identify or exclude Paget's disease, then WBR utilises considerably less radioactivity than a bone scan (approximately 1/300th of the dose). Also a WBR result provides a quantitative measure of tracer uptake which is likely to reflect severity of disease. In addition, WBR is a simple method for accurately documenting alterations in skeletal metabolism in sequential patient studies (a theme developed more fully in chapter 6) and several groups have subsequently suggested that quantitation of diphosphonate uptake by bone may accurately document the effect of therapy in Paget's disease (Espinasse et al, 1981; Vattimo et al,1981).

While the number of patients studied with primary hyperparathyroidism and osteomalacia are small, these preliminary results appear to suggest that WBR may be a sensitive means of differentiating patients with these conditions from normal subjects. Certainly, in clinical practice, if osteomalacia or primary hyperparathyroidism are suspected additional information indicating whether the disease is present or not would be useful. If osteomalacia is taken as an example, this condition may be suspected in

various clinical settings, for example, in an Asian population, in subjects receiving anticonvulsant therapy or in elderly women who present with a femoral neck fracture. However, the only way at present to exclude osteomalacia, once suspected, is to perform a bone biopsy. If a normal WBR result were shown to exclude osteomalacia then clearly many patients would be spared an invasive test. Similarly I believe that a normal WBR result makes a diagnosis of primary hyperparathyroidism extremely unlikely, although in this case I expect that eventually a small amount of overlap between patients with very mild disease and normal subjects will be found.

It is clear, however, that an elevated WBR result is of no differential diagnostic value and in general if the diagnosis is not apparent, then a bone scan should be obtained to image the distribution of tracer.

It may be argued that useful WBR measurements could be obtained earlier than 24 hours after injection. However I believe that at 4 hours there is too much patient variability as regards urinary clearance of tracer. While this may also apply to both 6 and 8 hours after injection there are further difficulties with the scheduling of studies, as measurements would have to be obtained late in the afternoon or early in the evening, and thus the number of patients

that could be studied would be limited. Twenty-four hours after injection is free from the problem of patient compliance as regards adequately emptying the bladder, and patients can be given appointments throughout the whole working day. This does mean, however, that a patient is required to attend for study on two consecutive days (each visit is approximately 20 minutes), but this has not been found to be a problem in practice.

Measurement of 24-hour whole-body retention of diphosphonate is essentially a very simple test, which uses extremely low amounts of radioactivity and appears to provide a sensitive measure of increased bone turnover. However the problem of assessing the extent to which WBR truly reflects skeletal metabolism is a very real one, for at the present time there is no satisfactory means available to measure skeletal metabolism accurately. Commonly used biochemical tests such as serum alkaline phosphatase or urinary hydroxyproline excretion, while generally believed to reflect skeletal metabolism do not precisely measure this, and the results of these investigations show a huge overlap between patients with metabolic bone disease and control subjects (Nordin et al, 1976). The subject of calcium kinetic studies has been discussed previously in this chapter. While these tests appear to provide a

mathematically derived measure of skeletal metabolism, they are extremely inconvenient to perform and results once again show a large degree of overlap between patients and control subjects. Bone biopsy with histomorphometric analysis, is an invasive test, but does provide a direct means of assessing skeletal metabolism. Unfortunately only a very small area of bone can be sampled and the extent to which this is representative of the whole skeleton and, therefore, of total skeletal metabolism, is unclear.

Thus there is no external standard by which to compare WBR performance as a measure of skeletal metabolism. While the data presented in this thesis does support the belief that WBR accurately reflects skeletal metabolic activity and provides a sensitive means of identifying patients with increased bone turnover, the mechanism by which diphosphonate localises in bone is nevertheless not fully understood. It would, therefore, appear as so often occurs in medicine, the application of a new technique may precede a full understanding of the precise mechanisms involved. Validation of the WBR technique will depend upon independent confirmation of its results as well as its general usefulness in clinical practice.

Paper 10. Accuracy of 24 hour whole-body (skeletal) retention of diphosphonate measurements

European Journal of Nuclear Medicine (in press)

I Fogelman, R G Bessent, J E Scullion, G F Cuthbert

Purpose of Investigation

Initial experience with 24-hour whole-body retention of diphosphonate (WBR) measurements had shown that the technique held considerable promise for providing a sensitive measure of increased bone turnover. Nevertheless, the reproducibility of the technique, the accuracy and possible sources of error in WBR measurements had not previously been studied and are now reported.

Accuracy of 24 Hour Whole-Body (Skeletal) Retention of Diphosphonate Measurements

I Fogelman, R G Bessent, J E Scullion, G F Cuthbert

SUMMARY

We have shown that 24 hour whole-body retention (WBR) of diphosphonate is a valuable test for the assessment of skeletal metabolism. However, the reproducibility, accuracy and possible sources of error in WBR measurements have not previously been studied.

In 21 paired studies the technique was found to be highly reproducible ($r = 0.998$, $p<0.0001$). The coefficient of variation for whole-body counts on day 1 was 0.1% and on day 2, 1.1%. A phantom was used to assess the possible error introduced by redistribution of tracer. The net whole-body count of the phantom representing the 24 hour distribution was 98% of that of a uniform phantom. Ten subjects were counted twice within a few minutes to study the effect of repositioning, and showed a mean difference between counts of only 0.8%.

Eleven subjects with traumatic fractures were studied to assess the possible contribution of focal lesions to WBR. It was found that 9 subjects had normal values for WBR, while 2 had minimally elevated results. Twenty patients with renal disease but no apparent skeletal disease were also studied to assess the possible contribution of soft-

tissue retention to WBR. A significant correlation between serum creatinine and WBR was found ($r = 0.72$, $p < 0.001$). However WBR results were always normal when serum creatinine values were <130 μmol/l.

It is suggested that WBR measurement is accurate and the technique is highly reproducible. The presence of a focal lesion is unlikely to affect a WBR result significantly and if serum creatinine is in the normal range then an elevated WBR result can be assumed to reflect increased skeletal metabolism without further concern as to renal function.

INTRODUCTION

Twenty-four hour whole-body retention (WBR) of diphosphonate has been shown to be a sensitive measure of skeletal metabolism (1-5). This test has considerable potential for widespread application as a screening procedure in the identification of patients with increased bone turnover (3). In order to assess the accuracy of WBR measurements we have studied the reproducibility of the technique and have also examined the following sources of error:-

1. Statistical counting errors.
2. Redistribution of tracer within the body, between the initial and 24-hour whole-body count.
3. Repositioning of subjects on whole-body monitor couch.
4. Unsuspected focal lesions, such as fractures, causing locally increased tracer retention.

5. Reduced excretion of tracer not taken up by the skeleton as a result of poor renal function.

METHODS

Measurement of 24-hour WBR

Each subject was given an intravenous bolus of 50μCi of 99m Tc-HEDP* and the initial whole-body count was begun at five minutes after injection, using a scanning-couch, shadow-shield, whole-body monitor (WBM) with two opposed 12.5 x 7.5 cm scintillation detectors 1.0 m apart. The pulse height analyser window was set to cover the energy range 115-165 KeV and energy setting and counting sensitivity were checked with a standard source at the start of each day. The scanning speed was controlled to within 0.2% over the normal scan time of 1000s by tachometer feedback to the thyristor-controlled, D-C drive motor. To correct for any small difference in speed from day to day, two microswitches caused a digital timer to record to a precision of 0.1% the time taken for the couch to move a fixed distance of 141 cm, corresponding to the passage of the subject's trunk and thighs between the two detectors. This time was used to normalise the net counts on each occasion.

The presence of the subject increases the background reading of the WBM because of scattering. Since this background cannot be measured directly at 24 hours a control study was carried out with 50 non-radioactive subjects of various

* Procter & Gamble "Osteoscan"

builds, to measure the ratio between the background count with the subject on and off the monitor. The mean ratio was 1.35 with a standard deviation 0.025 and this factor was used to estimate the subject background from that measured by the empty monitor.

After correcting the normalised net counts for radioactive decay the ratio between the 24-hour and initial whole-body counts gives the 24-hour whole-body retention of 99m Tc-HEDP.

Reproducibility

WBR measurements were obtained on two separate occasions in 21 subjects (10 normal and 11 with metabolic bone disease). For 14 subjects repeat studies were within 4 weeks of each other, for 3 subjects within 5 to 8 weeks, and for the remaining 4, within 11 to 19 weeks (table 1).

Redistribution

The effect on the whole-body count of change in tracer distribution from uniformly vascular on day 1 to skeletal on day 2 was studied using a 65 Kg phantom* composed of 9 water-filled elliptical cylinders assembled to represent the body tissue distribution (6). After measuring the background count with the phantom in position the appropriate fraction of 50 μCi of 99m Tc-pertechnetate was added to each cylinder to give a uniform concentration of activity throughout the phantom and a 1000s count was taken. After this activity

* James Girdler and Co Ltd. London SE16

had decayed considerably overnight the phantom was flushed out and refilled with tap water and the background measured. 99m Tc-pertechnetate was then added to simulate the 24-hour skeletal distribution of 99m-Tc-HEDP. Since most of the skeletal uptake and blood clearance of HEDP occurs by 4 hours (7), the relative activities in different parts of the skeleton at 24 hours were estimated by quantitating count rates within regions of interest on all views of standard 4-hour, normal skeleton scans. Neglecting limb activity the percentage distribution found was: skull 15%, pelvis 42%, spine 31%, sternum 12%. The appropriate percentages of 50 μCi were added uniformly to the pelvic and head sections of the phantom but the spinal and sternal activities were placed in sealed tubes of suitable dimensions, fixed in position inside the water-filled thorax section of the phantom. The remaining sections were non-active and a 1000s count was made. The activities used on the two occasions were compared by counting three aliquots of each initial dose on a gamma counter and correcting for decay to the time of the corresponding phantom count.

Repositioning

Although the whole-body monitor geometry gives very uniform response, small errors in the measured ratio of the two whole-body counts may occur if subjects are in different positions on the monitor couch on the two occasions. They are normally positioned with feet at a standard mark and as

nearly as possible on the centre line of the couch. The effects of repositioning was investigated n 10 subjects who were each counted 3 times in quick succession. For counts 1 and 2 the subjects were positioned normally, having got off the monitor in between. For count 3 the subject was moved as far sideways as the couch would allow. Background was subtracted from each count which was then corrected for decay.

Control Values for Whole-Body Retention

Control values for WBR were obtained from a group of 98 male and 152 female normal volunteers (age range 20-67 years). The control WBR at any age was obtained from the median results for a five-year span centred on the age in question for each sex.

Focal Lesions

WBR was measured in 11 male subjects, otherwise normal, who had sustained traumatic fractures two to ten days previously. Clinical details and WBR results from these subjects are shown in Table 2. Serum calcium, phosphate, alkaline phosphatase and creatinine were normal in all cases.

Reduced Excretion of Tracer

WBR was measured in 20 subjects with established renal disease but with no clinical, biochemical (serum calcium, phosphate and alkaline phosphatase were normal) or radiological evidence of skeletal disease. All had serum creatinine levels not greater than 200 μmol/l (normal <120 μmol/l) (Table 3).

RESULTS

Counting Statistics

Gross counts on day 1 were approximately 10^6 and on day 2 for a normal subject 2×10^4 with subject backgrounds of about 5,000 counts. Thus the coefficient of variation of day 1 counts was 0.1% and on day 2 it was 1.1%. In addition the method used to estimate the patient background on day 2 has a coefficient of variation of 2% or 100 counts in addition to the statistical counting error. Thus the total coefficient of variation on the derived net counts for day 2 was 1.25% while errors in the day 1 measurements are insignificant.

Reproducibility

Measured WBR covered a wide range of 17 to 87%. The linear correlation coefficient between the repeat measurements was 0.998 with a regression line (Fig 1):

$$WBR_2\ (\%) = WBR_1 \times 0.99 + 0.22.$$

The mean difference in percentage whole-body retention between the 21 repeated studies was -0.01% WBR with a standard deviation of 1.21% WBR. No results which were normal on one occasion become abnormal on repeat.

Redistribution

After making the corrections described above the net whole-body count from the phantom representing the 24-hour distribution was 97.95% that of the uniform phantom. The net counts were over 700,000 giving negligible statistical error.

REPOSITIONING

The mean difference between the two counts for ten subjects with the patient correctly repositioned was 0.80% ± 0.66% S.D. The greatest difference for one subject was 2.52% but the next largest was only 1%. The mean difference between the first two counts and the third, where the subject was displaced sideways, was 4.8% ± 2.0% S.D. with a greatest reduction of 7.8%. These latter results are for extreme mispositioning of the subject. For normal practice the effect of repositioning is likely to contribute an error of not more than 2.1% to the 24 hour WBR i.e. a result of (20 ± 0.4%) for a normal subject.

Control Population

The overall median WBR for the 98 male controls was 19.3% with 2.5 and 97.5 percentiles of 14.0% and 25.3% respectively. For the 152 female controls the corresponding results were 18.5%, 12.3% and 25.9%.

Traumatic Focal Lesions

WBR ranged from 14.0% to 27.0% of which only two were just above the 97.5 percentile of the male controls with values of 26.5% and 27.0%. Comparison of individual whole-body retentions with the median control values for males of the same age (five year band) using the Wilcoxon test for pair differences showed no significant difference from normal for the group.

Reduced Excretion of Tracer

Measured WBR in the group with mild renal impairment ranged up to 57% with 10 of the 20 results above the control 97.5 percentile for their sex. However, these all corresponded to serum creatinine values above the normal maximum of 120 μmol/l (Fig 2).

There was a significant linear correlation coefficient between WBR and serum creatinine of 0.72 ($p<0.001$) with regression line: creatinine (μmol/l) = WBR (%) x 4.77 - 5.0. Using the Spearman test there was also a significant correlation between WBR and parathyroid hormone ($R = 0.65$, $p < 0.005$). Comparison of the WBR of the 12 subjects with serum creatinine greater than 120 μmol/l using the Wilcoxon test for pair differences showed them to be significantly greater than the median 5-year control values for the same age and sex ($p<0.005$). However, the WBR for the eight subjects with normal serum creatinine were not significantly different from control values ($p>0.05$).

DISCUSSION

Technical Factors

Errors in counting at 24 hours and background estimation indicate that there is a 95% probability of the derived 24-hour WBR being within 2.5% of the true value, that is, a result of approximately (20 $\pm$ 0.5)% for a normal subject.

Because of the close speed control of the monitor and timing of the important part of the scan time to 0.1%, errors from this cause are negligible. Changes in monitor sensitivity are checked and corrected daily by counting a standard. Patient repositioning on the couch, within the limits normally achieved, contributes a mean error of about 2% to the measured WBR i.e. 0.4% in 20%.

The redistribution results indicate, within the limits of the model, that redistribution within a subject of normal build will cause a systematic error producing a result that is 98% of the true value. Other technical factors include the proportion of unbound activity in the injected 99m Tc-HEDP and the injection technique. No check was made on binding but the pertechnetate was added to the HEDP vial not more than two hours before use and this method has previously given extremely consistent quality, with low-background images over several thousand gamma camera skeletal surveys. At injection blood was drawn back to ensure that the needle tip was truly intravascular.

The reproducibility studies indicate that 95% of repeat studies will be within a range of difference of 2.5% WBR. Since statistical considerations would suggest a similar range of difference there is little error to be ascribed to physiological changes between WBR measurements even for those made 19 weeks apart. There was no correlation found between the time interval between repeat studies and the size of the difference found.

Clinical Factors

If WBR is to be widely applied and used to screen population for high bone turnover it is important to be aware of both the effect of renal impairment, and focal lesions due to trauma or fracture, on WBR results.

Patients with osteoporosis often have crush vertebral fractures present and if these were to lead to a marked increase in WBR then patients could be falsely considered to have high skeletal turnover. In the 11 patients studied with traumatic fractures it is clear that a single fracture or even multiple fractures do not necessarily and indeed are unlikely to lead to an elevation of whole-body retention outwith the normal range. While nine patients had normal values for WBR, seven of these had values which were less than or equal to 20%, and only two had elevated results which were only just outwith the normal range at 26.5 and 27.0%. The two patients with vertebral fractures had unequivocally normal results for WBR at 14.3 and 21.7%. Thus where WBR is significantly elevated in such patients it is likely that a diffuse skeletal problem is indeed present. However, elevated values for WBR, particularly in the elderly, are also found in Paget's disease or in widespread metastatic involvement of the skeleton. To clarify such situations we would recommend obtaining a bone scan in any patient with an elevated WBR result, to image the distribution of tracer throughout the skeleton.

In those patients with established renal disease but with no apparent skeletal involvement a significant positive correlation between the serum creatinine and WBR values was found. No patient had an abnormal result for WBR with a serum creatinine value below 130 µmol/l but above this level WBR was generally (but not always) elevated. Where WBR was elevated it was not possible to separate the two main potential contributing factors, i.e. renal impairment leading to (1) soft-tissue retention of tracer or (2) skeletal disease. While those patients with elevated WBR had normal biochemistry it is possible that they had unsuspected skeletal disease. However the correlation between elevated serum creatinine and abnormal WBR indicates direct dependence upon renal function and the elevated WBR results probably reflect soft-tissue retention of tracer. It is clearly important to be aware of renal function when interpreting WBR data. Nevertheless we find that if serum creatinine is in the normal range then an elevated WBR result can be accepted as reflecting increased skeletal metabolism without further concern as to renal function.

Whole-body retention measurements are therefore not subject to large technical errors and are not significantly affected by the presence of focal abnormalities. The test is simple to perform, is non-invasive using very low activity, and requires only two brief out-patient attendances. Because of the narrow range of results found in normal subjects 24-hour whole-body retention of diphosphonate has

promise of providing a simple and sensitive screening test for increased bone turnover.

REFERENCES

1 Fogelman I, Bessent R G, Turner J G, Citrin D L, Boyle I T, Greig W R.
The use of whole-body retention of Tc-99m diphosphonate in the diagnosis of metabolic bone disease.
J Nucl Med 19: 270-275, 1978.

2 Fogelman I, Bessent R G, Beastall G, Boyle I T.
Estimation of skeletal involvement in primary hyperparathyroidism. Ann Int Med 92: 65-67, 1980.

3 Fogelman I, Bessent R G, Cohen H N, Hart D M, Lindsay R.
Skeletal uptake of diphosphonate: method for prediction of post-menopausal osteoporosis.
Lancet II: 667-670, 1980.

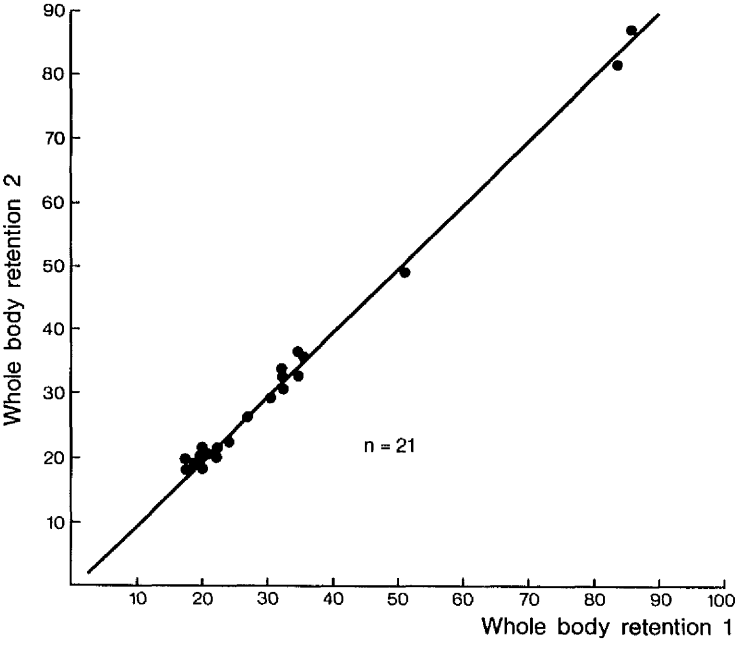
4 Fogelman I.
The value of 24-hour skeletal uptake of diphosphonate in the exclusion of metabolic bone disease.
Nucl Med Comm 1: 351-356, 1980.

5 Caniggia A, Vattimo A.
Kinetics of 99m technetium-tin-methylene-diphosphonate in normal subjects and pathological conditions: a single index of bone metabolism. Calcif Tissue Int 30: 5-13, 1980.

6 Bush F.
Energy absorption in radium therapy. Br J Radiog 19: 14-21, 1946.

7 Fogelman I, Citrin D L, Bessent R G, Mazess R.
The development and validation of measurement of 24 hour bone uptake of 99m Tc HEDP as an index of metabolic bone disease. In: Proceedings of Fourth International Conference on Bone Measurement. Mazess R B, ed.
NIH Publication No 80-1938, 447-453, 1980

Figure 1
Comparison of repeat measurements of whole-body retention.



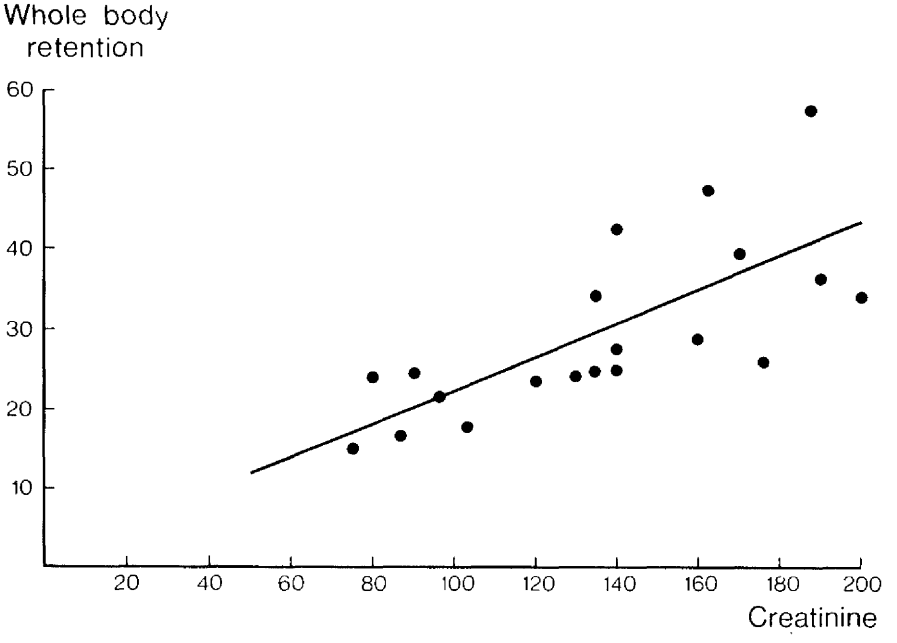


Figure 2

Relationship of serum creatinine to whole-body retention.

T A B L E 1

REPRODUCIBILITY STUDIES

Patient*	Age	Sex	WBR_1 (%)	WBR_2 (%)	Time Interval Between Studies (weeks)
1	28	M	21.1	20.78	19
2	24	M	21.86	20.24	3
3	23	F	19.2	19.94	2
4	24	M	19.49	18.4	6
5	31	M	21.65	21.89	1
6	23	M	17.62	17.97	2
7	41	M	20.22	21.52	15
8	52	M	18.77	19.33	11
9	31	M	17.2	19.63	8
10	40	M	23.82	22.58	5
11	58	F	35.3	36.67	1
12	20	M	83.3	81.66	1
13	59	M	30.22	29.41	1
14	75	F	85.9	87.1	4
15	49	M	50.66	49.55	1
16	75	F	32.74	34.27	3
17	61	F	27.09	26.58	15
18	56	F	35.41	33.58	1
19	55	F	32.08	31.23	3
20	47	F	32.78	33.57	2
21	59	F	35.94	36.27	2

* Patients 1-10 Normal subjects.
Patients 11-21 Metabolic Bone disease.

T A B L E 2

PATIENTS WITH TRAUMATIC FRACTURE

Patient	Age	Site of Fracture	WBR %
1	36	Os Calcis	20.26
2	49	Lumbar vertebra 2	14.31
3	42	Right 2nd-5th ribs Right scapula Right fibula	18.22
4	39	Right 2nd metacarpal and medial cuneiform	26.98
5	49	Left 6th rib	20.4
6	30	Lumbar vertebra 2	21.7
7	49	Left 10th and 11th rib	26.45
8	41	Right 9th-11th ribs	14.0
9	54	Left 8th-10th ribs	22.43
10	27	Left 5th-8th ribs Right humerus	17.46
11	47	Left ankle	19.49

T A B L E 3

PATIENTS WITH RENAL DISEASE

Patient	Age	Sex	Diagnosis	WBR	Serum Creatinine (normal 40-120 µmol/l)	Plasma Parathyroid Hormon (normal<600 ng/l)
1	33	F	Chronic pyelonephritis	24.94	140	510
2	38	F	Chronic pyelonephritis	27.89	140	340
3	51	F	Chronic pyelonephritis	57.49	187	900
4	37	M	Polycystic kidney disease	25.98	177	320
5	51	F	Chronic pyelonephritis	34.29	135	280
6	33	F	Chronic pyelonephritis Left renal dysplasia	39.57	170	440
7	50	M	Polycystic kidney disease	24.64	135	150
8	30	F	Chronic pyelonephritis Bilateral hydronephrosis	36.32	190	270
9	40	F	Chronic pyelonephritis	21.71	97	200
10	41	F	Chronic pyelonephritis	16.84	87	230
11	48	F	Chronic pyelonephritis	17.73	102	150
12	58	F	Bilateral staghorn calculi	47.36	162	430
13	36	F	Chronic pyelonephritis	29.06	160	350
14	24	F	Previous left nephrectomy Hydronephrosis and pyelonephritis right kidney	42.42	140	560
15	45	F	Chronic pyelonephritis	15.10	75	200
16	33	M	Polycystic kidney disease	23.12	120	480
17	51	F	Chronic pyelonephritis	24.24	130	230
18	57	M	Chronic renal failure Hypertension	34.25	200	370
19	33	F	Chronic pyelonephritis	24.53	90	320
20	21	F	Chronic pyelonephritis	23.68	80	310

Comment

This series of investigations illustrate that measurements of 24-hour whole-body retention of diphosphonate (WBR) are highly reproducible and are not subject to significant technical errors. Redistribution of radio-isotope from an initially vascular compartment on the first day, to a predominantly skeletal one on the second day was evaluated using phantom studies. The net whole-body count of the phantom representing 24-hour distribution of tracer was 98% of the uniform phantom. This is a small systematic error which could be corrected for if required, but in practice we do not do this. Repositioning of subjects on the whole-body monitor couch within the limits normally achieved was not found to cause any significant error.

It was considered important to ascertain whether the presence of focal lesions in the skeleton, which on occasion may be present, for example due to degenerative disease or trauma, could affect WBR results. WBR measurements were thus obtained in subjects who had sustained traumatic fractures but were otherwise healthy. The results from this study suggested that such fractures (which have higher tracer uptake than degenerative disease) are extremely unlikely to elevate WBR results outside the normal range. It would have been desirable to have repeated these measurements after the fractures had healed, to document

whether any alterations in WBR had occurred, but this unfortunately was not possible. Some WBR measurements have been carried out previously in patients with skeletal metastases (with documented focal disease) and many of these subjects had normal results for WBR (Citrin D L, personal communication). WBR was elevated only when extensive skeletal involvement by tumour was present, supporting the view that the presence of several focal lesions will not elevate WBR outside the normal range.

The question of whether mild renal impairment might influence WBR results was also studied. It was shown that in patients with established renal disease, WBR was always in the normal range if the serum creatinine was $\leq$130µmol/l (normal $\leq$ 120). Once again it is uncertain whether WBR was elevated in these subjects within the normal range, although no difference in patient results was found when compared with age matched controls. Thus an elevated WBR result cannot be explained on the basis of impaired renal function if serum creatinine is within the normal range. However, it should be noted that a significant correlation was found between serum creatinine values and WBR results, and it would, therefore, appear that with deteriorating renal function, WBR has a direct dependence on the degree of renal impairment with a corresponding increase in soft-tissue retention of tracer.

Paper 11. Age-related alterations in skeletal metabolism - 24-hr whole-body retention of diphosphonate studies in 250 normal subjects: Concise communications (1982)

Journal of Nuclear Medicine 23: 296-300

I Fogelman, R G Bessent

Purpose of Investigation

The purpose of the present study was to analyse the results for 24-hour whole-body retention of diphosphonate from the first 250 healthy volunteer subjects studied to assess whether there was any age or sex dependence.

Age-Related Alterations in Skeletal Metabolism—24-hr Whole-Body Retention of Diphosphonate in 250 Normal Subjects: Concise Communication

Ignac Fogelman and Rodney Bessent

Royal Infirmary, Glasgow, Scotland

Twenty-four-hour measurements of whole-body retention (WBR) of Tc-99m diphosphonate (a sensitive measure of skeletal metabolism) have been obtained in 250 healthy volunteer subjects. WBR values were found to fall from the age of 20 yr until 35 yr and then in men to rise linearly thereafter. Women showed a similar pattern initially but there was a marked rise in WBR corresponding to the menopausal years. Our results lend support to the belief that skeletal metabolism increases with age. It is suggested that some imbalance must always exist between resorption and formation in bone, with net loss of bone mineral, and increasing levels of skeletal metabolism will exaggerate this imbalance and accelerate the rate of bone loss.

J Nucl Med 23: 296–300, 1982

Alterations in skeletal metabolism with age and those occurring at the time of the menopause are of obvious importance with regard to bone loss and the development of osteoporosis. Until recently, however, there was no satisfactory technique for the assessment of skeletal metabolism. While bone histomorphometry can provide relevant data, bone biopsy is an invasive procedure that yields information pertinent to only a small area of bone and thus may not reflect changes in the skeleton as a whole (*1*). In addition, there is often disagreement regarding the interpretation of age-related changes seen in histological sections (*2*). Alterations in skeletal metabolism may also be deduced from changes in the rate of bone loss. This is usually assessed by measuring the mineral content of bone (by photon absorptiometry), either in cross-sectional studies over a wide age range or in individual subjects in whom sequential studies are performed. However, it is necessary to perform sequential studies in individual patients for at least 2–3 yr to obtain data reflecting rates of bone loss (*3*). Moreover, measurements of bone mineral content are usually made at the radius, and changes there may not accurately reflect change throughout the entire skeleton.

With the introduction of the current bone-seeking radiopharmaceuticals (the technetium-99m-labeled diphosphonates), agents extremely sensitive to skeletal abnormality are now available, and their uptake in bone is thought to reflect osteoblastic activity and to a lesser extent skeletal vascularity (*4*). Skeletal uptake of tracer therefore reflects skeletal metabolism, and we have previously shown by using a whole-body monitor that measurement of 24-hr whole-body retention of Tc-99m diphosphonate provides a simple, sensitive measure of skeletal metabolism (*5,6*). This communication presents our results with this technique in 250 healthy volunteer subjects in the age range 20–70 yr.

PATIENTS

Two hundred and fifty healthy volunteer subjects were studied (Table 1). There was no history of associated skeletal, renal, or malabsorptive disease.

METHODS

Measurement of whole-body retention (WBR) of Tc-99m diphosphonate. Each subject was given an in-

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TABLE 1. MEDIAN AND FULL RANGE OF BIOCHEMICAL RESULTS

Serum	Median	Range
Calcium* (mmol/l) (normal 2.2–2.6)		
Male (N = 77)	2.4	2.2–2.6
Female (N = 130)	2.4	2.2–2.6
All	2.4	2.2–2.6
Albumin (g/L) (normal 35–55)		
Male (77)	47	40–55
Female (130)	46	39–53
All	46	39–55
Alk. phosphatase (U/l) (normal 80–280)		
Male (73)	187	96–280
Female (128)	163	87–275
All	168	87–280
Creatinine (μmol/l) (normal 35–120)		
Male (74)	90	60–120
Female (122)	80	40–120
All	80	40–120

* Individual serum calcium values were corrected for the corresponding serum albumin by a procedure described by Imrie et al. (*23*).

travenous bolus of 50 μCi of Tc-99m hydroxyethylidene diphosphonate (HEDP) and the WBR at 24 hr was measured using a shadow-shield whole-body monitor as previously described (*5*).

Biochemistry. As a general screen for skeletal or renal disease, serum calcium, alkaline phosphatase, albumin, and creatinine values were obtained in 90% of all subjects over 30 yr of age. All results for these parameters (Table 1) were in the normal range.

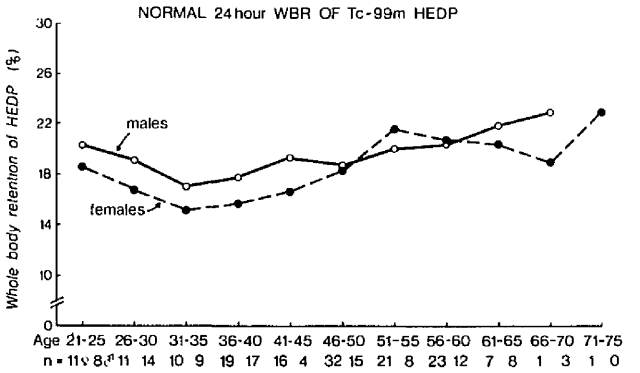

FIG. 1. Whole-body retention results in 5-yr groupings in 250 normal subjects.

RESULTS

Figure 1 shows the results for 24-hr whole-body retention (WBR) of HEDP obtained in the study population, divided on the basis of 5-yr age groupings and sex. Median values for WBR with 95% confidence range are presented in Table 2. The only significant difference in values between male and female was for the 41–45 yr group ($p < 0.05$), but the male group was small with only four results available, so no great weight should be placed on this result.

Table 3 indicates where significant differences in WBR occur between the 5-yr age groupings within the male and female groups separately. For males, all age groups from 26 to 50, except those from 41–45, have significantly lower WBR than those over 60. This is not the case for the eight in the 21–25-yr group, whose WBR is a little higher than those between 26 and 50. These results suggest a male pattern of WBR falling from ad-

TABLE 2. WHOLE-BODY RETENTION RESULTS IN 250 NORMAL SUBJECTS, DIVIDED ON THE BASIS OF SEX AND 5 YR AGE GROUPINGS, WITH MEDIAN AND 95% CONFIDENCE RANGE OF THE MEDIAN VALUES

Age range (yr)	Male			Female		
	No.	Median WBR (%)	95% Confidence range (%)	No.	Median WBR (%)	95% Confidence range (%)
21–25	8	20.67	16.10–23.70	11	18.86	15.20–20.30
26–30	14	19.52	17.10–21.70	11	17.26	14.80–21.90
31–35	9	17.42	15.50–21.70	10	15.20	14.50–17.30
36–40	17	18.27	15.40–19.40	19	16.0	15.00–16.60
41–45	4	19.72	—	16	17.02	15.60–19.50
46–50	15	19.07	17.20–20.30	32	18.61	16.70–21.40
51–55	8	20.56	18.80–25.30	21	22.1	18.40–24.70
56–60	12	20.76	18.01–23.80	23	21.58	19.70–23.70
61–65	8	23.36	16.30–25.30	7	21.06	17.80–26.70
66–70	3	23.54	—	1	19.41	—
71–75	—	—	—	1	23.52	—

TABLE 3. COMPARISON OF WHOLE-BODY RETENTION RESULTS BETWEEN 5-YR AGE GROUPINGS WITHIN THE MALE AND FEMALE GROUPS

Male

Age	21–25	26–30	31–35	36–40	41–45	46–50	51–55	56–60	61–65	66–70
21–25		—	—	—	—	—	—	—	—	—
26–30	—		—	$P < 0.05$	—	—	—	—	$P < 0.05$	$P < 0.02$
31–35	$P < 0.05$	—		—	—	—	$P < 0.05$	$P < 0.05$	$P < 0.05$	$P < 0.02$
36–40	$P < 0.02$	—	—		—	—	$P < 0.002$	—	$P < 0.01$	$P < 0.02$
41–45	—	—	—	—		—	—	—	—	$P < 0.05$
46–50	—	—	$P < 0.01$	$P < 0.001$	—		$P < 0.01$	—	$P < 0.05$	$P < 0.05$
51–55	$P < 0.02$	$P < 0.02$	$P < 0.001$	$P < 0.001$	$P < 0.001$	$P < 0.02$		—	—	—
56–60	$P < 0.01$	$P < 0.02$	$P < 0.001$	$P < 0.001$	$P < 0.001$	$P < 0.02$	—		—	—
61–65	$P < 0.02$	—	$P < 0.005$	$P < 0.001$	$P < 0.01$	—	—	—		—
66–70	—	—	—	—	—	—	—	—	—	

Female

olescence to about age 35 and then rising gently thereafter.

In women by contrast, groups from 51–60 have significantly higher WBR than all younger groups. In the adjacent group (ages 61–65), they have higher WBR than in the 31–45 groups, and the 46–50 group is higher than the 31–40 groups. This demonstrates the pattern of WBR again falling from adolescence to about 35 followed by an initial gentle rise, but this is markedly accelerated during the menopausal years of 46–55.

DISCUSSION

Skeletal uptake of diphosphonate is predominantly related to sites of new bone formation and is thought to be dependent upon osteoblastic activity (*4*). Measurements of 24-hr whole-body retention (WBR) of diphosphate thus reflect bone formation. In the context of bone remodeling, however, osteoblastic activity always follows osteoclastic activity (*7*) and it is recognized that with alterations in skeletal metabolism, rates of bone formation and resorption change in the same direction, although not necessarily to the same degree (*3,8*). WBR measurements will therefore also reflect bone resorption. Nevertheless, an absolute loss of bone can occur only because of an imbalance between formation and resorption, and WBR will be unable to quantitate this difference.

The results from our WBR studies suggest that in both men and women there is a fall in skeletal metabolism from 20 yr of age until approximately 35. Thereafter in men there is a nearly linear increase in skeletal metabolism until age 65. We have not studied enough subjects over age 65 to be confident of the variation of WBR in old age. While WBR results in women initially follow a similar pattern, there is a marked rise in skeletal metabolism at about 55 yr of age, presumably related to the menopause. While the falling values for WBR between ages 20 and 35 are unexplained, Frost (*7*) has shown a very similar pattern of change with age in active osteoid seams (reflecting bone formation) and osteoclastic activity (reflecting bone resorption) in human rib biopsies. Frost suggests that "some important change in internal regulation of bone remodelling becomes apparent at age thirty-five." In addition, it has been suggested that bone mineral content is at a maximum in both men and women at age 35 (*9*), and this would be in keeping with our findings if the rise in WBR after 35 yr of age indicates the time at which bone loss commences.

While it is widely believed that skeletal metabolism increases with age (*10–12*), there is nevertheless some conflicting evidence in the literature. Certainly bone loss appears to commence at around 30 yr of age (*7,13,14*) and the rate of loss seems to increase steadily thereafter. In women there is an additional accelerated phase of bone loss that occurs following the menopause (*11,13–15*). This is the pattern of results shown with WBR. Heaney et al. (*11,16*), using simultaneous radiocalcium kinetics and external calcium balance techniques, studied a group of women at 5-yr intervals before and after menopause and showed that skeletal metabolism increases after menopause. It has also been demonstrated that parathyroid levels increase with age (*12*), and this may be of considerable importance to the control of skeletal metabolism, although this has yet to be proven. Other suggested factors affecting control of skeletal metabolism may be decreased calcium absorption (*17*), a reduction in physical activity (*18*), or a fall in sex-hormone levels (*19*), all of which occur with aging.

The major area of dispute relating to changes in skeletal metabolism with age evolves from the published results of quantitative analysis of bone histology. While Frost (*7*) and Jowsey (*10*) have found an increase in both

resorption and formation with age, other groups have been unable to confirm such changes (*20*,*21*). Studies on normal bone have generally been carried out on relatively small numbers of subjects, and there is a clear need for the indices of formation and resorption to be studied in a sufficiently large population with adequate numbers in all decades.

Taking the mean WBR at each year of age between 20 and 45 for males and females separately in a paired comparison, we find a small yet significant difference ($p < 0.05$) in values for WBR between men and women. This difference is small, however, approximately 1% in 20% WBR, and although unexplained, it may reflect differences in hormonal control of skeletal metabolism. Differences in height and weight exist between the male and female groups, but we were unable to find any correlation between height or weight and WBR in the 133 subjects (86 female, 47 male) for whom these data were available. Moreover, within each age decade there was no correlation at all between height and WBR or weight and WBR for males or females. Furthermore, there was no correlation between the mean WBR and mean height or mean weight for each 5-yr age range in males or females: Women in the 36–40- and the 51–55- yr groups were significantly shorter than in most other groups, but the former does not match the minimum in the curve of WBR against age, and the latter is in the region of high WBR (Fig. 1). There were no significant differences between female weights in the 5-yr age groups. For the males the 31–35 group was significantly lighter than the 21–25 group ($p < 0.05$), but there were no other differences. Thus we conclude that weight and height are not significant factors in the behavior of WBR.

Large individuals may be expected to have their blood volume and skeletal mass increased in proportion to their total mass when compared with smaller individuals. It is therefore likely that relative blood flow to the skeleton and the percentage of the bone surface that is metabolically active would be independent of body size. Since WBR reflects the percentage of injected activity adsorbed onto the bone surface, this will provide a measure of skeletal metabolism that is unaffected by the size of the individual.

Accurate interpretation of WBR data depends upon normal renal function, and it is well recognized that the latter deteriorates with age. However, the changing trends in WBR noted in our studies occurred at relatively early ages (less than 55 yr) when age-related renal impairment is almost certainly not a factor. In addition, renal function was checked, giving normal values for serum creatinine in all subjects. We have previously shown that if serum creatinine is within the normal range, there is no abnormality of WBR, even in patients with established renal disease, when these are compared with age-matched controls (*22*).

On the basis of our results, we propose a simple hypothesis relating alterations in skeletal metabolism to the changes in bone mineral content that occur with age. Whereas skeletal growth stops by the age of 18 to 20 yr, osteoblastic activity appears to continue falling from the high adolescent levels (when bone modeling and remodeling coexist) until the mid 30s. Perhaps this is due to a prolonged period of withdrawal of growth stimuli before bone remodeling alone remains. Thereafter, bone resorption is the only drive to bone formation. After about age 35, the rate of resorption appears to increase following, perhaps, parathyroid hormone secretion, reduction in physical activity, falling sex hormone levels, or other factors as yet unknown. There will be a resulting increase in rate of bone formation, as detected by WBR, but it is probable that it will not quite match the increase in rate of resorption. For example, if there is a simple linear feedback system, causing the formation rate to increase in proportion to the difference between resorption and formation rates, then there must always remain a small imbalance between the two rates to provide the "error signal" that is necessary to maintain an increased formation rate. Thus we suggest that there will always be some imbalance between resorption and formation associated with bone remodeling, with a net loss of bone mineral. Consequently, once bone remodeling is established there is negative calcium balance, but initially this may be small and not detectable by standard techniques. Increases in skeletal metabolism with age, or following the menopause, will exaggerate the difference between resorption and formation and accelerate the rate of bone-mineral loss. In short, increases in skeletal metabolism lead to an increasing calcium debt that cannot be repaid, resulting in irreversible bone loss.

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REFERENCES

1. HARRIS WH, HAYWOOD EA, LAVORGNA J, et al: Spatial and temporal variations in cortical bone formation in dogs. *J Bone Joint Surg* 50A:1118–1128, 1968
2. KRUSE HP, KUHLENCORDT T: Pathogenesis and natural course of primary osteoporosis. *Lancet* 1:280–282, 1980
3. THOMSON DL, FRAME B: Involuntional osteopenia: current concepts. *Ann Int Med* 85:789–803, 1976
4. FOGELMAN I: Skeletal uptake of diphosphonate: a review. *Eur J Nucl Med* 5:473–476, 1980
5. FOGELMAN I, BESSENT RG, TURNER JG, et al: The use of whole-body retention of Tc-99m diphosphonate in the diagnosis of metabolic bone disease. *J Nucl Med* 19:270–275, 1978
6. FOGELMAN I, BESSENT RG, COHEN HN, et al: Skeletal uptake of diphosphonate: Method for prediction of postmenopausal osteoporosis. *Lancet* 2:667–670, 1980
7. FROST HM: *Bone Remodelling Dynamics*. Springfield, Il-

linois, Charles C Thomas, 1963
8. PARFITT AM: Quantum concept of bone remodeling and turnover: implications for the pathogenesis of osteoporosis. *Calcif Tissue Int* 28:1-5, 1979
9. GOLDSMITH NF, JOHNSTON JO, PICETTI G, et al: Bone mineral in the radius and vertebral osteoporosis in an insured population. *J Bone Joint Surg* 55A:1276-1293, 1973
10. JOWSEY J, KELLY PJ, RIGGS BL, et al: Quantitative microradiographic studies of normal and osteoporotic bone. *J Bone Joint Surg* 47A:785-806, 1965
11. HEANEY RP, RECKER RR, SAVILLE PD: Menopausal changes in bone remodeling. *J Lab Clin Med* 92:964-970, 1978
12. WISKE PS, EPSTEIN S, BELL NH, et al: Increases in immunoreactive parathyroid hormone with age. *N Engl J Med* 300:1419-1421, 1979
13. SMITH DA, ANDERSON JB, SHIMMINS J, et al: Changes in metacarpal mineral content and density in normal male and female subjects with age. *Clin Radiol* 20:23-31, 1969
14. GARN S, ROHMANN CG, WAGNER B: Bone loss as a general phenomenon in man. *Fed Proc* 26:1729-1736, 1967
15. CRILLY RG, JONES MM, HORSMAN A, et al: Rise in plasma alkaline phosphatase at the menopause. *Clin Sci* 58:341-342, 1980
16. HEANEY RP, RECKER RR, SAVILLE PD: Menopausal changes in calcium balance performance. *J Lab Clin Med* 92:953-963, 1978
17. GALLAGHER JC, RIGGS BL, EISMAN J, et al: Intestinal calcium absorption and serum vitamin D metabolites in normal subjects and osteoporotic patients. *J Clin Invest* 64: 729-736, 1979
18. ARNOLD JS: Excessive endosteal resorption in ageing and senile osteoporosis. In *Osteoporosis*, Barzel US, Ed. New York, Grune and Stratton, 1970, pp 80-100
19. GREENBLATT RB, NEZHAT C, ROESEL RA, et al: Update on the male and female climacteric. *J Am Geriatr Soc* 27: 481-490, 1979
20. MELSEN F, MELSEN B, MOSEKILDE L, et al: Histomorphometric analysis of normal bone from the iliac crest. *Acta Path Microbiol Scand* 86:70-81, 1978
21. WAKAMATSU E, SISSONS HA: The cancellous bone of the iliac crest. *Calcif Tissue Res* 4:147-161, 1969
22. FOGELMAN I, BESSENT RG, SCULLION JE, et al: A critical evaluation of 24-hour whole-body (skeletal) retention of diphosphonate measurements. In *Radioaktive Isotope In Klinik und Forschung.* Hofer R, Bergmann H, Eds. Vienna, Verlag H. Egermann, 1982, pp 323-329
23. IMRIE CW, ALLAM BF, FERGUSON JC. Hypocalcaemia of acute pancreatitis: the effect of hypoalbuminaemia. *Curr Med Res Opin* 4:101-116, 1976

Comment

As stated in the paper clear age-related trends exist for the results of 24-hour whole-body retention of diphosphonate (WBR) in normal adult subjects. A male pattern of falling WBR values from 20 years of age to 35 years, with a gentle, approximately linear rise thereafter was seen. In females a similar pattern of results was found initially but a more marked rise in WBR occurred between 46 to 50 years of age, which I believe is related to accelerated bone turnover following the menopause.

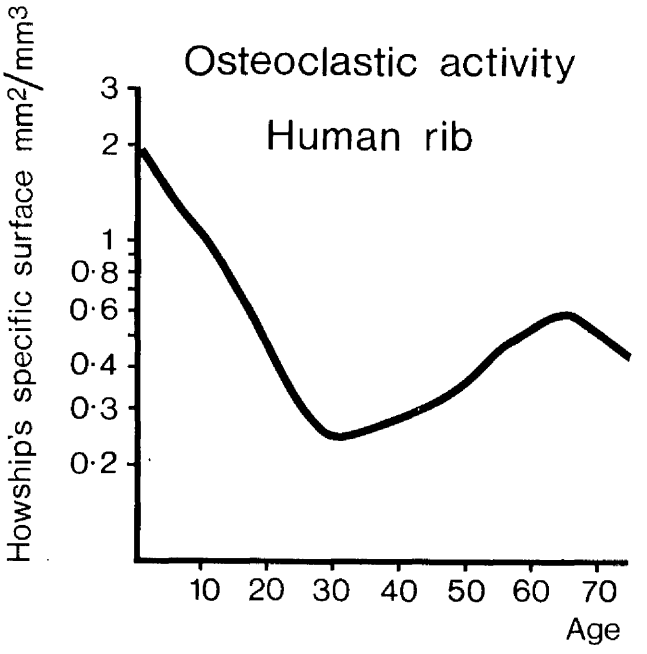
While all the clinical studies to date suggest that WBR does accurately reflect alterations in skeletal metabolism (see chapter 6), the exact mechanism and site of diphosphonate localisation in bone is not fully understood. It is therefore true to state that we do not know what precisely WBR is measuring. Thus it is necessary to question whether the results obtained in the present study could be artefactual in any way. Factors such as the individual's height and weight, and minor alterations in renal function of individual subjects are discussed fully in the paper, and although considered unimportant clearly cannot be absolutely excluded as contributing to the changes noted. However, large numbers of subjects were studied in

all age groups and the pattern of WBR results between the years 20 and 45 is very similar for both men and women. It is not surprising to find a sharper rise in WBR results for women thereafter due to the known increase in bone turnover which occurs following the menopause. All the trends in WBR results described are occurring in the age range 20 to 50 years, when age-related alterations in renal function are very unlikely to affect results. In addition the overall pattern of results is similar to data published by Frost (1963) based on histomorphometric analysis of bone biopsy sections from human ribs (figure 3). It should be noted, however, that bone at this site is predominantly cortical whereas trabecular bone is more active metabolically. Nevertheless the great majority of bone in the body is cortical and its relative contribution to total skeletal metabolism is not known.

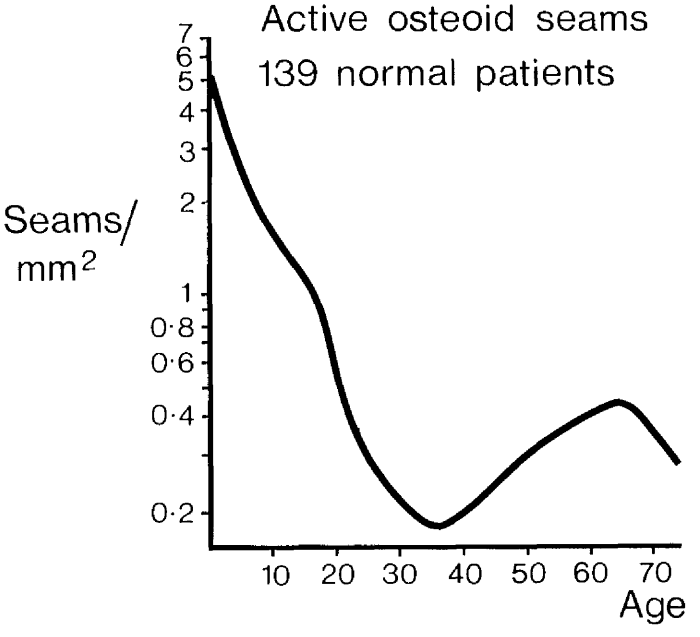
It is of interest to note that the mean WBR value for the study group as a whole (250 subjects) is 19.2% $\pm$ 3.5% (1SD). The first publication relating to WBR in 1978 (paper 9) reported 12 normal subjects and the mean WBR was 19.2% $\pm$ 1.7%. In 1980 (paper 16) a control group of 111 subjects was reported and the mean WBR was 19.4% $\pm$ 3.4%. The mean results for WBR are therefore remarkably consistent with a relatively small value for

Figure 3

a) Alterations with age in osteoclastic activity from 139 human rib biopsies.



b) Alterations with age in number of osteoid seams from 139 human rib biopsies.



(From H M Frost, Bone Remodelling Dynamics, 1963.
Courtesy of Charles C Thomas, Publisher, Springfield, Illinois).

the standard deviation. This presents a narrow control range for normal subjects and facilitates identification of abnormality, although as illustrated in the present paper any result requires to be related to age-matched controls.

On the basis of the results obtained in this study a simple hypothesis has been proposed relating alterations in skeletal metabolism with age, to changes in bone mineral content. It is generally accepted that there is "coupling" between bone resorption and bone formation, and it is believed that in early adult life the skeleton is in calcium balance (implying bone resorption and formation are equal). It is now suggested that if bone resorption and formation are linked along the lines of a simple linear feedback system, then once bone remodelling is established, and bone resorption is the only stimulus to bone formation, then there must always be some imbalance between resorption and formation to provide the "error signal" necessary to maintain bone formation. Thus a net negative calcium balance must always exist but will be small until the fourth decade when levels of skeletal metabolism are relatively low, and this calcium loss may

not be detectable by standard analytical techniques. The results of the present study suggest that skeletal metabolism rises throughout most of adult life, and any rises in skeletal metabolism with age or related to disease will exaggerate differences between bone resorption and formation leading to an increasingly negative calcium balance, and bone loss.

Paper 12. Measurement of 24-hour whole-body retention of Tc-99m HEDP by a gamma camera (1981)

Journal of Nuclear Medicine 22: 542-545

W Martin, I Fogelman, R G Bessent

Purpose of Investigation

While I considered that the 24-hour whole-body retention of diphosphonate (WBR) technique had considerable potential for application in clinical practice, I nevertheless realised that whole-body monitors are not widely available and this would limit the possible use of the WBR technique to relatively few centres. The purpose of the present investigation was therefore to assess whether WBR measurements could be obtained with a gamma camera (which is widely available) and compare results with those obtained with the whole-body monitor.

Measurement of 24-Hour Whole-Body Retention of Tc-99m HEDP by a Gamma Camera

William Martin, Ignac Fogelman, and Rodney G. Bessent

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Measurement of 24-hr whole-body retention of Tc-99m HEDP, using a shadow-shield, whole-body monitor, has been shown to be a sensitive measure of skeletal metabolism and of value in the diagnosis of metabolic bone disease. A new method of measuring the retention using a gamma camera, with a scanning (fishtail) collimator and patient placed at 2.3 m distance, has been evaluated in 18 patients undergoing routine bone scans. The patients also had whole-body retention measured using the whole-body monitor (WBM), and the two methods correlated well, yielding a regression line GC% = −0.82 +0.98 WBM%, r =0.975, p < 0.001. The limitations to, and repeatability of, the gamma-camera measurements are discussed. This work shows that measurements of whole-body retention can be obtained in any nuclear medicine department possessing a gamma camera with a suitable collimator.

J Nucl Med 22: 542–545, 1981

Bone scanning with the technetium-labeled diphosphonates has proved somewhat disappointing in the assessment of patients with metabolic bone disease, since scan appearances are often apparently normal when the skeleton is diffusely involved (*1–5*). In such cases an awareness of abnormality depends upon a subjective impression of increased tracer uptake throughout the skeleton. Accurate quantitation of tracer uptake by bone is required for a positive identification of increased skeletal metabolic activity. Measurement of 24-hr whole-body retention (WBR) of Tc-99m diphosphonate (Tc-HEDP) is a new technique by which total skeletal uptake of tracer is obtained. We have shown that patients with primary hyperparathyroidism, osteomalacia, renal osteodystrophy, and Paget's disease can be clearly differentiated from a control population by this technique (*5–7*).

Whole-body retention of diphosphonate provides a simple and sensitive measure of skeletal metabolism, and potentially has widespread application in clinical practice (*5–9*). However, since whole-body monitors (WBM) are not widely available, the means to perform such studies appear to be limited to only a few centres (*1*). This is not the case, and this communication describes how accurate measurement of 24-hr WBR of Tc-HEDP may be made using a gamma camera with a suitable collimator, which makes the technique available in most nuclear medicine departments.

MATERIALS AND METHODS

Eighteen patients with suspected abnormalities of skeletal metabolism were given 15 mCi of Tc-HEDP* by intravenous injection as part of a standard bone scan. Diagnoses were: Paget's disease, six; osteoporosis, four; primary hyperparathyroidism, three; renal osteodystrophy, one; thyrotoxic, one; unestablished, three. The whole-body count was measured 5–15 min after injection by positioning the patient 2.3 m from a wide-field gamma camera fitted with the "fishtail" collimator normally used for whole-body imaging with a scanning

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gamma camera. This collimator is parallel in one dimension and diverging in the other. When the collimator face is vertical, this gives a field of view of 0.35 m (FWHM) horizontally and 2.5 m vertically at a distance of 2.3 m, where patients could be accurately positioned standing against the wall of the room. This enabled a rather distorted image of the whole patient to be obtained by the gamma camera. Anterior, posterior, and lateral views of 30 sec each were acquired, typically yielding 120 K counts per view anteriorly and posteriorly, with 100 K counts per view laterally, using the Tc-99m photopeak with a 20% window. The anterior and posterior views were then repeated. These measurements were carefully repeated at 24 hr, with 100-sec timing, giving approximately 5 K counts (not including background) for patients with a normal whole-body retention of 20%. Using appropriate background, which was measured on both days, and decay corrections, the 24-hr WBR of Tc-HEDP was calculated. Within 18 days of the bone scan, each subject also had a 24-hr WBR of Tc-HEDP measured in the standard way using the whole-body monitor and an activity of 50 μCi (*5*). On the whole-body monitor, patients lie on a table and pass between detectors above and below them. Thus the mean of the anterior and posterior views, as measured with the gamma camera, is best for comparison with the whole-body monitor's results.

RESULTS

Figure 1A plots the 24-hr WBR for 18 patients, as measured by gamma camera (mean of the two anterior and two posterior views), against the results obtained on the WBM. The individual values for the various diagnoses as measured on the whole-body monitor were consistent with those reported previously (*5*). The mean

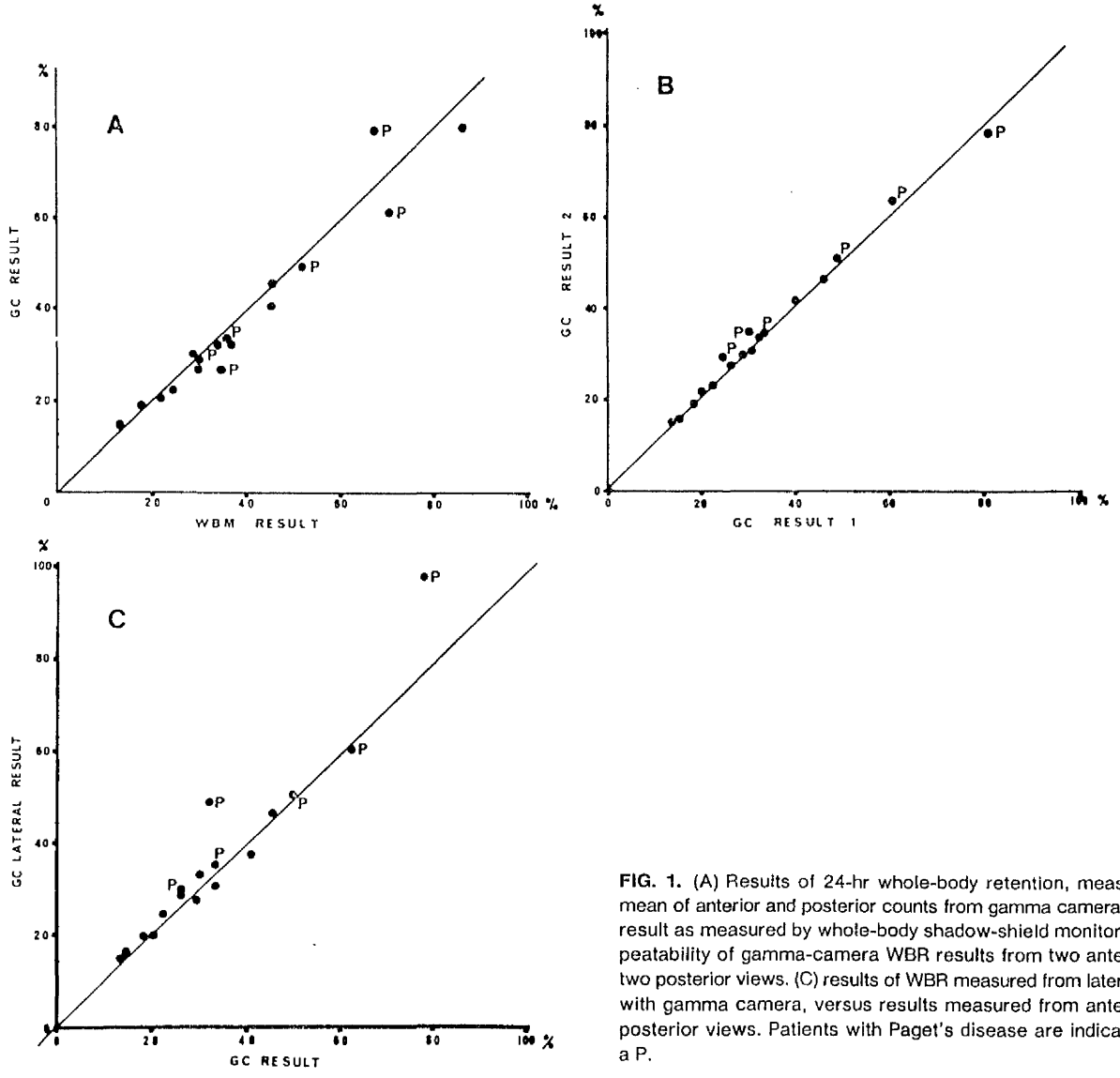

FIG. 1. (A) Results of 24-hr whole-body retention, measured as mean of anterior and posterior counts from gamma camera, against result as measured by whole-body shadow-shield monitor. (B) Repeatability of gamma-camera WBR results from two anterior and two posterior views. (C) results of WBR measured from lateral views with gamma camera, versus results measured from anterior and posterior views. Patients with Paget's disease are indicated with a P.

TABLE 1. APPROXIMATE PARAMETERS FOR GE MAXICAMERA II (WIDE FIELD) AND OHIO NUCLEAR STANDARD-FIELD GAMMA CAMERA, AS USED TO MEASURE WHOLE-BODY RETENTION*

Camera	Collimator	Area of crystal (cm^2)	Field of view at 2 m† (cm)	Background (count/sec)	Sensitivity to point source (2 m) (cps/μCi)	Sensitivity to patient (2 m) (cps/μCi)
Wide-field	scanning	1090	240 × 34	30	0.663	0.270
Wide-field	none	1590		525	52	21
Standard	diverging	546	circle, 185 cm diam.	12	0.192	0.078
Standard	none	918		290	37	15

* A 20% window was centered on Tc-99m photopeak.

† Initial sensitivity measurements were made at 2 m and patient studies at 2.3 m for convenience. Results at the two distances were not significantly different.

percentage difference between the results is 7.6% and a least-squares linear regression gives GC% = −0.82 + 0.98 WBM%, $r = 0.975$, $p < 0.001$. The two methods for measuring WBR agree well and show that a gamma camera can be used to measure WBR satisfactorily in patients undergoing routine bone scans. The results obtained on the whole-body monitor tend to be higher than those with the gamma camera, probably due to the different detector geometries, but the variations in the results are not significant. Figure 1B shows the variation of 24-hr WBR measured when the patient is repositioned in the posterior and anterior views. Repeatability is good, the mean percent difference between the results being 3.3%. Figure 1C indicates the results obtained for 24-hr WBR as measured by the lateral against the anterior and posterior views. The results again agree well, but as can be seen in all three graphs, the patients with Paget's disease tend to show the greatest differences. This is due to the focal uptake of Tc-HEDP in these patients, which leads to significant redistribution between the Day 1 and Day 2 measurements. In the case of the patient with nearly 100% WBR measured laterally in Fig. 1C, the side of one fibula took up an unusually high proportion of the dose causing the variation between the results (see Discussion).

DISCUSSION

There are several factors to be considered when using a gamma camera for 24-hr WBR: (a) the count rate response of the gamma camera; (b) background count rate; (c) sensitivity and uniformity of the collimator; and (d) redistribution of radiopharmaceutical in the patient.

Normal patients retain approximately 20% of the injected HEDP at 24 hr; thus approximately 1/80th of the injected activity remains at that time. This, along with the sensitivity of the gamma camera and the background count rate (Table 1), provides the limitations to the injected dose from statistical considerations (Appendix). Since the gamma camera is approximately 80 times more sensitive without a collimator (Table 1), this might be thought to present a better method of measuring WBR, even though the background is increased by a factor of 17.5. However, for patients undergoing routine bone scans, the initial measurement after the injection of 15 mCi of Tc-HEDP results in the camera's being operated in its nonlinear count rate response region on Day 1. Simple count-rate corrections, such as can be determined by a standard phantom with water scattering, are inapplicable due to the well-known problems of scattering within the patient, pulse pileup, source geometry variations, and scattered radiation from around the room, all affecting the pulse-height distribution at high count rates (*10, 12*). These effects vary considerably from patient to patient, and could be corrected for only by using phantoms with properties identical to those of each individual patient.

Use of the fishtail collimator enables the initial count rate on Day 1 to be within the linear count-rate response of the camera, as well as reducing the background. The pulse-height distribution from the patients is also similar on both days due to the elimination of much of the scattered radiation. The varying sensitivity of the collimator in the diverging (vertical) direction is relatively unimportant, since only redistribution of radiopharmaceutical affects results, and the initial vascular distribution on Day 1 has similar geometry to the Day 2 bone distribution. This problem is most obvious in cases with focal abnormalities such as Paget's disease (as mentioned earlier), where considerable changes in distribution of radiopharmaceutical occur. In such cases, however, the 24-hr WBR is markedly increased (*5*), yielding clear distinction from the normal group of patients (Fig. 1). The large patient-to-camera distance (2.3 m) reduces the effects of changes in source-to-detector distance, besides which patients can be accurately repositioned.

If a bone scan is not required, but only a measure of skeletal metabolism, 24-hr WBR could be measured by a gamma camera using a considerably lower activity than 15 mCi. If one needs to measure a normal 24-hr

WBR to a precision of 5% [i.e., result = (20 ± 1)%] within a total time on Day 2 of 1000 sec for patient and background measurements, then statistical considerations (Appendix) show that an activity of 2 mCi could be used. Here again use of the gamma camera without a collimator is not practical, since the much higher background, with significant fluctuations within a nuclear medicine department, requires a Day 1 activity that would cause nonlinear operation of the camera. Evaluation of WBR at a shorter time interval (e.g., 6 or 8 hr) might be a suitable addition to this test (*5*), since even at this time WBR is a measure reflecting skeletal uptake, although incomplete and variable excretion of nonskeletal Tc-HEDP would affect the result. Moreover, if there were any uncertainty, the result could be confirmed by a measurement at 24 hr. Note again that considerably lower activities could be used if a 6, 8, or even a 12-hr result were used as standard.

Although the fishtail collimator has desirable properties, WBR could also be measured using a gamma camera with any collimator capable of including the whole body in its field of view at a reasonable distance. For example, a 25-cm camera detector with a conventional diverging collimator can be used (Table 1), taking account of the factors already discussed.

CONCLUSION

We have shown that measurement of 24-hr WBR can be made using a gamma camera and could be used either independently or in addition to standard bone scans. This test provides a sensitive measure of skeletal metabolism (*5–7*) and is simple, noninvasive, has good reproducibility, and can be performed in any nuclear medicine department possessing a gamma camera with suitable collimator.

FOOTNOTE

Osteoscan, Procter and Gamble, Cincinnati, OH.

ACKNOWLEDGMENTS

We thank Mrs. E Scott of the Dept. of Nuclear Medicine for her measurements of whole-body retention on the Whole-Body Monitor.

APPENDIX

Statistical accuracy of the measurement of 24-hr WBR by a gamma camera. The random error in a normal WBR of 20% will be estimated as a worst case. On injection of 15 mCi Tc-HEDP and the patient positioned at 2.3 m from the camera, typical anterior and posterior count rates are 4000 cps for the IGE camera with fishtail collimator, these being well within the linear range. The background count rate (B) is typically 30 cps. At 24-hr, with a normal patient, the net anterior and posterior count rates are $1/5 \times 1/16 \times 4000 = 50$ cps (C), to which background (which must be counted correctly on both days) will be added ($S = C + B$). Only the second-day measurement has significant random error.

The standard deviation (σ) in the measurement of C, the net cps from the patient ($C = S - B$) is

$$\sigma = \sqrt{\frac{S}{t_S} + \frac{B}{t_B}}$$

which for $t_S = t_B = 100$ sec, as was used in this investigation, yields

$$\sigma = \sqrt{\frac{80}{100} + \frac{30}{100}} = 1.05 \text{ cps.}$$

Thus the fractional error in C is: $1.05/50 = 2\%$, and the probable range of 24-hr WBR is $(20 \pm 0.4)\%$ for a normal patient. It must be emphasized again that there are other, systematic, sources of error, such as those involved in repositioning both patient and camera, photopeak variation, etc., but steps can be taken to minimize these.

REFERENCES

1. HOLMES RA: Quantification of skeletal Tc-99m labelled phosphates to detect metabolic bone disease. *J Nucl Med* 19:330–331, 1978
2. WIEGMANN T, ROSENTHALL L, KAYE M: Technetium-99m-pyrophosphate bone scans in hyperparathyroidism. *J Nucl Med* 18:231–235, 1977
3. FOGELMAN I, MCKILLOP JH, BESSENT RG, et al: The role of bone scanning in osteomalacia. *J Nucl Med* 19:245–248, 1978
4. FOGELMAN I, CARR D: A comparison of bone scanning and radiology in the evaluation of patients with metabolic bone disease. *Clin Radiol* 31:321–326, 1980
5. FOGELMAN I, BESSENT RG, TURNER JG, et al: The use of whole-body retention of Tc-99m diphosphonate in the diagnosis of metabolic bone disease. *J Nucl Med* 19:270–275, 1978
6. FOGELMAN I, BESSENT RG, BEASTALL G, et al: Estimation of skeletal involvement in primary hyperparathyroidism. Use of 24-hour whole-body retention of technetium-99m diphosphonate. *Ann Intern Med* 92:65–67, 1980
7. FOGELMAN I, BESSENT RG, COHEN HN, et al: Skeletal uptake of diphosphonate. Method for prediction of postmenopausal osteoporosis. *Lancet* II:667–670, 1980
8. FOGELMAN I: The value of 24 hour skeletal uptake of diphosphonate in the exclusion of metabolic bone disease. *Nucl Med Comm* 1:351–356, 1980.
9. CANIGGIA A, VATTIMO A: Kinetics of ^{99m}technetium-tin-methylene-diphosphonate in normal subjects and pathological conditions: a simple index of bone metabolism. *Calcif Tissue Int* 30:5–13, 1980
10. ARNOLD JE, JOHNSTON AS, PINSKY SM: The influence of true counting rate and the photopeak fraction of detected events on Anger camera deadtime. *J Nucl Med* 15:412–416, 1974
11. SORENSON JA: Methods of correcting Anger camera deadtime losses. *J Nucl Med* 17:137–141, 1976
12. STRAND S-E, LARSSON I: Image artifacts at high photon fluence rates in single-crystal NaI(Tl) scintillation cameras. *J Nucl Med* 19:407–413, 1978

Comment

This study illustrates clearly that a gamma camera with a suitable collimator can be used to obtain a 24-hour whole-body retention of diphosphonate (WBR) measurement. Extremely good correlation was found between results obtained in this way and those obtained with the standard whole-body monitor (WBM). While the amount of radioactivity required for WBR is somewhat higher than with the WBM (approximately 2mCi compared with 50 μCi) it is still a very small dose and considerably less than for a bone scan (approximately 15 mCi). If a bone scan is being performed anyway, then a WBR measurement can be obtained as an extension of that study with no extra radioactivity required.

WBR measurements are easily obtained using a gamma camera, the technique is reproducible and in addition results correlate well with those from the WBM. It is concluded that WBR can be measured in any nuclear medicine department possessing a gamma camera with a suitable collimator.

SUMMARY

CHAPTER 4

QUANTITATION OF 24-HOUR WHOLE-BODY RETENTION OF TECHNETIUM-99m DIPHOSPHONATE - A TRACER TECHNIQUE FOR THE ASSESSMENT OF SKELETAL METABOLISM

Chapter 4 commences with a review of the historical aspects of the use of radioactive tracer techniques in the assessment of skeletal metabolism. The complexity of radiocalcium measurements and their lack of diagnostic value is emphasised. The development and validation of the technique of 24-hour whole-body retention of technetium-99m diphosphonate (WBR) as a measure of skeletal uptake of tracer, and as a means of identifying increased bone turnover is then described. The analysis and evaluation of WBR results in 250 healthy volunteer subjects is presented and it is also shown that the WBR technique can be carried out in any nuclear medicine department possessing a gamma camera.

Paper 9 is the original publication relating to the WBR technique and it introduces the concept that measurements of 24-hour whole-body retention of diphosphonate may provide a sensitive index of altered skeletal metabolism. Initial studies demonstrate that patients with osteomalacia, primary hyperparathyroidism, renal osteodystrophy and Paget's disease can be clearly differentiated from control subjects. While the exact site and mechanism of diphosphonate localisation in bone is not known, it is nevertheless suggested that in spite of these uncertainties

the WBR technique may have great potential value in clinical practice due to its proven ability to identify patients with increased bone turnover. Several studies relating to the accuracy of the WBR technique are detailed in paper 10 and it is seen that the test is highly reproducible and not subject to any significant technical errors. In addition the results from further studies assessing whether the presence of focal lesions in bone or minor impairment of renal function may affect WBR are presented. It is concluded that these clinical factors are unlikely to affect WBR to any significant extent. While the possibility of these factors contributing to minor alterations in WBR cannot be excluded, it is shown that they are extremely unlikely to elevate a WBR result outside the normal range.

An analysis of results of WBR in 250 healthy volunteer subjects is presented in paper 11. A clear age-related pattern of results is shown. In men there is a fall in WBR results between the ages of 25 to 35 years with a gentle, approximately linear rise thereafter. In women a similar pattern of WBR results is seen although there is a sharper rise at around 50 years of age which is thought to be related to increased bone turnover following the menopause.

On the basis of the findings in this study a hypothesis relating alterations in skeletal metabolism to age-related bone loss is presented.

This chapter concludes with a comparative study of WBR measurements obtained with a gamma camera and with the standard whole-body monitor (WBM) technique (paper 12). The relevance of this study is that there are relatively few centres which have WBM's while gamma cameras are widely available. An extremely good correlation was found between results obtained with the two techniques and it is concluded that WBR measurements can be obtained in any nuclear medicine department possessing a gamma camera.

CHAPTER 5

COMPARISON OF THE AVAILABLE DIPHOSPHONATE BONE SCANNING AGENTS

This chapter consists of three papers (13-15) which relate to the evaluation of various diphosphonate bone scanning agents in clinical practice. Striking differences in skeletal affinity between these agents are found and the implications of these results in both benign and malignant disease are discussed.

Paper 13. A clinical comparison of Tc-99m HEDP and Tc-99m MDP in the detection of bone metastases: Concise communication (1979)

Journal of Nuclear Medicine 20: 98-101

I Fogelman, D L Citrin, J H McKillop, J G Turner, R G Bessent, W R Greig

Purpose of Investigation

The purpose of this investigation was to evaluate a new bone scanning agent, Tc-99m methylene diphosphonate, and compare this with Tc-99m hydroxyethylidene diphosphonate in the detection of bone metastases in patients with known malignancy.

A Clinical Comparison of Tc-99m HEDP and Tc-99m MDP in the Detection of Bone Metastases: Concise Communication

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Glasgow Royal Infirmary, Glasgow, Scotland, and University of Wisconsin Hospitals, Madison, Wisconsin

We have compared bone scintigrams made with Tc-99m-tagged HEDP (1-hydroxyethylidene diphosphonate) and MDP (methylene diphosphonate), the former at 4 hr after injection, the latter at both 2 and 4 hr. In 17 patients with skeletal metastases, there was no significant difference in lesion count or scan quality between the 4-hr images. The tumor-to-bone ratio (T/B) was significantly higher with Tc-HEDP ($p < 0.02$). Lesion detection rate and T/B ratios were both lower with Tc-MDP at 2 hr when compared with the 4-hr values for both Tc-HEDP ($p < 0.02$, $p < 0.005$) and Tc-MDP ($p < 0.02$, $p < 0.01$). The 4-hr Tc-MDP scan was of significantly higher quality than the 2 hr Tc-MDP scan ($p < 0.01$). Although Tc-HEDP produces a higher T/B ratio at 4 hr, the present study does not suggest that either agent is superior in clinical practice.

J Nucl Med 20: 98–101, 1979

Since the introduction of the Tc-99m-labeled phosphate and diphosphonate bone-scanning agents, it has been generally accepted that of the available agents the diphosphonates are the most satisfactory (*1–6*). Two diphosphonates are in routine clinical use at present, Tc-99m hydroxyethylidene diphosphonate (Tc-HEDP) and Tc-99m methylene diphosphonate (Tc-MDP). The soft-tissue clearance is apparently more rapid with Tc-MDP than with Tc-HEDP. For this reason it has been suggested that scans may be obtained with Tc-MDP 2 hr after injection, and that Tc-MDP is therefore the agent of choice (*3*). A recent clinical comparison of the two agents has also suggested that Tc-MDP is superior to Tc-HEDP (*7*).

In this report we describe a comparison of 4-hr bone scans obtained with Tc-HEDP and Tc-MDP in 17 patients with bone metastases. Additionally, a comparison has been made between the 2-hr and 4-hr bone scans with Tc-MDP.

PATIENTS AND METHODS

Seventeen patients with bone metastases (Table 1) were studied on two occasions. A radionuclide bone scan was obtained 4 hr after the i.v. injection of 15 mCi of Tc-HEDP*. Approximately one week later a repeat study was performed 2 and 4 hours after the injection of 15 mCi of Tc-MDP†. During the period between the paired studies no patient received specific chemotherapy or radiotherapy.

Bone scans were obtained by recording multiple views of the skeleton on Polaroid film using a gamma camera fitted with a high-resolution medium-sensitivity collimator. Spinal views were obtained with 500,000 counts, and all others with 100,000 counts. In addition, all scintigrams were recorded and stored on a minicomputer by means

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of Laben analog-to-digital converters. Subsequent analysis of the digitized computer images permitted calculation of bone to soft-tissue ratios (B/ST) by selecting regions of interest around lumbar vertebra 2 and an adjacent soft-tissue area clear of renal activity (*8*). Similarly tumor-to-bone ratios (T/B) were measured as ratios of activity in tumor-involved bone to activity in corresponding normal bone.

The bone images were evaluated independently by three observers, (DLC, JHMcK, JGT), without knowledge of patient details or the ratiotracer used. The overall quality of scan image was recorded on a scale of 1–3: 1 was considered poor quality, 2 average quality, and 3 a very good-quality image. In addition each physician recorded the total number of focal abnormalities identified in each patient.

All statistical comparisons between Tc-MDP and Tc-HEDP were performed using a paired Wilcoxon test, since each patient was studied with both agents.

RESULTS

The correlation between the lesion counts obtained by the three independent observers was very good for all studies, the correlation coefficient (r) ranging from 0.84–0.96 ($p < 0.001$, in all cases). Regarding image-quality assessment, there was fairly good correlation for both 4-hr studies (r ranging from 0.49–0.76, $p < 0.05$ in all cases). In the 2-hr Tc-MDP study, however, two observers correlated well with each other ($r = 0.60$, $p < 0.01$) but not with the third observer ($r = 0.17$ and 0.45, $p > 0.05$).

Image-quality score (Table 1). Overall there was no significant difference in quality between the 4-hr images obtained with Tc-HEDP and both the 2-hr and 4-hr Tc-MDP images. There was, however, a significant improvement in quality between the images obtained with Tc-MDP at 2 and 4 hr ($p < 0.01$).

Lesion counts (Table 2). There was no significant difference between the number of bone lesions (metastases) identified on the 4-hr Tc-HEDP and Tc-MDP scans. The 2-hr Tc-MDP scans gave significantly fewer identifiable lesions than did the 4-hr studies with either Tc-MDP ($p < 0.02$) or Tc-HEDP ($p < 0.02$).

Bone-to-soft-tissue ratios (Table 3). There was no significant difference in B/ST ratios between the 4-hr Tc-HEDP study and either the 2- or 4-hr Tc-MDP study. However, a significant increase in B/ST ratio was noted between 2- and 4-hr Tc-MDP studies ($p < 0.05$).

Tumor-to-bone ratios (Table 4). The T/B ratios obtained with Tc-HEDP were significantly higher than those obtained in both the 2-hr Tc-MDP ($p < 0.005$) and 4-hr MDP study ($p < 0.02$). In addition, there was a significant increase from 2 to 4 hr in the Tc-MDP studies ($p < 0.01$).

TABLE 1. PATIENT CHARACTERISTICS AND OVERALL SCAN IMAGE QUALITY SCORE*

Patient No.	Age	Sex	Primary Site	HEDP (4 hr)	MDP (2 hr)	MDP (4 hr)
1	62	F	Breast	2.2	1.7	1.5
2	75	F	Breast	2.0	2.0	2.0
3	46	F	Breast	2.0	2.2	2.5
4	58	F	Bladder	2.5	2.2	2.7
5	53	M	Lung	1.5	1.2	1.2
6	72	F	Breast	1.0	1.0	1.7
7	83	M	Prostate	2.5	2.5	2.5
8	55	F	Breast	1.3	1.7	1.7
9	47	F	Breast	3.0	2.7	3.0
10	71	M	Prostate	2.0	1.7	1.7
11	42	F	Breast	1.7	1.7	2.3
12	72	F	Breast	1.0	2.3	2.7
13	49	F	Breast	2.3	2.3	2.3
14	57	F	Breast	2.7	2.0	2.7
15	58	F	Breast	2.0	2.0	2.0
16	41	F	Breast	2.3	2.0	3.0
17	64	F	Breast	1.3	1.0	1.7
Mean ± s.d.				2.0 ± 0.6	1.9 ± 0.5	2.2 ± 0.06
					NSD**	$p < 0.01$**
						NSD**

* Mean of three independent observers.
** Results of comparison by paired Wilcoxon test; NSD = no significant difference.

DISCUSSION

The clinical superiority of the Tc-99m diphosphonate vectors HEDP and MDP, when compared with pyrophosphate and the polyphosphates in terms of quality of scan image and lesion detection rate, is now generally accepted. Since the early work demonstrating that MDP has a slightly faster blood clearance than HEDP, it has been suggested that the former is the preferred agent for routine clinical studies (*3*). Of particular importance in this respect has been the suggestion that a time interval of only 2 hr between injection and scanning is required with MDP, compared with 3 to 4 hr with HEDP (*3*). This suggestion, however, was made by Subramanian (*3*) on the basis of studies of blood clearance in only six healthy volunteers without bone disease, and was not based on any data regarding either the visualization or quantitation of bone lesions. A clinical comparison of MDP and HEDP has been performed in 11 volunteers and 20 patients (*7*). On the basis of faster blood clearance, improved quality of scan image and higher bone to soft-tissue ratios, the authors concluded that MDP was the preferred radiopharmaceutical for bone imaging. However, only seven of their patients had skeletal metastases and in these cases no lesions identified with one compound were missed with the other. Also no quantitative data were presented regarding tumor-to-bone ratios.

The results of the present work, performed as a critical paired study of patients with unequivocal bone metastases, have shown no major difference between the 4-hr HEDP and MDP scans in terms of overall image quality, number of lesions de-

TABLE 2. NUMBER OF BONE LESIONS COUNTED*

Patient No.	HEDP (4 hr)	MDP (2 hr)	MDP (4 hr)
1	15.0	14.7	16.3
2	2.0	2.0	2.0
3	13.3	11.7	14.3
4	28.0	28.3	29.0
5	3.7	4.3	6.0
6	4.3	4.7	4.7
7	29.7	22.7	25.7
8	9.7	10.0	12.3
9	21.3	14.0	16.7
10	17.7	16.0	12.3
11	8.7	8.3	8.7
12	9.7	8.0	9.0
13	12.7	12.7	14.4
14	13.3	12.0	13.0
15	3.0	2.3	2.0
16	3.0	2.0	2.7
17	17.3	16.7	17.7
Mean ± s.d.	12.5 ± 8.4	11.2 ± 7.3	12.2 ± 7.7
		$p < 0.02$**	$p < 0.02$**
		NSD**	

* Mean of three independent observers.
** Results of comparison by paired Wilcoxon test; NSD = no significant difference.

TABLE 3. $\frac{\text{NORMAL BONE}}{\text{SOFT TISSUE}}$ RATIO

Patient No.	HEDP (4 hr)	MDP (2 hr)	MDP (4 hr)
1	5.8	4.7	5.2
2	5.7	6.5	6.8
3	5.3	4.2	5.2
4	4.1	2.8	2.7
5	3.2	2.5	3.8
6	2.9	3.1	4.7
7	7.7	5.1	5.4
8	4.5	3.3	4.1
9	7.0	6.8	8.2
10	4.1	5.5	4.5
11	4.9	6.0	6.0
12	2.7	2.9	2.4
13	12.1	9.9	10.9
14	4.0	4.4	5.5
15	4.7	4.1	5.3
16	4.0	4.7	4.7
17	3.5	3.9	3.3
Mean ± s.d.	5.07 ± 2.26	4.72 ± 1.85	5.22 ± 2.04
	NSD*		$p < 0.05$*
	NSD*		

* Results of comparison by paired Wilcoxon test; NSD = no significant difference.

TABLE 4. $\frac{\text{TUMOR}}{\text{BONE}}$ RATIO

Patient No.	HEDP (4 hr)	MDP (2 hr)	MDP (4 hr)
1	2.0	1.9	1.7
2	2.1	2.0	2.2
3	1.7	1.7	1.8
4	2.1	2.4	2.8
5	2.6	1.8	1.9
6	2.7	2.2	2.2
7	2.2	2.0	2.0
8	1.8	1.7	1.7
9	2.3	2.0	2.1
10	4.5	3.2	3.9
11	3.3	2.5	3.0
12	5.3	3.7	4.1
13	1.5	1.6	1.7
14	2.3	1.8	1.9
15	1.4	1.4	1.3
16	1.8	1.6	1.6
17	1.9	1.6	1.8
Mean ± s.d.	2.45 ± 1.03	2.05 ± 0.61	2.2 ± 0.78
	$p < 0.005$*		$p < 0.01$*
	$p < 0.02$*		

* Results of comparison by paired Wilcoxon test.

tected, and bone to soft-tissue ratios. The only statistically significant difference between the two agents in this study was a high tumor-to-bone ratio with HEDP.

Following the initial independent random evaluation of image quality, the observers reassessed the scan images in sets of three for each of the 17 patients. Overall there was a subjective impression that MDP produced images of higher quality at 4 hr after injection when compared with HEDP. This was supported by a trend towards higher scores for MDP in image quality (Table 1) and bone-to-soft-tissue ratios (Table 3). However, it was felt that there was higher contrast between tumor and normal bone using HEDP, and this was supported by higher tumor-to-bone ratios (Table 4). The subjective impression of a "good image" is influenced by a high bone to soft-tissue ratio, but in clinical practice tumor visualization is paramount. For this purpose the agent with the highest tumor-to-normal-bone ratio may well be superior.

Comparison of the 2- and 4-hr MDP scans shows improvement in all aspects of image quality, lesion detection rate, and tumor-to-bone ratios in the later study. A similar trend was noted in a previous study, which compared 2- and 4-hr scans obtained with HEDP (*9*). Although satisfactory bone scan images are obtained with both HEDP and MDP at 2 hr after injection, 4-hr images are superior.

There was no significant difference for any parameter between the results from the nine patients receiving one commercial MDP and the eight receiving the other MDP. This is similar to our previous experience with HEDP obtained from three different commercial sources, where the products all provided similar, highly reproducible results (*10*).

On the basis of the present study we conclude that, although Tc-HEDP produces higher tumor-to-bone ratios, there is no significant clinical difference between Tc-HEDP and Tc-MDP in terms of image quality and lesion detection rate. In the case of Tc-MDP, scanning at 2 hr will result in some missed lesions, so the longer delay after injection is recommended particularly where subtle abnormalities are anticipated.

FOOTNOTES

* Osteoscan, Proctor and Gamble, Cincinnati, OH.

† Patients Nos. 1–9 with Tc-MDP from Radiochemical Center, Amersham Corp., Arlington Heights, IL; patients Nos. 10–17 with Tc-MDP from New England Nuclear Corp., North Billerica, MA.

REFERENCES

1. CITRIN DL, BESSENT RG, GREIG WR: Clinical evaluation of ^{99m}Tc-labelled monofluorphosphate: A comparison with ethane-hydroxy-diphosphonate. *J Nucl Med* 15: 1110–1112, 1974

2. CITRIN DL, BESSENT RG, TUOHY JB, et al: Comparison of phosphate bone-scanning agents in normal subjects and patients with malignant disease. *Br J Radiol* 48: 118–121, 1975

3. SUBRAMANIAN G, MCAFEE JG, BLAIR RJ, et al: Technetium-99m-methylene diphosphonate—A superior agent for skeletal imaging: Comparison with other technetium complexes. *J Nucl Med* 16: 744–755, 1975

4. DAVIS MA, JONES AG: Comparison of ^{99m}Tc-labelled phosphate and phosphonate agents for skeletal imaging. *Sem Nucl Med* 6: 19–31, 1976

5. RUDD TG, ALLEN DR, HARTNETT DE: Tc-99m methylene diphosphonate versus Tc-99m pyrophosphate: Biologic and clinical comparison. *J Nucl Med* 18: 872–876, 1977

6. BULL U, PFEIFER JP, NIENDORF HP, et al: A computer assisted comparison of ^{99}Tc^{m}-methylene-diphosphonate and ^{99}Tc^{m}-pyrophosphate bone imaging. *Br J Radiol* 50: 629–636, 1977

7. ROSENTHALL L, ARZOUMANIAN A., LISBONA R, et al: A longitudinal comparison of the kinetics of ^{99m}Tc-MDP and ^{99}mTc-HEDP in humans. *Clin Nucl Med* 2: 232–234, 1977

8. FOGELMAN I, BESSENT RG, TURNER JG, et al: The use of whole-body retention of Tc-99m diphosphonate in the diagnosis of metabolic bone disease. *J Nucl Med* 19: 270–275, 1978

9. FOGELMAN I, GOLL C, MCKILLOP JH, et al: A clinical comparison of 2 h and 4 h bone scans obtained with ^{99m}Tc HEDP. *Eur J Nucl Med* 3: 15–17, 1978

10. CITRIN DL: The use of radioactive nuclides in the investigation of malignant disease (A laboratory and clinical evaluation of the ^{99m}Tc phosphates as bone scanning agents in the detection of skeletal metastases). Ph.D. Thesis, University of Glasgow, 1975.

Comment

This study involving patients with malignant disease is included in a thesis dealing essentially with benign disorders because the finding of higher lesion to bone ratios with hydroxyethylidene diphosphonate (HEDP) than with methylene diphosphonate (MDP) was the first indication to me that higher absolute bone uptake of tracer may not necessarily be desirable in clinical practice. While no significant difference in lesion detection was found between MDP and HEDP in the present study, it is theoretically possible that lesions in bone will be less apparent against a background of higher tracer uptake by the normal skeleton. However fashions are such that because MDP produces slightly more pleasing normal bone scan images, it is the most widely used scanning agent and HEDP is now no longer commercially available. A comprehensive review of the differences between various diphosphonates as regards skeletal uptake, lesion to bone ratios, bone to soft-tissue contrast, and the implications of their use in malignant and benign disease is presented in paper 15.

Paper 14. A comparison of skeletal uptakes of three diphosphonates by whole-body retention: Concise communication (1981)

Journal of Nuclear Medicine 22: 880-883

I Fogelman, D W Pearson, R G Bessent, A J Tofe, M D Francis.

Purpose of Investigation

While differences in the skeletal affinity of the various diphosphonates had been shown in animal studies and in vitro experiments, such findings had not been confirmed in human subjects. The purpose of the present study was to assess relative skeletal uptake of three different technetium-99m labelled diphosphonates using the 24-hour whole-body retention technique in 20 healthy volunteer subjects.

A Comparison of Skeletal Uptakes of Three Diphosphonates by Whole-Body Retention: Concise Communication

I. Fogelman, D. W. Pearson, R. G. Bessent, A. J. Tofe, and M. D. Francis

Glasgow Royal Infirmary, Glasgow, Scotland and Miami Valley Laboratories, Procter & Gamble Company, Cincinnati, Ohio

Twenty normal volunteers had measurements of 24-hr whole-body retention (WBR) of three structurally related Tc-99m-labeled phosphonate skeletal imaging agents: (1-hydroxyethylidene) diphosphonate (HEDP), methylene diphosphonate (MDP), and hydroxymethylene diphosphonate (HMDP). The average WBR values, reflecting skeletal uptake, were 18.4, 30.3, and 36.6%, respectively. These results clearly illustrate that slight alterations in diphosphonate molecular structure have a significant effect upon specificity for osseous tissue, and thus may affect skeletal image quality and the usefulness of the WBR technique in diagnosing metabolic bone disease.

J Nucl Med 22: 880–883, 1981

The development of skeletal imaging agents has been focused around structural modifications of the methylene diphosphonate (MDP) molecule. The addition of the hydroxyl group to the central carbon atom of MDP to produce hydroxymethylene diphosphonate (HMDP), or an additional methyl group to the hydroxylated central carbon atom to produce 1-hydroxyethylidene diphosphonate (HEDP), have been shown in vitro and in animal studies to produce significant differences in both the pharmacokinetics and osseous specificity of the agents (*1–4*).

Clinically, the accurate comparative quantitation of skeletal uptake at times shortly after administration of the skeletal imaging agents presents a number of technical problems that can be circumvented by using the 24-hr whole-body retention (WBR) technique (*5*). In this paper, the WBR values for the three structurally similar diphosphonates HEDP, MDP, and HMDP (Fig. 1), were all compared in 20 normal subjects to assess the relative skeletal affinities of these agents. The clinical utility of the differences in absolute skeletal uptake has implications for skeletal image quality, the time required to obtain images, and the use of the WBR technique in diagnosing metabolic bone disease.

METHODS AND MATERIALS

Twenty normal volunteers (age range 22–65 yr, mean 40.2) had 24-hr WBR measurements following intravenous injections of Tc-99m-labeled HEDP, MDP, and HMDP. All three were prepared according to manufacturer's instructions with the exception of the activity level, which was only 50 μCi per dose. The whole-body count was measured at 5 min and again at 24 hr after injection, using a standard shadow-shield whole-body monitor (*5*). Twenty-four-hour WBR values for the three agents were calculated, after appropriate background subtraction, by taking the 5-min count as 100% and correcting for radioactive decay. The WBR measurements were performed at least one week apart, with 17 of the 20 triple studies falling within a 2-mo period. The remaining three studies were over a 3- to 4-mo period.

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Diphosphonate Carrier Molecules

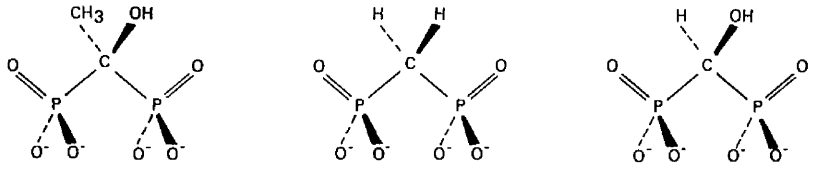

FIG. 1. Unprotonated structures of HEDP, MDP, and HMDP.

This study uses a randomized block design wherein each subject was treated with each of the three agents studied. Therefore, the data were analyzed using analysis of variance for randomized blocks (*6*). Comparisons of HMDP with each of the other agents were done using the *t*-distribution procedure described in Sec. 23.4 of Ref. 6.

RESULTS

The absolute whole-body retention values for each of the 20 normal volunteers are given in Fig. 2. Tests of difference for the three treatments in the individuals are highly significant ($P < 0.001$). As shown in Fig. 3, the mean WBR and standard deviation values for HEDP, MDP, and HMDP are 18.41% ± 2.94, 30.30% ± 4.16, and 36.55% ± 5.0, respectively. The WBR values ranged from 12.89–22.45% for the HEDP agent, 23.22–36.4% for the MDP, and 25.07–44.23% for the HMDP. Thus the mean WBR of HMDP is about double that of HEDP, and is 20% greater than that of MDP. The differences, at 95% confidence interval, between the HMDP and HEDP agents, and the HMDP and MDP agents, are 18.2% ± 1.2 and 6.3% ±1.1, respectively. The small standard deviations of the differences reflect the fact that results for individual subjects are in closely similar order for the three agents (Fig. 2). In other words, even within this control group, individual small differences are demonstrated similarly by the three agents.

The quantitative differences between HEDP and MDP are in excellent agreement with WBR values previously reported for a small group of subjects (*7*).

DISCUSSION

In theory, high skeletal uptake of tracer is desirable for bone scanning, since this may allow clearer delineation of the skeleton and minimize the time required to perform a study. At present there are no reports of significant differences between HEDP, MDP, and HMDP when used for the detection of metastatic disease—i.e.,

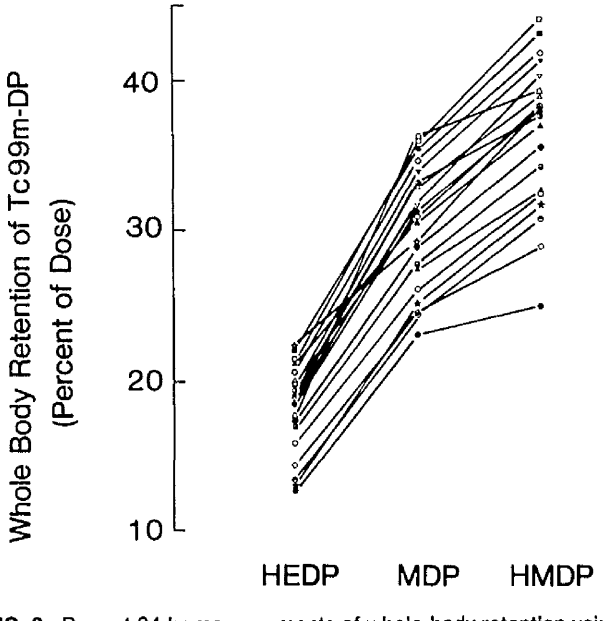

FIG. 2. Repeat 24-hr measurements of whole-body retention using Tc-99m HEDP, Tc-99m MDP, and Tc-99m HMDP skeletal imaging agents in 20 normals.

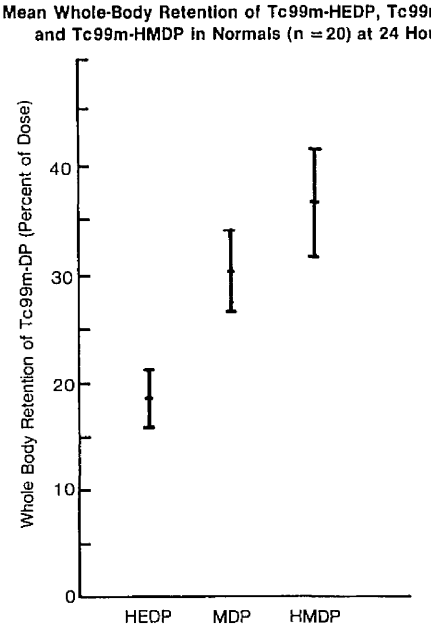

FIG. 3. Mean 24-hr values, with standard deviation, for whole-body retention of Tc-99m HEDP, Tc-99m MDP, and Tc-99m HMDP.

increased skeletal uptake of tracer is not necessarily advantageous for lesion detection—and indeed we have previously suggested that where there is high uptake of tracer by normal bone, lesions may even be less clearly visualized (*7*). However, in a recent comparison between the lowest-uptake agent, HEDP, and the highest, HMDP, this was not found to be the case (*8*). In the studies where images obtained at both 2 and 4 hr after injection with either HEDP or MDP have been compared, a significant improvement in image quality was seen at the later time (*9,10*). It therefore appears that while bone scans using HEDP and MDP can provide satisfactory diagnostic information at 2 hr after injection, the quality of such images might be considered poor and perhaps even unacceptable by current standards. Image quality is principally related to the absolute retention of the skeletal imaging agent on bone and the time available to allow the soft-tissue tracer component to be excreted by the kidneys. The diagnostic quality of images obtained with HMDP at scanning times earlier than 4 hr after injection has still to be established.

Whereas differences in diphosphonate uptake at 24 hr cannot necessarily be extrapolated to routine clinical scanning times, the validity of the 24-hr value is clinically supported by Khedkar et al., who quantitated MDP and HMDP bone uptake in the pelvic bones of 12 patients and showed higher skeletal retention of HMDP at 0.5, 3, and 24 hr (*11*). Similar quantitative differences between MDP and HMDP were obtained by Bevan et al. (*3*) at 1.5 hr in beagle dogs, a model we feel can be extrapolated to humans.

The exact mechanism of diphosphonate uptake in bone is as yet incompletely understood (*12*), but a common factor for all three agents is the ability of the diphosphonate to coordinate with technetium, with subsequent sorption of the tracer onto bone (*13*). The 20% differential in WBR value between MDP and HMDP is most probably related to differences in the bridging (binding) between the agents and hydroxyapatite, primarily the postulated bidentate-bidentate binding for nonhydroxy molecules such as MDP and bidentate-tridentate binding for molecules with a hydroxy group such as HMDP (*2,13*). Kinetic studies by Arnold et al. (*14*) suggest that such variations in molecular structure do affect osseous affinity and lead to tighter binding of HMDP and subsequent higher retention on bone. Less understood is the dramatic difference observed between HEDP and HMDP, both capable of bidentate-tridentate binding. Increased steric hindrance associated with the methyl group on the central carbon atom, differences in solubility, and differences in molecular size as well as in the diphosphonate polymeric complexes themselves have all been suggested (*2,4,13*).

This study has possible implications relating to the use of (a) different diphosphonates for bone scanning, and (b) WBR in the evaluation of patients with metabolic bone disease. Whereas in metastatic disease focal abnormalities are seen on the bone scan, in metabolic bone disease the skeleton is usually diffusely involved by the metabolic process and typically focal abnormalities are absent. An awareness of abnormality then depends upon a subjective impression of increased tracer uptake throughout the whole skeleton. With HEDP several metabolic features have been recognized on the scan, and these have allowed differentiation of various metabolic bone disorders from a control population (*15*). In the case of either MDP or HMDP, the higher absolute uptake relative to HEDP raises the possibility that it will be more difficult to identify a metabolic process against this higher background of normal skeletal uptake. Where 24-hr WBR of diphosphonate is used to identify patients with increased skeletal metabolism (*5,16–18*), HEDP, with its tighter normal range at lower absolute skeletal uptake, would seem to be the agent of choice, since it provides a wider range in which to detect abnormality with less overlap between normal and abnormal.

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REFERENCES

1. WANG TS, FAWWAZ RA, JOHNSON LL, et al: Bone-seeking properties of Tc-99m carbonyl diphosphonic acid, dihydroxymethylene diphosphonic acid and monohydroxymethylene phosphonic acid. *J Nucl Med* 21: 767–770, 1980
2. BEVAN JA, TOFE AJ, BENEDICT JJ, et al: Tc-99m HMDP (hydroxymethylene diphosphonate): A radiopharmaceutical for skeletal and acute myocardial infarct imaging. I. Synthesis and distribution in animals. *J Nucl Med* 21: 961–966, 1980
3. BEVAN JA, TOFE AJ, BENEDICT JJ, et al: Tc-99m HMDP (hydroxymethylene diphosphonate): A radiopharmaceutical for skeletal and acute myocardial infarct imaging. II. Comparison of Tc-99m HMDP with other technetium-labeled bone-imaging agents in a canine model. *J Nucl Med* 21: 967–970, 1980
4. FRANCIS MD, FERGUSON DL, TOFE AJ, et al: Comparative evaluation of three diphosphonates: In vitro adsorption (C-14 labeled) and in vivo osteogenic uptake (Tc-99m complexed). *J Nucl Med* 21: 1185–1189, 1980.
5. FOGELMAN I, BESSENT RG, TURNER JG, et al: The use of whole-body retention of Tc-99m diphosphonate in the diagnosis of metabolic bone disease. *J Nucl Med* 19: 270–275, 1978
6. NETER J, WASSERMAN W: *Applied Linear Statistical Models.* Homewood, Richard D. Irwin, Inc., 1974, Chap. 23.
7. FOGELMAN I, BESSENT RG: What do we want from a bone-scanning agent? *J Nucl Med* 21: 296, 1980
8. SILBERSTEIN EB: A radiopharmaceutical and clinical comparison of Tc-99m-Sn-hydroxymethylene diphosphonate and Tc-99m-Sn-hyroxyethylidene diphosphonate. *Radiology* 136: 747–751, 1980

9. FOGELMAN I, GOLL C, MCKILLOP JH, et al: A clinical comparison of 2 hour and 4 hour bone scans obtained with 99m Tc-HEDP. *Eur J Nucl Med* 3: 15–17, 1978
10. FOGELMAN I, CITRIN DL, MCKILLOP JH, et al: A clinical comparison of Tc-99m HEDP and Tc-99m MDP in the detection of bone metastases: Concise communication. *J Nucl Med* 20: 98–101, 1979
11. KHEDKAR N, ARNOLD JS, MILO T, et al: Qualitative and quantitative digital comparison of Tc-99m HMDP and MDP. *J Nucl Med* 20: 655, 1979
12. FOGELMAN I: Skeletal uptake of diphosphonate: a review. *Eur J Nucl Med* 5: 473–476, 1980
13. DEUTSCH E, BARNETT BL: Synthetic and structural aspects of technetium chemistry as related to nuclear medicine. *Inorg Chem in Biology and Medicine.* ACS Symp Series No. 140, 1980, MARTELL AE, Ed
14. ARNOLD JS, BARNES WF, KHEDKAR N, et al: Kinetic studies of a new and superior Tc-99m diphosphonate bone imaging agent. *J Nucl Med* 20: 653–654, 1979
15. FOGELMAN I, CITRIN DL, TURNER JG, et al: Semi-quantitative interpretation of the bone scan in metabolic bone disease: definition and validation of the metabolic index. *Eur J Nucl Med* 4: 287–289, 1979
16. FOGELMAN I, BESSENT RG, BEASTALL G, et al: Estimation of skeletal involvement in primary hyperparathyroidism. *Ann Int Med* 92: 65–67, 1980
17. FOGELMAN I, BESSENT RG, COHEN HN, et al: Skeletal uptake of diphosphonate: method for prediction of postmenopausal osteoporosis. *Lancet* 2: 667–670, 1980
18. FOGELMAN I: The value of 24 hour skeletal uptake of diphosphonate in the exclusion of metabolic bone disease. *Nucl Med Commun* 1: 351–356, 1980

Comment

As stated in the paper there are understandable reasons for seeking relatively higher skeletal uptake of tracer - clearer delineation of the skeleton may be obtained with the likelihood of more pleasing images, and also the time required to carry out a study could be reduced. The current trend does indeed appear to be to develop bone seeking radiopharmaceuticals with higher skeletal affinity, and it has been previously shown in animal studies that the most widely used bone scanning agent methylene diphosphonate (MDP) has higher absolute skeletal uptake than hydroxyethylidene diphosphonate (HEDP) (Subramanian et al, 1975). Recently a new diphosphonate, hydroxymethylene diphosphonate (HMDP) has become available which on the basis of animal studies appears to have even higher skeletal affinity (Bevan et al, 1980). The present study is the first to quantitate the relative differences in skeletal uptake between these diphosphonates in human subjects. Striking differences in skeletal affinity were found. HMDP had the highest absolute uptake followed by MDP, and both these agents had significantly higher skeletal uptake than HEDP (assuming the distribution of tracer in soft-tissue is the same or similar in each case). These results are in keeping with the published findings from animal studies (Bevan et al, 1980) and from in vitro experiments assessing

the relative affinity of each diphosphonate for hydroxy-apatite crystals (Francis et al, 1980).

The three diphosphonates studied are structurally similar and it is clear that slight alterations in molecular structure can have a significant effect upon specificity of a diphosphonate for bone. Why this should be so is not clear, and while a possible explanation is provided, based on whether or not there is a hydroxyl group present on the central carbon atom, it must be realised that the exact method of binding between the diphosphonate molecule and bone remains incompletely understood.

The implication of higher skeletal uptake of diphosphonate for lesion detection in metastatic disease is briefly discussed and this topic is more fully dealt with in paper 15. As regards metabolic bone disease, it is suggested that metabolic features are less likely to be recognised on the bone scan image if there is higher background uptake of tracer by bone. However, this view has still to be tested by critical study. Where 24-hour whole-body retention of diphosphonate measurements are used to identify patients with increased skeletal metabolism, HEDP with its lower absolute skeletal uptake (and narrower normal range) would seem to be the agent of choice, as it provides a wider range in which to detect abnormality with less overlap between normal and abnormal. However this belief has also not been tested by critical study.

Paper 15. Diphosphonate bone scanning agents - current concepts

European Journal of Nuclear Medicine (in press)

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Purpose of Investigation

The purpose of this review is to stimulate thought and provoke discussion as to which properties are considered desirable in a bone scanning agent. My own views are presented and discussed in the context of both metastatic and metabolic bone disease. In addition, I have critically summarised the results of all comparative studies between diphosphonate bone scanning agents in clinical practice.

DIPHOSPHONATE BONE SCANNING AGENTS - CURRENT CONCEPTS

Ignac Fogelman

ABSTRACT

The bone scan is generally recognised to be an extremely powerful investigational tool in the evaluation of patients with skeletal disease. Currently Tc-99m methylene diphosphonate is the most widely used bone scanning agent, but recently several new diphosphonate compounds have been introduced which appear to have relatively higher skeletal affinity, leading to greater absolute uptake of tracer by bone. While the resulting improved contrast between bone and background soft-tissue may provide more pleasing scan images, it is not clear that increased bone uptake of tracer is equally desirable for identification of disease. Nevertheless, to date, no significant difference in lesion detection has been found in any comparative study of diphosphonate compounds.

In this review the clinical studies evaluating diphosphonate bone scanning agents are summarised and the properties required of an ideal bone scanning agent in both benign and malignant disease discussed.

INTRODUCTION

The ability to image the skeleton was dramatically transformed by the development of Tc-99m labelled polyphosphate by Subramanian and McAfee (1971). This important advance meant that a compound with high skeletal affinity could at long last be combined with a radionuclide with near ideal physical properties. Nevertheless, there was a continuing search for further improvement and several phosphate compounds rapidly became available (Subramanian et al, 1972a; Fletcher et al, 1973; Citrin et al, 1974). A Tc-99m labelled diphosphonate (hydroxyethylidene diphosphonate) bone scanning agent was independently proposed and evaluated by several groups of workers (Tofe and Francis, 1972; Castronovo and Callahan, 1972; Subramanian et al, 1972b; Yano et al, 1973). Since their introduction, cumulative experience has shown that the diphosphonates are the bone scanning agents of choice (Subramanian et al, 1972b; Silberstein et al, 1973; Pendergrass et al, 1973; Citrin et al, 1975; Fogelman et al, 1977). Currently Tc-99m methylene diphosphonate (Subramanian et al, 1975) is the most widely used bone scanning agent.

Recently, several new diphosphonate compounds have been introduced and there seems to be a trend at present amongst radiopharmaceutical companies to develop agents with relatively

higher skeletal affinity, leading to greater absolute uptake of tracer by bone. While this may lead to more pleasing images being obtained in normal subjects, due to higher bone to background ratios, it is not clear that higher bone uptake will be equally valuable in the identification of disease.

The purpose of this review is to discuss the properties required of an ideal bone scanning agent and to summarise comparative studies that have been carried out with the diphosphonate bone scanning compounds.

PROPERTIES REQUIRED OF A BONE SCANNING AGENT

The search for metastatic disease remains the most important single indication for performing a bone scan. Abnormalities in this situation are identified by the presence of focal lesions. Visualisation of a focal lesion depends upon the contrast between the lesion and the surrounding bone, that is to say the ratio of counts in the lesion to those in background bone (L/B). The contrast between bone and soft-tissue (B/ST) is important for visualisation of the skeleton itself and for a normal subject, a higher B/ST ratio will lead to an improved bone scan. However a higher B/ST ratio does not signify that lesions will be better visualised on the bone scan, nor that disorders leading to diffuse abnormality on the bone scan, such as metabolic bone disease, will be more easily identified.

It is even possible that different bone scanning agents may be preferred in various clinical situations. Where visualisation of normal skeletal anatomy is required (although the bone scan is not the technique of choice for this) high uptake of tracer throughout the skeleton is desirable. In metastatic disease the contrast between tumour and background bone is of most importance and it may be argued that if there is high background uptake of tracer then lesions may be less clearly seen against this background, unless there is even higher specific uptake of tracer by bone involved with tumour. In the metabolic bone disorders a recognition of generalised high uptake of tracer depends upon a subjective evaluation of the scan and it is also likely that this will be more difficult to recognise against high background uptake of tracer by the skeleton.

Thus if an extremely satisfactory bone scanning agent is available, then on theoretical grounds it would seem that no clear advantage is to be derived from further increasing skeletal uptake of tracer by the normal skeleton. Certainly if two bone scanning agents are to be compared in metastatic disease then a simple subjective evaluation of scan appearances or even measuring B/ST ratios is not adequate, as it does not really matter if one scan looks nicer than the other. What is relevant is lesion visualisation and the L/B ratios. Similarly, to state that one agent has faster blood clearance than another

does not imply that it is a better agent in clinical practice. If other properties are similar then the agent with higher skeletal affinity will of course have the faster blood clearance.

It should be clear that it is not possible to evaluate a bone scanning agent by randomly allocating patients with metastatic disease to one or another agent and then measuring B/ST ratios or subjectively evaluating the visual quality of these scans. Paired studies in individual patients, using both agents, should be performed. Lesion counts and L/B ratios must be obtained.

THE DIPHOSPHONATE BONE SCANNING AGENTS

(a) Tc-99m Hydroxyethylidene Diphosphonate (HEDP)

Tc-99m HEDP was the first diphosphonate to be introduced into clinical practice and is undoubtedly the diphosphonate which has been most extensively evaluated. Several early studies demonstrated that HEDP had improved biological properties, with faster blood clearance, when compared with polyphosphate or pyrophosphate (Dunson et al, 1973; Ackerhalt et al, 1974; Krishnamurthy et al, 1974; Hughes et al, 1975). Not all reports, however, were favourable. In an evaluation of 140 patient studies Nelson et al (1977) considered HEDP to be inferior to both pyrophosphate and trimetaphosphate. Also Weber et al (1976) in 90 patient studies preferred pyrophosphate to HEDP. However in both cases, evaluation was essentially based on normal scans, and paired studies using both agents in individual patients were not obtained.

Silberstein et al (1973) carried out paired studies in 10 patients with carcinoma using both HEDP and fluorine-18 and found that F-18 detected only 56% of the lesions found with HEDP. Pendergress et al (1973) reviewed their experience with over 500 scan studies using HEDP. They suggested that HEDP was more sensitive for detection of skeletal metastases than F-18.

Serafini et al (1974) compared HEDP and pyrophosphate in 18 paired studies; 7 normal subjects and 11 with lesions present on scan. In general it was felt that pyrophosphate gave more variable results and while the lesion detection rate was the same with both agents, L/B ratios were higher with HEDP in approximately half the cases. In no case was the L/B ratio higher with pyrophosphate. Silberstein et al (1978) compared HEDP and pyrophosphate in paired studies in 30 patients with carcinoma. While it was considered that there was no difference in scan quality between agents, 10 of 30 lesions detected with HEDP were not seen with pyrophosphate. Citrin et al (1975) in an excellent study of 29 patients with skeletal metastases compared HEDP, pyrophosphate and polyphosphate. All patients had studies with 2 or all 3 agents. Citrin concluded that HEDP was clearly superior to the other agents and showed that significantly higher L/B ratios were obtained with HEDP when compared with either pyrophosphate or polyphosphate. Fogelman et al (1977) confirmed these findings in a smaller study of 11 patients with metastatic disease when the quality of scan image, lesion detection and L/B ratios were

all shown to be superior with HEDP compared to pyrophosphate.

Lundell et al (1975) studied each of 9 women, who had radiologically proven metastases, with HEDP, pyrophosphate and polyphosphate. The scans were visually evaluated and while no significant difference in lesion detection was found, it was concluded that HEDP provided superior images with higher lesion to bone contrast. In addition computer quantitation of the bone scan images was obtained in 3 patients (B/ST and L/B ratios), and although these results are not presented, the authors comment that the findings were in agreement with the visual interpretation.

(b) Tc-99m Methylene Diphosphonate (MDP)

Following the introduction of Tc-99m MDP by Subramanian in 1975 (Subramanian et al, 1975), MDP is today the most widely used bone scanning agent. However Subramanian's original suggestion that MDP was superior to HEDP as a scanning agent was based on higher bone uptake in rats, higher whole-body retention of tracer in beagle dogs and faster plasma clearance in human volunteer subjects. Faster blood clearance of MDP compared to HEDP has now been confirmed by many groups (Davis and Jones, 1976; Rosenthall et al, 1977; Rudd et al, 1979). The superiority of MDP over HEDP in clinical practice has not however been established.

While Rosenthall et al (1977) in 11 volunteer and 20 patient studies found higher B/ST ratios with MDP than with HEDP, and concluded that MDP was the preferred radiopharmaceutical, only 7 patients had skeletal metastases, and in these no difference in lesion detection was found. Rudd et al (1979) carried out paired studies comparing MDP and HEDP in 10 patients (6 with carcinoma) and found higher B/ST ratios with MDP. They concluded that MDP produced superior images although no difference in lesion detection was seen. Indeed Rudd commented that in various clinical situations MDP and HEDP may have different binding mechanisms as in one patient with prostatic carcinoma a lesion was better visualised with HEDP, while in a patient with benign collapse, this was better visualised with MDP. Fogelman et al (1979) compared MDP and HEDP in paired studies in 17 patients with skeletal metastases. While no difference in the number of lesions detected was found, L/B ratios were, however, significantly higher with HEDP.

(c) Tc-99m Hydroxymethylene Diphosphonate (HMDP)

Recently a new diphosphonate, Tc-99m HMDP has become available for clinical practice. Early studies demonstrated that it had faster blood clearance (Bevan et al, 1980) and higher skeletal uptake (Bevan et al, 1980; Francis et al, 1980; Fogelman et al, 1981) than MDP.

Domstad et al (1980) randomly allocated 102 patients to either HMDP or MDP and found higher B/ST ratios with HMDP.

However overall image quality, bone delineation, soft-tissue uptake and L/B ratios were the same with both agents. Silberstein (1980) compared HMDP and HEDP in paired studies in 20 patients with carcinoma and found that HMDP provided superior images in about half the cases. Quantitative data was only available in 7 cases, and L/B ratios in 4. Only marginal differences in L/B ratios between HMDP and HEDP (although in HMDP's favour) were found. Rosenthall et al (1981) in paired studies compared HMDP and MDP in 10 volunteers and 20 patients with carcinoma and found scan quality, B/ST ratios and lesion detection to be the same. In addition no difference in blood clearance was seen between HMDP and MDP, and it was concluded that there was no significant difference between these agents.

(d) Tc-99m Dicarboxypropane Diphosphonate (DPD)

Tc-99m is the newest of the diphosphonates and as yet has not been fully evaluated. Nevertheless as with HMDP it is claimed that DPD has significantly higher skeletal uptake than MDP (Schwarz and Kloss, 1981).

Schwarz and Kloss (1981) found DPD to have 15% higher bone uptake when compared with MDP in rat studies. In addition in 300 patient studies it was considered that DPD showed superior skeletal visualisation when compared with MDP. Hale et al (1981) in 60 patient studies comparing DPD and MDP also found improved skeletal visualisation and higher B/ST ratios with DPD.

COMMENTS

There seems little doubt that the Tc-99m labelled diphosphonates deserve their virtual monopoly in the bone scanning field. Early studies exhaustively evaluated HEDP and showed it clearly superior to the other available agents such as F-18, Tc-99m pyrophosphate and polyphosphate. However later diphosphonates have not been so extensively evaluated and as can be seen from the above there is no evidence that any diphosphonate is superior to HEDP as regards lesion detection in malignancy.

In the only study comparing L/B ratios in scans obtained with both MDP and HEDP, HEDP showed higher values (Fogelman et al, 1979). Arnold et al (1978) using a computerised technique for subtracting blood and soft-tissue backgrounds from sequential images of bone, found that marked differences between the kinetic behaviour of MDP and HEDP exist, with each having different binding characteristics. It was suggested that while MDP may be the better agent for imaging the skeleton, HEDP may image osteoblastic lesions better. However, while this evidence perhaps marginally favours HEDP over MDP as regards lesion detection, HEDP is no longer commercially available and MDP is currently the most popular bone scanning agent. This is because of MDP's higher bone uptake and improved skeletal visualisation. Physicians generally seem

to have a strong preference for bone scans obtained with MDP.

In Figure 1 the relative skeletal uptake of DPD, HMDP, MDP and HEDP, obtained by the 24-hour whole-body retention of diphosphonate technique (Fogelman et al, 1978) is shown. This confirms that both DPD and HMDP do indeed have higher skeletal uptake than MDP, although there is some suggestion that DPD may have slightly higher muscle uptake than other diphosphonates (Subramanian et al, in press) and it is not clear to what extent this is reflected in the WBR results. It is still to be seen whether either or both of these newer agents will displace MDP in popularity.

It is of interest that Subramanian et al (in press) using a rabbit model where lesions were drilled in bone found lower L/B ratios with both DPD and HMDP when compared with MDP. This supports the view that the higher background bone uptake of tracer, the lower the L/B ratio is likely to be. Nevertheless it has not been shown that higher bone uptake of tracer (with the agents presently available) leads to lesions being missed in clinical practice.

Where quantitative tracer techniques such as 24-hour whole-body retention of diphosphonate measurements are used to identify patients with increased bone turnover, it has previously been suggested that HEDP with its tighter normal range at lower absolute skeletal uptake, may be the agent of choice, since it

provides a wider range in which to detect abnormality, with less overlap between normal and abnormal (Fogelman et al, 1981).

It is to be expected that there will be much academic interest when any new bone scanning agent becomes available, and there is a natural tendency amongst physicians to try something new. Also the bone scanning market is extremely large and there are commercial interests in showing that any one bone scanning agent is the 'agent of choice'. Thus any 'favourable' differences between agents are likely to be emphasised and widely proclaimed. At present there does not appear to be any significant difference amongst the diphosphonates as regards lesion detection. However, the published studies have generally evaluated gross disease and were it possible to study early metastatic involvement of the skeleton then differences between agents might emerge. The nuclear medicine community should at least reflect on what it expects from an ideal bone scanning agent, and whether continuing to search for agents with merely higher and higher bone uptake is desirable. It is possible that by increasing bone uptake of tracer further, a significant reduction in lesion detection could occur because of reduced contrast between lesions and high background activity. Nevertheless at the present time this does not appear to be a real concern, and all the diphosphonates available appear to be excellent bone scanning agents.

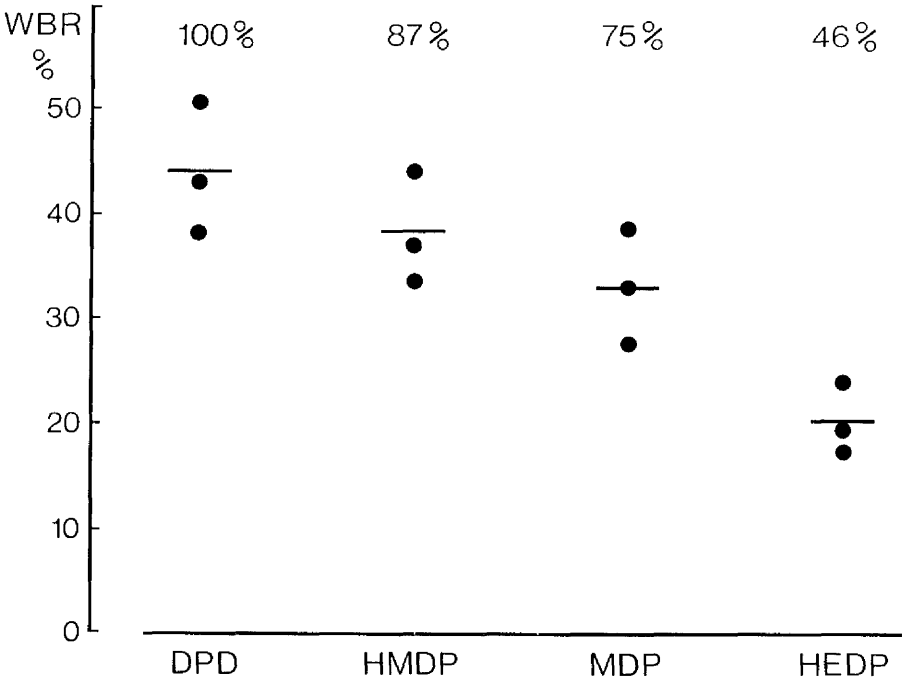

Figure 1

Twenty-four hour whole-body retention of diphosphonate measurements in 3 volunteer subjects showing the relative skeletal uptakes of Tc-99m DPD (taken as 100%), HMDP, MDP and HEDP.

REFERENCES

Ackerhalt R E, Blau M, Bakshi S, Sondel J A (1974).
A comparative study of three 99m Tc-labeled phosphorus compounds and 18F-fluoride for skeletal imaging.
J Nucl Med 15, 1153-1157.

Arnold J S, Barnes W E, Khedkar N, Nelson M (1978).
Computerized kinetic analysis of two 99m-Tc-Sn-diphosphonates demonstrating different binding characteristics (Abstract). AJR 131, 553.

Bevan J A, Tofe A J, Benedict J J, Francis M D, Barnett B L (1980).
Tc-99m HMDP (Hydroxymethylene Diphosphonate): A radiopharmaceutical for skeletal and acute myocardial infarct imaging. 1. Synthesis and distribution in animals. J Nucl Med 21, 961-966.

Castronovo F P, Callahan R J (1972). New bone scanning agent: 99m Tc labeled 1-hydroxyethylidene-1, 1-disodium phosphonate.
J Nucl Med 13, 823-827.

Citrin D L, Bessent R G, Greig W R (1974). Clinical evaluation of 99m Tc-labeled monofluorophosphate: A comparison with ethane-hydroxy-diphosphonate. J Nucl Med 15, 1110-1112.

Citrin D L, Bessent R G, Tuohy J B, Elms S T, McGinley E, Greig W R, Blumgart L H (1975).
A comparison of phosphate bone-scanning agents in normal subjects and patients with malignant disease. Br J Radiol 48, 118-121.

Davis A G, Jones A G (1976). Comparison of 99m Tc-labeled phosphate and phosphonate agents for skeletal imaging.
Semin Nucl Med 6, 19-31.

Domstad P A, Coupal J J, Kim E E, Blake J S, DeLand F H (1980).
99m Tc-Hydroxymethane diphosphonate: A new bone imaging agent with a low tin content. Radiology 136: 209-211.

Dunson G L, Stevenson J S, Cole C M, Mellor M K, Hosain F (1973).
Preparation and comparison of technetium-99m diphosphonate, polyphosphate and pyrophosphate in nuclear bone imaging radiopharmaceuticals. Drug Intell Clin Pharm 7, 470-474.

Fletcher J W, Solaric-George E, Henry R E, Donati R M (1973).
Evaluation of 99m Tc-pyrophosphate as a bone imaging agent.
Radiology 109, 467-469.

Fogelman I, McKillop J H, Citrin D L (1977). A clinical comparison of 99m Tc-hydroxyethylidene diphosphonate (H.E.D.P.) and 99m Tc-pyrophosphate in the detection of bone metastases. Clin Nucl Med 2, 364-367.

Fogelman I, Bessent R G, Turner J G, Citrin D L, Boyle I T, Greig W R (1978).
The use of whole-body retention of Tc-99m diphosphonate in the diagnosis of metabolic bone disease. J Nucl Med 19, 270-275.

Fogelman I, Citrin D L, McKillop J H, Turner J G, Bessent R G (1979). A clinical comparison of 99m Tc-HEDP and 99m Tc-MDP in the detection of bone metastases: concise communication. J Nucl Med 20, 98-101.

Fogelman I, Pearson D W, Bessent R G, Tofe A J, Francis M D (1981). A comparison of skeletal uptake of three diphosphonates by whole-body retention: concise communication. J Nucl Med 22, 880-883.

Francis M D, Ferguson D L, Tofe A J, Bevan J A, Michaels S E (1980). Comparative evaluation of three diphosphonates: in vitro adsorption (C-14 labeled) and in vivo osteogenic uptake (Tc-99m complexed). J Nucl Med 21, 1185-1189.

Hale T I, Jucker A, Vgenopoulos K, Sauter B, Wacheck W, Bors L (1981). Clinical experience with a new bone seeking 99m Tc radiopharmaceutical. Nuc Compact 12, 54-55.

Hughes S P F, Jeyasingh K, Lavender P J (1975). Phosphate compounds in bone scanning. J Bone Joint Surg 57B, 214-216.

Krishnamurthy G T, Tubis M, Endow J S, Singhi V, Walsh C F, Blahd W H (1974).
Clinical comparison of the kinetics of 99m Tc-labeled polyphosphate and diphosphonate. J Nucl Med 15, 848-855.

Lundell G, Marell E, Backstrom A, Casseborn S, Ruden B-I (1975). Bone scanning with $^{99}Tc^{m}$ compounds in metastasizing mammary carcinoma. Acta Radiol Ther Phys Biol 14, 333-336.

Nelson M F, McKee L C, Van Wazer J R (1977). Clinical evaluation of some phosphorus bone-imaging agents: concise communication. J Nucl Med 18, 566-569.

Pendergrass H P, Potsaid M S, Castronovo F P (1973). The clinical use of 99m Tc-diphosphonate (HEDSPA). Radiology 107, 557-562.

Rosenthall L, Arzoumanian A, Lisbona R, Itoh K (1977). A longitudinal comparison of the kinetics of 99m Tc-MDP and 99m Tc-HEDP in humans. Clin Nucl Med 2, 232-234.

Rosenthall L, Arzoumanian A, Damtew B, Tremblay J (1981). A crossover study comparing Tc-99m-labeled HMDP and MDP in patients. Clin Nucl Med 6, 353-355.

Rudd T G, Allen D R, Smith F D (1979). Technetium-99m-labeled methylene diphosphonate and hydroxyethylidine diphosphonate-biologic and clinical comparison: concise communication. J Nucl Med 20, 821-826.

Schwarz A, Kloss G (1981). Technetium-99m DPD - A new skeletal imaging agent (Abstract). J Nucl Med 22, 77.

Serafini A N, Watson D D, Nelson J P, Smoak W M (1974) Bone scintigraphy - comparison of 99m Tc-polyphosphate and 99mTc-diphosphonate. J Nucl Med 15, 1101-1104.

Silberstein E B, Saenger E L, Tofe A J, Alexander G W, Park H-M (1973). Imaging of bone metastases with 99m Tc-Sn-EHDP (diphosphonate), 18F, and skeletal radiography. A comparison of sensitivity. Radiology 107, 551-555.

Silberstein E B, Maxon H R, Alexander G W, Rauf C, Bahr G K (1978). Clinical comparison of technetium-99m diphosphonate and pyrophosphate in bone scintigraphy: concise communication. J Nucl Med 19, 161-163.

Silberstein E B (1980). A radiopharmaceutical and clinical comparison of 99mTc-Sn-hydroxymethylene diphosphonate with 99mTc-Sn-hydroxyethylidene diphosphonate. Radiology 136, 747-751.

Subramanian G, McAfee J G (1971). A new complex of 99mTc for skeletal imaging. Radiology 99, 192-196.

Subramanian G, McAfee J G, Bell E G, Blair R J, O'Mara R E, Ralston P H (1972a). 99mTc-labeled polyphosphate as a skeletal imaging agent. Radiology 102, 701-704.

Subramanian G, McAfee J G, Blair R J, Mehter A, Connor T (1972b) 99mTc-EHDP: a potential radiopharmaceutical for skeletal imaging. J Nucl Med 13, 947-950.

Subramanian G, McAfee J G, Blair R J, Kallfelz F A, Thomas F D (1975). Technetium-99m-methylene diphosphonate - A superior agent for skeletal imaging: Comparison with other technetium complexes. J Nucl Med 16, 744-755.

Subramanian G, McAfee J G, Thomas F D, Feld T, Zapf-Longo C, Palladino E (in press). Localization of new Tc-99m labeled diphosphonates in experimental bone lesions. In: Proceedings of 19th International Annual Meeting of the Society of Nuclear Medicine Europe.

Tofe A J, Francis M D (1972). In vitro optimization and organ distribution studies in animals with the bone scanning agent 99mTc-Sn-EHDP (Abstract). J Nucl Med 13, 472.

Weber D A, Keyes J W, Wilson G A, Landman S (1976). Kinetics and imaging characteristics of 99mTc-labeled complexes used for bone imaging. Radiology 120, 615-621.

Yano Y, McRae J, Van Dyke D C, Anger H O (1973). Technetium-99m-labeled stannous ethane-1-hydroxy-1 1-diphosphonate: a new bone scanning agent. J Nucl Med 14, 73-78.

Comment

When Tc-99m hydroxyethylidene diphosphonate (HEDP) was first introduced it was extensively evaluated and clearly shown to be superior to the other bone scanning agents available at that time as regards lesion detection and quality of scan image. However, since the introduction of methylene diphosphonate (MDP), and its almost instant success, HEDP is no longer commercially available. MDP was not as extensively evaluated as HEDP, and has not been shown to be superior to HEDP as regards lesion detection. In addition in the only study comparing lesion to bone (L/B) ratios (a measure of how well a lesion will be seen against background bone), HEDP was found to have higher values (see paper 13). This finding has been confirmed by Pauwels (personal communication) and is in keeping with the kinetic data from Arnold et al (1978). Further Subramanian et al (in press) using a rabbit model with lesions drilled in bone showed that the diphosphonates with higher skeletal uptake had lower L/B ratios. Thus higher uptake of tracer by bone may not in itself be a desirable goal as regards lesion detection, although with the agents presently available there does not appear to be any significant difference in clinical performance. However, it is possible that the studies to date are too crude and were it possible to study very early metastatic

involvement of the skeleton then subtle differences between agents might emerge.

As stated in the paper, when comparing two bone scanning agents in metastatic disease, paired studies in individual subjects are required and simple subjective evaluation of scan images or even measuring bone to background soft-tissue activity is not adequate. What is relevant is lesion visualisation and the L/B ratios. It does not matter if one agent produces particularly pleasing images in normal subjects but it does matter if that agent is less likely to detect early metastatic disease.

SUMMARY

CHAPTER 5

COMPARISON OF THE AVAILABLE DIPHOSPHONATE BONE SCANNING AGENTS

This chapter deals with clinical comparisons between the available diphosphonate bone scanning agents both in metastatic and benign disease.

Paper 13 presents a comparison of Tc-99m methylene diphosphonate (MDP) and Tc-99m hydroxyethylidene diphosphonate (HEDP) in patients with metastatic disease. While no difference in lesion detection was found, it was commented upon that higher lesion to bone ratios were obtained with HEDP than with MDP, even although MDP showed higher contrast between bone and surrounding soft-tissue. It was suggested that for identification of metastatic disease, the agent with higher lesion to bone ratios may be superior, as there is greater contrast between the lesion and surrounding bone.

The results of a study comparing three different diphosphonates, hydroxymethylene diphosphonate (HMDP), MDP and HEDP in volunteer subjects, using the 24-hour whole-body retention of diphosphonate technique are presented in paper 14. Striking differences in relative skeletal affinity are found with HMDP >MDP >HEDP. It was suggested that higher skeletal uptake of radiopharmaceutical may make it more difficult to recognise metabolic features on the scan image, but this has not yet been proven by critical study. Similarly where 24-hour whole-body retention

measurements are used to identify patients with increased skeletal metabolism it is argued that lower mean skeletal uptake of tracer and narrower range in normal subjects may be an advantage, but again this remains to be shown by critical study.

The question of whether high skeletal uptake of tracer is desirable for lesion detection in metastatic disease is once again raised in paper 15, and it was suggested that theoretically a point may be reached when a fall off in detection could occur if tracer uptake were further increased. The desirable properties for a bone scanning agent in clinical practice are discussed and the relevant investigations for any comparison between radiopharmaceuticals in metastatic disease are suggested. The published studies comparing diphosphonate bone scanning agents in clinical practice are then critically reviewed. It was found that while HEDP had been extensively evaluated and shown to be clearly superior to the other available bone scanning agents at that time, subsequent diphosphonates have been less extensively evaluated and in clinical practice no difference has been shown between agents as regards lesion detection in metastatic disease.

CHAPTER 6

STUDIES WITH THE TECHNIQUE OF 24-HOUR WHOLE-BODY RETENTION OF DIPHOSPHONATE IN CLINICAL PRACTICE

In this chapter, three papers (16-18) are presented which illustrate the application of the technique of 24-hour whole-body retention of Tc-99m diphosphonate in clinical practice.

Paper 16. Estimation of skeletal involvement in primary hyperparathyroidism. Use of 24-hour whole-body retention of technetium-99m diphosphonate (1980)
Annals of Internal Medicine 92: 65-67
I Fogelman, R G Bessent, G Beastall, I T Boyle

Purpose of Investigation

Primary hyperparathyroidism is being diagnosed with increasing frequency with the advent of routine serum calcium estimations and sensitive parathyroid hormone assays. The majority of patients with this condition are asymptomatic and it is uncommon nowadays for patients to have skeletal complaints. Nevertheless bone histology demonstrates increased bone turnover in a high percentage of cases. The purpose of this study was to assess whether measurements of 24-hour whole-body retention of diphosphonate (WBR) could be used to identify altered skeletal metabolism in patients with primary hyperparathyroidism and whether the WBR results would correlate with serum alkaline phosphatase and parathyroid hormone levels, conventional biochemical markers of disease activity. In addition WBR measurements were obtained in several patients pre and post parathyroidectomy to assess whether alterations in skeletal metabolism could be documented in sequential studies.

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Estimation of Skeletal Involvement in Primary Hyperparathyroidism

Use of 24-Hour Whole-Body Retention of Technetium-99m Diphosphonate

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The 24-h whole-body retention of technetium-99m diphosphonate was elevated in 16 patients with primary hyperparathyroidism (mean whole body retention, 50.6%, compared to controls, 19.4%), with each result out of the control range. There was a rank correlation between whole-body retention and plasma parathyroid hormone ($r = 0.86, P < 0.001$) but the correlation with serum alkaline phosphatase and calcium values was less significant ($r = 0.58, P < 0.05$ in each case). Repeat studies of whole body retention performed in five patients before and after parathyroidectomy showed a fall to normal or near normal values. Measurement of 24-h whole-body retention of diphosphonate is a simple, sensitive test to aid in the diagnosis and evaluation of patients with primary hyperparathyroidism. The test could be used as a screening procedure in patients with recurrent renal stones, for example, or to assess the extent of skeletal involvement in patients with an established diagnosis.

In primary hyperparathyroidism it is unusual for patients to present with skeletal complaints, but on histologic examination of biopsy specimens from such patients, there is evidence of skeletal involvement in virtually all cases (1). Even though 50% of these patients may show nonspecific generalised osteopenia on conventional radiologic examination, more specific changes (for example, subperiosteal resorption of phalanges, absence of lamina dura, brown tumours, or cysts), are seen in only 10% of cases (2).

The current bone-seeking radiopharmaceutical agents are very sensitive for skeletal abnormality, and several groups have assessed the role of bone scanning in primary hyperparathyroidism (3-5). However, the bone scan appearances are nonspecific and, although we have found them to be abnormal in 50% of cases of primary hyperparathyroidism (6), it has been suggested that the bone scan is not as sensitive as routine radiologic examination in this condition (4). The major limitation of bone scanning in metabolic bone disease, where the whole skeleton is diffusely involved by a metabolic process, is that an awareness of "abnormality" depends on a subjective impression of increased tracer uptake by the skeleton, and the scan image may often appear indistinguishable from a normal image. However, in primary hyperparathyroidism the rate of bone turnover is increased and this should be detectable if total skeletal uptake of the radiopharmaceutical agent could be quantitated accurately, as uptake is believed to depend on osteoblastic activity and to a lesser extent on skeletal vascularity (7).

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Using a shadow-shield whole-body monitor we have previously shown that measurement of 24-h whole-body (skeletal) retention of technetium-99m (^{99m}Tc) diphosphonate can differentiate patient groups with renal osteodystrophy, osteomalacia, Paget's disease, and primary hyperparathyroidism from a control population (8). Our findings using this technique in 16 patients with primary hyperparathyroidism, five of whom were studied before and after parathyroidectomy, are described.

Patients and Methods

Sixteen patients with primary hyperparathyroidism were studied (Table 1). Histologic confirmation of a parathyroid adenoma was obtained in 12 patients, and one patient was found to have parathyroid carcinoma. Two patients (Patients 1 and 5) had hypercalcaemia with elevated parathyroid hormone values and are currently being considered for surgery. Patient 2 has been intermittently hypercalcaemic over the past 3 years and recently has had increasing levels of parathyroid hormone. However, he has no symptoms attributable to hypercalcaemia and, as he has severe ischaemic heart disease, surgery has not been recommended.

Our control range for whole-body retention of ^{99m}Tc diphosphonate was obtained in 111 healthy volunteers (age range, 20 to 66 years) who had no history of skeletal disease, gastrointestinal disorders, or renal impairment.

Serum calcium, inorganic phosphate, and alkaline phosphatase were estimated in all patients with standard techniques used by the Department of Clinical Biochemistry in the Royal Infirmary, Glasgow. Plasma parathyroid hormone (PTH) (immunoreactive PTH) was measured by a double antibody radioimmunoassay adapted from the method of Conaway and Anast (9) (normal range undetectable to 600 ng/L). Any detectable immunoreactive PTH in peripheral blood is considered as inappropriate in hypercalcaemic patients (10).

Radiologic skeletal surveys were obtained in all patients and were assessed for the standard radiologic features associated with hyperparathyroidism (11).

Each subject was given an intravenous bolus of 50 μCi of ^{99m}Tc hydroxyethylidene diphosphonate (HEDP) and the whole-body count was measured at 5 min and again at 24 h after injection, using a standard shadow-shield whole-body monitor. Twenty-four-hour whole-body retention of the radiopharmaceutical agent was calculated after appropriate background substraction by taking the 5-min count as 100% and correcting for radioactive decay. Five patients (Patients 3, 4, 8, 10, and 15) had whole-body retention studies performed before and after parathyroidectomy.

Technetium-99m HEDP is either taken up by the skeleton or totally excreted via the urinary tract (12), and usually approximately 70% of an intravenously administered dose is excreted via the urinary tract within 6 h of injection (13). Therefore, the value for whole-body retention of ^{99m}Tc HEDP at 24 h almost entirely represents skeletal uptake of radiopharmaceutical agent.

All correlations between values were performed using the Spearman rank correlation test.

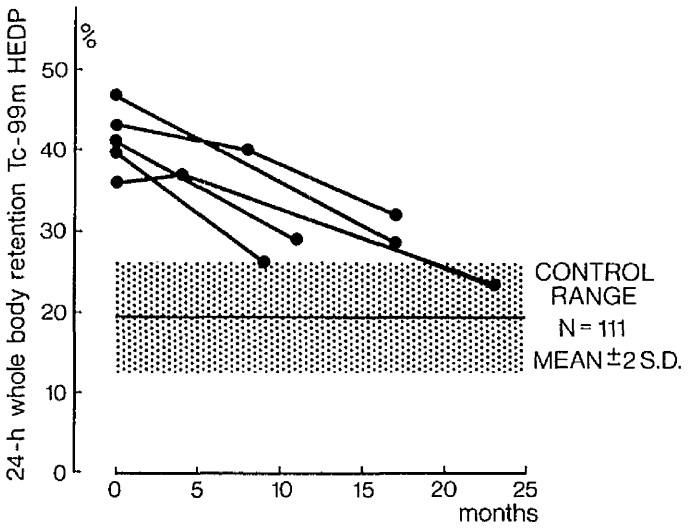

Figure 1: Results for 24-h whole-body retention of technetium-99m hydroxyethylidone diphosphonate *(HEDP)* before and after parathyroidectomy. Stippled area is control range.

Results

Results for serum calcium, inorganic phosphate, alkaline phosphatase, plasma PTH, and radiologic tests are shown in Table 1. The mean whole-body retention of ^{99m}Tc HEDP for the control group of 111 subjects (age range, 20 to 66 years) was 19.37% ± 3.37 (1 SD). We have taken our control range for whole-body retention to be 12.6% to 26.1% (that is, mean ± 2 SD). The mean whole-body retention for the primary hyperparathyroidism group was 50.6%. Results for whole-body retention for individual patients with primary hyperparathyroidism are shown in Table 1. Each patient result lay outside the control range. The following correlations were found between whole-body retention of ^{99m}Tc HEDP and plasma immunoreactive PTH, serum alkaline phosphatase, and serum calcium: $r = 0.86$, $P < 0.001$; $r = 0.58$, $P < 0.05$; and $r = 0.58$, $P < 0.05$, respectively. Figure 1 shows the results for whole-body retention, obtained before and after parathyroidectomy in five patients.

Discussion

Of the 16 patients with primary hyperparathyroidism, routine radiologic tests showed evidence of skeletal disease in only two cases, and alkaline phosphatase values were within the normal range in eight subjects. However, the 24-h whole-body retention of ^{99m}Tc diphosphonate was abnormal in all subjects.

These are preliminary results in a relatively small group of patients and it will be necessary to study larger numbers, particularly those with "borderline" hypercalcaemia to establish whether this test can reliably identify those with primary hyperparathyroidism. It is still to be proved that a normal result for whole-body retention excludes this condition as a diagnosis, but if this were so then many patients may be spared prolonged and costly investigation.

Even though this test provides a sensitive means of detecting conditions with increased bone turnover (8) such as primary hyperparathyroidism, an abnormal result does not of itself identify any specific condition, and further investigation will be required to define the particular disease state.

The repeat studies in five patients before and after parathyroidectomy have shown a fall to normal or near normal values for diphosphonate retention in all cases, but it is clear that a considerable period of time is required

Table 1. Patients with Primary Hyperparathyroidism

Patient	Sex	Age	Parathyroid Adenoma Removed	Serum Calcium (Normal, 2.2 to 2.6)	Serum Alkaline Phosphatase (Normal, 80 to 280)	Parathyroid Hormone (Normal, <600)	Whole-Body Retention (Normal, <26)	Radiologic Findings
		yr		*mmol/L*	*U/L*	*ng/L*	*%*	
1	F	73	No	2.78	223	660	32.8	Normal
2	M	67	No	2.75	252	240	29.3	Normal
3	F	57	Yes	2.86	400	540	35.7	Normal
4	M	53	Yes	3.07	246	1150	46.9	Normal
5	F	58	No	2.68	265	670	29.5	Normal
6	F	74	Yes	2.67	1822	3100	85.9	Evidence of hyperparathyroidism
7	M	52	Yes	2.97	259	470	35.0	Normal
8	F	59	Yes	2.83	153	1130	40.7	Normal
9	F	43	Yes—parathyroid carcinoma	3.54	2723	5000	86.9	Evidence of hyperparathyroidism
10	F	64	Yes	2.88	590	800	70.8	Normal
11	F	53	Yes	2.96	339	1200	70.8	Normal
12	F	60	Yes	2.42	245	440	27.1	Normal
13	F	66	Yes	2.87	455	700	55.1	Normal
14	F	80	Yes	3.12	390	550	48.4	Normal
15	F	62	Yes	2.75	284	760	43.0	Normal
16	F	77	Yes	3.3	231	1200	72.3	Normal

(probably 1 to 2 years) before the skeleton returns to "normal" metabolic activity.

Technetium-99m diphosphonate is believed to be adsorbed on to hydroxyapatite crystals in bone (14), but the factors affecting the rate of uptake have not been clearly defined. It seems likely that osteoblastic activity and vascularity are the main factors involved, however, and measurement of 24-h whole-body retention of ^{99m}Tc diphosphonate may provide a dynamic test of skeletal metabolism. We have found a positive correlation between plasma PTH, serum alkaline phosphatase values, and 24-h whole-body retention of diphosphonate. Although the exact significance of this finding is unclear, these results do support the view that the skeletal uptake of diphosphonate is proportionately related to metabolic activity as in hyperparathyroidism increased production of immunoreactive PTH is the prime factor promoting bone resorption and alkaline phosphatase is regarded as a marker for the compensatory increase in activity of the bone-forming osteoblasts. The absolute values for 24-h whole-body retention of ^{99m}Tc diphosphonate may reflect the severity of skeletal disease in primary hyperparathyroidism because, in general terms, the higher the immunoreactive PTH and alkaline phosphatase values the higher is the value for whole-body retention.

Measurement of 24-h whole-body retention of ^{99m}Tc diphosphonate is a simple, sensitive (but not specific) test in the diagnosis and evaluation of patients with suspected primary hyperparathyroidism. It may be of value in individual patients to detect skeletal abnormality and to assess the severity of bone involvement, identifying those who are at risk of developing severe postoperative hypocalcaemia and who might benefit from preoperative treatment with an active metabolite of vitamin D (15). The technique also has potential value as a screening procedure—for example, in patients with recurrent renal stones because there is up to a 10% incidence of primary hyperparathyroidism (16) associated with this condition and measurement of 24-h whole-body retention of ^{99m}Tc diphosphonate may identify those patients.

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References

1. PARFITT AM. The actions of parathyroid hormone on bone: relation to bone remodeling and turnover, calcium homeostasis, and metabolic bone disease. *Metabolism.* 1976;**25:**1033-69.
2. GENANT HK, HECK LL, LANZI LH, ROSSMANN K, HORST JV, PALOYAN E. Primary hyperparathyroidism: a comprehensive study of clinical, biochemical and radiographic manifestations. *Radiology.* 1973;**109:**513-24.
3. SY WM. Bone scan in primary hyperparathyroidism. *J Nucl Med.* 1974;**15:**1089-91.
4. WIEGMANN T, ROSENTHALL L, KAYE M. Technetium-99m-pyrophosphate bone scans in hyperparathyroidism. *J Nucl Med.* 1977;**18:**231-5.
5. KRISHNAMURTHY GT, BRICKMAN AS, BLAHD WH. Technetium-99m-Sn-pyrophosphate pharmacokinetics and bone image changes in parathyroid disease. *J Nucl Med.* 1977;**18:**236-42.
6. FOGELMAN I, CARR D. Comparison of bone scanning and radiology in the evaluation of patients with metabolic bone disease. *Clin Radiol.* In press.
7. JONES AG, FRANCIS MD, DAVIS MA. Bone scanning: radionuclide reaction mechanisms. *Semin Nucl Med.* 1976;**6:**3-18.
8. FOGELMAN I, BESSENT RG, TURNER JG, CITRIN DL, BOYLE IT, GREIG WR. The use of whole-body retention of Tc-99m diphosphonate in the diagnosis of metabolic bone disease. *J Nucl Med.* 1978;**19:**270-5.
9. CONAWAY HH, ANAST CS. Double-antibody radioimmunoassay for parathyroid hormone. *J Lab Clin Med.* 1974;**83:**129-38.
10. POSEN S, KLEEREKOPER M, INGHAM JP, HIRSHORN JE. Parathyroid hormone assay in clinical decision-making. *Brit Med J.* 1976;**1:**16-19.
11. HODSON CJ. Endocrine and metabolic bone disease. In: SUTTON D, ed. *Textbook of Radiology.* London: Churchill Livingston, 1975:183-204.
12. MCDOUGALL IR, CITRIN DL. Bone scanning: the current position. *Scot Med J.* 1975;**20:**149-151.
13. CITRIN DL, BESSENT RG, MCGINLAY E, GORDON D. Dynamic studies with ^{99m} Tc-HEDP in normal subjects and in patients with bone tumours. *J Nucl Med.* 1975;**16:**886-90.
14. FRANCIS MD. The inhibition of calcium hydroxyapatite crystal growth by polyphosphonates and polyphosphates. *Calcif Tissue Res.* 1969;**3:**151-62.
15. BOYLE IT, FOGELMAN I, BOYCE B, et al. 1-hydroxyvitamin D_3 in primary hyperparathyroidism. *Clin Endocrinol.* 1977;**7:**(Suppl):215s-22s.
16. HALL R, ANDERSON J, SMART GA, BESSER M. Parathyroid glands and calcium metabolism. In: *Fundamentals of Clinical Endocrinology.* London: Pitman Medical; 1975:381-422.

Comment

In the present study all 16 patients with primary hyperparathyroidism had elevated values for 24-hour whole-body retention of diphosphonate (WBR). However radiological evidence of hyperparathyroidism was seen in only two patients, and serum alkaline phosphatase values were elevated in eight. An elevated WBR result is however non-specific (see paper 9) and this technique does not provide a diagnostic test for primary hyperparathyroidism. Nevertheless WBR could be used as a screening procedure in populations where there is known to be an increased incidence of primary hyperparathyroidism, for example, in subjects with recurrent renal stones. A normal result for WBR makes a diagnosis of primary hyperparathyroidism extremely unlikely, although larger studies would be required to define the extent of overlap of results, if any, with control subjects. WBR also provides a means of assessing patients with extensive skeletal involvement who may be at risk of developing profound hypocalcaemia post-operatively. However in view of the good correlations found between WBR and plasma parathyroid hormone and alkaline phosphatase levels, perhaps this information could be obtained more easily from these results.

This study is the first to document change in WBR results in sequential studies in individual patients. In the five patients studied pre and post parathyroidectomy WBR values fell to or towards normal with time after operation. It was suggested from these results that a considerable period of time is required, of the order of 1 to 2 years, before the skeleton returns to "normal" levels of metabolic activity following definitive treatment for primary hyperparathyroidism.

Paper 17. The value of 24 hour skeletal uptake of diphosphonate in the exclusion of metabolic bone disease (1980)

Nuclear Medicine Communications 1: 351-356

I Fogelman

Purpose of Investigation

This short communication presents four case histories which illustrate potential clinical applications of the 24-hour whole-body retention of diphosphonate technique in the exclusion of metabolic bone disease.

THE VALUE OF 24 HOUR SKELETAL UPTAKE OF DIPHOSPHONATE IN THE EXCLUSION OF METABOLIC BONE DISEASE

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Summary

Measurement of 24 hour skeletal retention of technetium-99m diphosphonate is a new test which provides a sensitive means of detecting increased skeletal metabolism. Four patients are presented where this test was of predictive value in excluding the presence of metabolic bone disease. In all patients bone histology was normal and it is suggested that in many such cases a normal value for diphosphonate retention will reduce the extent and duration of investigation required.

Introduction

Once the possibility of a metabolic bone disorder (eg osteomalacia) has been raised in a patient it is often difficult to prove or disprove this without resorting to a bone biopsy. In addition to diagnosis, bone histomorphometry provides a means of studying the pathophysiology of disease and the response of the skeleton to therapy. However bone biopsy is an invasive procedure which provides information pertinent to only a small area of bone which may not be representative of the skeleton as a whole and a simple 'dynamic' test of total skeletal metabolism is clearly desirable.

We have recently shown that measurement of 24 hour whole-body retention (WBR) of technetium-99m diphosphonate provides a sensitive means of detecting patients with increased bone turnover (1, 2) and this communication illustrates 4 cases from clinical practice where the knowledge that the WBR result was in the normal range was of predictive value in excluding the presence of metabolic bone disease.

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Method

24 Hour Whole-Body Retention of Technetium-99m Diphosphonate

Each subject was given an intravenous bolus of 50 uCi of technetium-99m hydroxyethylidene diphosphonate (HEDP) and the whole-body count was measured at 5 minutes and again 24 hours after injection using a standard shadow shield whole-body monitor. Twenty-four hour WBR of radiopharmaceutical was calculated after appropriate background subtraction by taking the 5 minute count as 100% and correcting for radioactive decay.

Technetium-99m HEDP is either taken up by the skeleton or else totally excreted via the urinary tract (3) and usually approximately 70% of an intravenously administered dose is excreted via the urinary tract within 6 hours of injection (4). Therefore, the value of WBR of technetium-99m HEDP at 24 hours almost entirely represents skeletal uptake of radiopharmaceutical.

Patient 1

SJ, a 20 year old Pakistani male presented with a 2 year history of muscular pains and on examination had generalised bone and muscle tenderness. Although routine biochemistry (including serum calcium and alkaline phosphatase) was normal, he did belong to an at risk population (5) and because of the clinical findings, it was felt important to exclude osteomalacia. Twenty-four hour WBR of diphosphonate was normal at 23.7% (normal<26%) and the bone biopsy was also subsequently reported as normal. While this patients symptoms could not be fully explained it was considered that no organic disease was present.

Patient 2

MC, a 55 year old Religious Sister gave a 6 year history of vague aches and pains in her knees and lower back. Radiology showed osteoarthritic changes at these sites but initial biochemical screening revealed a low serum calcium at 2.1 mmol/l (normal 2.2-2.6) with normal serum albumin and alkaline phosphatase values. The 25-hydroxyvitamin D level was found to be low at 3.9 ng/l (normal 4-20)

and while clinically there was no bone or muscle tenderness it was once again considered important to exclude osteomalacia. The WBR was normal at 21.3% and no abnormality was detected on bone histology.

Patient 3

HT, a 37 year old overseas PhD student attended a health centre complaining of back pain. Radiology revealed a collapsed mid-thoracic vertebra, and raised the possibility of generalised osteopenia of the spine but there was some disagreement as regards this. Idiopathic osteoporosis, or increased bone turnover related to other diseases (eg tumour or primary hyperparathyroidism) were considered as possible diagnoses. Biochemical investigations (including thyroid function tests and parathyroid hormone estimation), radionuclide bone scan, bone biopsy and WBR (15.5%) were all normal. Subsequent history from the patient revealed that he had been electrocuted 10 years previously when he touched a 'live' gate and it is therefore likely that his vertebral collapse was an isolated incident due to unusually forcible involuntary muscular contraction.

Patient 4

AT, a 19 year old girl was referred with a 3 year history of recurrent renal colic and the finding of intermittently elevated serum calcium values. We were unable to confirm hypercalcaemia (although calcium values were persistently in the high normal range at 2.55 mmol/l) and skeletal radiology, parathyroid hormone values and cervical venous parathyroid hormone localisation studies, and all other biochemical parameters were normal. WBR (17.9%) and bone biopsy findings were also normal. After prolonged and very detailed investigations, it was felt that this girl did not have primary hyperparathyroidism.

Discussion

Twenty-four hour whole-body retention (WBR) of technetium-99m diphosphate provides a sensitive measure of skeletal metabolism but is non-specific and where an abnormal result is obtained, further investigation will be required to elucidate the problem. The most common cause of an elevated result for WBR, especially in the elderly, is

Paget's disease. A normal result will exclude certain conditions eg osteomalacia, renal osteodystophy, polyostotic Paget's disease and probably hyperparathyroidism (but this has still to be clearly established) (2). This potential role for WBR in excluding metabolic bone disease is illustrated by the 4 case histories presented. Patient 1 was an Asian with a history and clinical features suggestive of osteomalacia, but normal biochemistry. Patient 2, on the other hand, had some biochemical findings (low serum calcium and 25-hydroxyvitamin D values) which were in keeping with a diagnosis of osteomalacia but the clinical findings were unconvincing. Patient 3 was an unusual case where a young man presented with backache and radiology of his spine revealed a collapsed vertebra and possible osteopenia. It was initially suggested that he may have primary osteoporosis but it was considered important to exclude conditions associated with increased bone turnover. All investigations were negative and with the history of previous electrocution it was felt that his vertebral collapse was likely to have been an isolated incident due to unusually forcible involuntary muscular contraction. Patient 4 represents a not uncommon problem in clinical practice - where serum calcium measurements are borderline or intermittently elevated with parathyroid hormone values in the normal range. In this situation the knowledge that there is, or is not, increased bone turnover present may be of value in the assessment of a patient with suspected primary hyperparathyroidism.

In the United Kingdom there remains a significant problem with osteomalacia particularly amongst the Asian population (5, 6) and the elderly (7, 8). Patients who present with a fractured neck of femur may in addition to osteoporosis have associated osteomalacia (9). In many such 'at risk' patients osteomalacia is often considered but a bony biopsy is eventually required to establish or exclude this diagnosis. Primary hyperparathyroidism is a relatively common condition and is being diagnosed more frequently with

routine serum calcium measurements and the increasing availability of sensitive parathyroid hormone assays (10). However, as mentioned previously, in those patients with borderline serum calcium values there may be difficulty in establishing a diagnosis. In all such cases, or where metabolic bone disease (associated with increased bone turnover) is suspected, 24 hour WBR of diphosphonate can be of value as a screening test, and if normal will reduce the duration and extent of investigation required.

References

1 Fogelman I, Bessent R G, Turner JG, Citrin D L, Boyle I T, Greig W R.
The Use of Whole-Body Retention of Tc-99m Diphosphonate in the Diagnosis of Metabolic Bone Disease.
J Nucl Med 1978; 19: 270.

2 Fogelman I, Bessent R G, Beastall G, Boyle I T.
Estimation of Skeletal Involvement in Primary Hyperparathyroidism.
Ann Int Med 1980; 92: 65.

3 McDougall I R, Citrin D L.
Bone Scanning: The Current Position.
Scott Med J 1975; 20: 149.

4 Citrin D L, Bessent R G, McGinley E, Gordon D.
Dynamic Studies with 99m Tc-HEDP in Normal Subjects and in Patients with Bone Tumours.
J Nucl Med 1975; 16: 886.

5 Dunnigan M G, Paton J P J, Haase S, McNicol G W, Gardner M D, Smith C M.
Late Rickets and Osteomalacia in the Pakistan Community of Glasgow.
Scot Med J 1962; 7: 159.

6 Holmes A M, Enoch B A, Taylor J L, Jones M E.
Occult Rickets and Osteomalacia Amongst the Immigrant Population.
Q J Med 1973; 42: 125.

7 Chalmers J, Conacher W D H, Gardner D C, Scott P J.
Osteomalacia - A Common Disease in Elderly Women.
J Bone Jt Surg 1967; 49B: 403.

8 Rosin A J.
Clinical Features and Detection of Osteomalacia in the Elderly.
Postgrad Med J 1970; 46: 131.

9 Aaron J E, Gallagher J C, Nordin B E C.
Seasonal Variations of Histological Osteomalacia in Femoral Neck Fractures.
Lancet 1974; 2: 84.

10 Heath H III, Hodgson S F, Kennedy M A.
Primary Hyperparathryoidism: Incidence, Morbidity, and Potential Economic Impact in a Community.
N Engl J Med 1980; 302: 189.

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Comment

The four patients presented are not unusual, in representing the types of problems one may often see in any centre with a specialised interest in metabolic bone disease.

Once the possibility of a patient having osteomalacia has been considered then the only certain way to confirm or refute this diagnosis is by bone biopsy with histological analysis, thus necessitating an invasive procedure. A normal 24-hour whole-body retention of diphosphonate (WBR) measurement excludes osteomalacia and in our experience to date of 23 patients with this condition there has been no overlap whatsoever with control values. As regards primary hyperparathyroidism, this diagnosis can on occasion prove remarkably difficult to confirm when mild disease is present, even if more invasive tests such as neck vein catheterisation studies for localisation of parathyroid hormone levels are carried out. In practice, such cases are often observed over a period pending a final decision as to their management. An elevated result for WBR in such cases would support a diagnosis of primary hyperparathyroidism and a normal result would be against it. However it is likely that a small degree of overlap of results may eventually be shown with WBR between disease and normal subjects.

As our understanding of the aetiology of osteoporosis slowly advances, it is becoming apparent that this is a heterogeneous condition. It is recognised that a significant minority of patients have high bone turnover (Meunier et al, 1979) and if such patients could be simply identified by WBR then perhaps specific therapy to suppress skeletal metabolism could be used with benefit. When osteoporosis presents in a younger age group one is particularly anxious to exclude secondary causes of osteoporosis and document if accelerated bone loss is occurring.

At present further studies are required to confirm the above suggestions regarding the sensitivity of WBR in osteomalacia, primary hyperparathyroidism and 'high turnover' osteoporosis. However, if a normal result for WBR does indeed exclude these conditions then clearly many patients could be spared extensive, expensive and at times invasive investigation.

Paper 18. Skeletal uptake of diphosphonate. Method for prediction of post-menopausal osteoporosis (1980)

Lancet 2: 667-670

I Fogelman, R G Bessent, H N Cohen, D M Hart, R Lindsay

Purpose of Investigation

The most common and important metabolic bone disease is osteoporosis. However in the great majority of cases, by the time it is diagnosed the disease is irreversible and incurable. Thus it would clearly be desirable to identify those subjects at risk of developing osteoporosis prior to the development of significant bone loss, in order that they might benefit from prophylactic therapy. The purpose of the present study was to obtain 24-hour whole-body retention of diphosphonate (WBR) measurements reflecting skeletal metabolism, in a group of oophorectomised women participating in a long term study of oestrogen prophylaxis against bone loss, and to correlate the results with their rates of bone loss as measured by photon absorptiometry. It was hoped that assessment of skeletal metabolism with WBR would correlate with measured rates of bone loss, thus lending support to my belief that WBR may be able to identify women with increased bone turnover at a time prior to the development of osteoporosis.

Comment

In the present study, oophorectomised women receiving oestrogen therapy had significantly lower values for 24-hour whole-body retention of diphosphonate (WBR) and rate of bone loss than those receiving placebo, thus providing further evidence as to the efficacy of oestrogen in suppressing skeletal metabolism and bone loss. In addition it was found that those women who had defaulted from oestrogen therapy had the highest values for WBR and bone loss, in keeping with previous work suggesting accelerated bone loss after oestrogen withdrawal (Lindsay et al, 1978; Horsman et al, 1979). More recently Christiansen et al (1981) did not find accelerated bone loss after cessation of oestrogen therapy. However this finding was based on photon absorptiometry measurements obtained for only one year after discontinuation of therapy. The question of what happens to bone after oestrogen withdrawal is clearly important and requires further study. While it is generally accepted that oestrogens reduce or prevent bone loss in post-menopausal women, any previous benefit might be negated if cessation of therapy were to lead to accelerated bone loss. This would imply that only prolonged oestrogen therapy could maintain skeletal mass and this would introduce other

difficulties such as possible long term side effects and the cost effectiveness of treatment (Weinstein 1980).

A highly significant negative correlation was found between WBR and the dose of oestrogen taken. This finding suggests that it may be possible to adjust therapy and control skeletal metabolism at an optimal level.

Although WBR provides a measure of skeletal metabolism and photon absorptiometry a measure of peripheral bone mineral content, there was nevertheless good correlation between these two quite different investigations. It would thus appear that WBR with a single measurement of skeletal metabolism can provide parallel information relating to rate of bone loss as measured by photon absorptiometry over a three year period.

This study has for the first time shown differences in WBR measurements between groups of subjects when the results themselves were largely within the normal range. In addition for the study group as a whole these results correlated well with the rate of bone loss measured by photon absorptiometry. The WBR technique thus has exciting potential application in the identification of post-menopausal women who have slightly elevated levels of bone turnover and who may, therefore, go on to develop accelerated bone loss. Jeffcoat et al (1980)

have independently suggested that a quantitative measure of diphosphonate uptake in bone may indicate future bone loss. Their interest was in periodontal disease and in a prospective study of beagle dogs they measured diphosphonate uptake by alveolar bone and demonstrated a strong correlation between tracer uptake and subsequent bone loss over a two year period.

SUMMARY

CHAPTER 6

STUDIES WITH THE TECHNIQUE OF 24-HOUR WHOLE-BODY RETENTION OF DIPHOSPHONATE IN CLINICAL PRACTICE

This chapter deals with studies utilising the technique of 24-hour whole-body retention of diphosphonate (WBR) in clinical practice, and highlights potential applications for future use.

A study assessing the extent of skeletal involvement in primary hyperparathyroidism by WBR is described in paper 16. It was found that all 16 patients with primary hyperparathyroidism had elevated values for WBR, while only eight had elevated values for serum alkaline phosphatase and two abnormal skeletal radiology. It would thus appear that WBR is the most sensitive of these investigations for the detection of increased bone turnover. A significant correlation was, however, shown between WBR and both serum parathyroid hormone and alkaline phosphatase levels, supporting the view that diphosphonate uptake by bone is directly related to skeletal metabolic activity. In addition, sequential WBR studies were obtained in five patients pre and post parathyroidectomy and it was found that WBR values fell to or towards normal in all cases following operation.

Four case histories of patients with suspected osteomalacia, primary hyperparathyroidism and osteoporosis, are presented in paper 17. In this brief communication it is suggested that in such cases a normal WBR result would have been of value in the exclusion of metabolic bone disease.

On the basis of my experience to date with the WBR technique I believe that a normal result for WBR will exclude osteomalacia and makes a diagnosis of primary hyperparathyroidism extremely unlikely. It is also possible that an abnormal result may be of value in identifying patients with 'high turnover' osteoporosis. However, independent evaluation of the WBR technique is required to confirm these suggestions. Nevertheless if a normal result for WBR does indeed exclude these conditions then clearly many patients would be spared intensive and at times invasive investigations.

While the WBR technique has been shown in several studies to provide a sensitive indicator of increased bone turnover, the most important potential application of WBR would be as a predictor of accelerated bone loss. To obtain further information relating WBR to bone loss, oophorectomised women participating in a long term study of oestrogen therapy as prophylaxis against bone loss were studied and the results presented in paper 18. It was shown that women receiving oestrogen had significantly lower values for both skeletal metabolism and rate of bone loss as measured by photon absorptiometry. A negative correlation was found between the dose of oestrogen and skeletal metabolism, suggesting that it may be possible to adjust therapy to maintain skeletal metabolism at an optimal level. A strong positive correlation was found between WBR and rate of bone loss for the study group as a whole, indicating that WBR may indeed be able to predict

accelerated bone loss in prospective studies. Jeffcoat et al (1980) have independently suggested that quantitative uptake of diphosphonate by bone may predict future bone loss.

The most exciting potential application of WBR at present is in osteoporosis. If it were possible to identify post-menopausal women at risk of accelerated bone loss using the WBR technique, then these women might benefit from prophylactic therapy. However prospective studies are required to correlate WBR with bone loss in individual patients on a sequential basis.

S U M M A R Y

Bone scan imaging with the current bone seeking radiopharmaceuticals, the technetium-99m labelled diphosphonates, has dramatically improved our ability to evaluate skeletal pathology. In this thesis, chapter 1 presents a review of the history of bone scanning, summarises present concepts as to the mechanism of uptake of bone seeking agents and briefly illustrates the role of bone scanning in clinical practice.

In chapter 2 the applications of bone scan imaging and quantitative tracer techniques derived from the bone scan in the detection of metabolic bone disease are discussed. Since skeletal uptake of Tc-99m diphosphonate depends upon skeletal metabolism one might expect that the bone scan would be of considerable value in the assessment of metabolic bone disease. However in these disorders the whole skeleton is often diffusely involved by the metabolic process and simple visual inspection of the scan image may not reveal the uniformly increased uptake of tracer. Certain patterns of bone scan abnormality have, however, been reported in patients with primary hyperparathyroidism and renal osteodystrophy; the present studies extend these observations and introduce the concept of "metabolic features" which are often recognisable in conditions with generalised increased bone turnover. As an aid to systematic recognition of

these features on a given bone scan image a semi-quantitative scoring system, the metabolic index, was introduced. The metabolic index allowed differentiation between various groups of patients with metabolic disorders and a control population. In addition, in a bone scan study of patients with acromegaly, it was found that the metabolic index correlated well with disease activity as measured by serum growth hormone levels. The metabolic index was, however, found to be a relatively insensitive means of identifying disease in individual patients.

Patients with increased bone turnover will have an absolute increase in skeletal uptake of tracer. As a means of quantitating this uptake the use of bone to soft-tissue ratios derived from the bone scan image by computer was critically evaluated. The technique was shown to be observer dependent and again found to be of limited value due to the large overlap of patient results with those from control subjects.

In chapter 3 the use of bone scan imaging in metabolic bone disease has been compared with radiology. Despite the difficulties mentioned above the metabolic index was employed, and the bone scan found to be the more sensitive investigation in primary hyperparathyroidism, renal osteodystrophy and osteomalacia. In osteoporosis, however, the bone scan was often unable to identify disease

and radiology remains the investigation of choice. In a further study comparing bone scanning and radiology in Paget's disease, the bone scan was found to be clearly the more sensitive investigation.

As a result of the work described in chapter 2 it became apparent that a sensitive means of quantitating absolute bone uptake of tracer could be of diagnostic value. In chapter 4 a promising new quantitative technique is described in which the 24-hour whole-body retention of Tc-99m diphosphonate (WBR) is measured using a shadow-shield whole-body monitor. At 24 hours after injection, diphosphonate has reached a stable equilibrium in bone reflecting skeletal metabolic activity, while tracer in the soft-tissues of the body has been largely excreted via the urinary tract. It was found that this technique provided a sensitive means of detecting patients with primary hyperparathyroidism, osteomalacia, renal osteodystrophy and Paget's disease and that in these conditions all the results from individual patients lay outside the control range. In further studies the WBR technique was shown to be highly reproducible and not subject to any significant technical errors. In an analysis of WBR results from 250 normal subjects it was found that clear age-related changes were present. A comparative study of WBR measurements obtained

with a whole-body monitor and with a gamma camera showed an extremely good correlation between the two techniques.

Several studies comparing the available Tc-99m labelled diphosphonates in clinical practice are reported in chapter 5. Tc-99m hydroxyethylidene diphosphonate (HEDP) has been used for all the bone scan and WBR studies reported in this thesis. However, at the present time Tc-99m methylene diphosphonate (MDP) is the most widely used bone scanning agent and has been shown to have higher skeletal affinity than HEDP. It is suggested that this may be a disadvantage in metabolic bone disease for it would appear to be easier to recognise metabolic features against a relatively low background uptake in normal subjects. In a study comparing HEDP and MDP in patients with metastatic disease, higher lesion to bone ratios were obtained with HEDP and this raises the possibility that increased bone uptake of tracer could lead to poorer lesion visualisation with reduction in diagnostic information. In a further study, measurements of WBR with Tc-99m hydroxymethylene diphosphonate, MDP and HEDP were obtained in healthy volunteer subjects and striking differences in skeletal affinity were found.

In chapter 6 studies relating to the application and potential uses of the WBR technique in clinical practice are presented. In patients with primary hyperparathyroidism

WBR was found to be elevated in each individual case suggesting increased bone turnover. Radiology and routine biochemistry performed considerably less well in this respect. The thesis also includes a short report of four case histories illustrating how WBR may be of value in the exclusion of metabolic bone disease. Patients with suspected osteomalacia, primary hyperparathyroidism and "high turnover" osteoporosis are presented and it is suggested that a normal result for WBR could avoid extensive and at times, invasive investigations being performed in such cases.

In a study of oophorectomised women participating in the longterm evaluation of oestrogen prophylaxis against bone loss it was found that women receiving oestrogen had significantly lower values for WBR and rates of bone loss than those receiving a placebo preparation. These findings confirm the protective effect of oestrogen as regards suppression of skeletal metabolism and prevention of bone loss. In addition for the study group as a whole a highly significant correlation was found between WBR and the rate of bone loss as measured by photon absorptiometry over a three year period. This study raises the possibility that with a single measurement WBR may be able to identify those women who have a relative increase in skeletal

metabolism and may, therefore, be at risk of accelerated bone loss with the subsequent development of osteoporosis.

The skeleton remains a difficult organ to investigate and prior to this work there was no satisfactory simple technique for assessing skeletal metabolism. While it is apparent that we need to know much more about diphosphonate uptake in the body, and in particular the mechanism and site of its localisation in bone, it is nevertheless concluded that WBR measurements provide a sensitive means of detecting increased bone turnover. It is likely that this tracer technique combined with routine bone scan imaging will increasingly be used to assess metabolic bone disorders.

REFERENCES FROM COMMENTARY

Aaron J. (1976)

Histology and micro-anatomy of bone. In: Calcium, Phosphate and Magnesium Metabolism. (Nordin B E C. ed.). Churchill Livingstone, Edinburgh. pp. 298-356.

Alberts C, van der Schoot J B, Busemann-Sokole E. (1981)

Bone scintigraphy and densitometry in symptomatic haemodialysis bone disease. European Journal of Nuclear Medicine 6: 505-509.

Aloia J F, Cohn S H, Ostuni J A, Cane R, Ellis K. (1978)

Prevention of involutional bone loss by exercise. Annals of Internal Medicine 89: 356-358.

Amprino R. (1952)

Further experiments on the fixation in vitro of radiocalcium to sections of bone. Experientia 8: 380-382.

Anderson J, Emery E W, McAlister J M, Osborn S B. (1956)

The metabolism of a therapeutic dose of ^{45}Ca in a case of multiple myeloma. Clinical Science 15: 567-585.

Anger H O. (1964)

Scintillation cameras with multichannel collimators. Journal of Nuclear Medicine 5: 515-531.

Arnold J S, Barnes W E, Khedkar N, Nelson M. (1978)

Computerized kinetic analysis of two 99m-Tc-Sn-diphosphonates demonstrating different binding characteristics (abstract). American Journal of Roentgenology 131: 553.

Bassett C A L, Donath A, Macagno F, Preisig R, Fleisch H, Francis M D. (1969)

Diphosphonates in the treatment of myositis ossificans (letter) Lancet 2: 845.

Bauer G C H. (1954)

The importance of bone growth as a factor in the redistribution of bone salt. 1 Redistribution of radio-active calcium in the skeleton of rats. Journal of Bone and Joint Surgery 36A: 375-380

Bauer G C H, Carlsson A. (1955)

Metabolism of bone salt investigated by simultaneous administration of ^{45}Ca and ^{32}P to rats. Journal of Bone and Joint Surgery 37B; 658-662

Bauer G C H, Carlsson A, Lindquist B. (1961)

Metabolism and homeostatic function of bone. In: Mineral Metabolism (Comar C L, Bronner F, eds.) Academic Press, New York. pp. 609-676.

Baylor C H, Van Alstine H E, Keutmann E H, Bassett S H. (1950)

The fate of intravenously administered calcium. Effect on urinary calcium and phosphorus, fecal calcium and calcium - phosphorus balance. Journal of Clinical Investigation 29: 1167-1176

Bellin J, Laszlo D. (1953)

Metabolism and removal of Ca^{45} in man. Science 117: 331-334.

Bevan J A, Tofe A J, Benedict J J, Francis M D, Barnett B L. (1980)
Tc-99m HMDP (hydroxymethylene diphosphonate): A radiopharmaceutical for skeletal and acute myocardial infarct imaging. 1. Synthesis and distribution in animals. Journal of Nuclear Medicine 21: 961-966.

Bhandarkar S D, Nordin B E C. (1962)
The 4-hour calcium-retention test. Scottish Medical Journal 7: 82-84.

Blau M, Nagler W, Bender M A. (1962)
Fluorine-18: a new isotope for bone scanning. Journal of Nuclear Medicine, 3: 332-334

Blau M, Ganatra R, Bender M A. (1972)
^{18}F-Fluoride for bone imaging. Seminars in Nuclear Medicine 2: 31-37.

Blum T. (1924)
Osteomyelitis of the mandible and maxilla. Journal of American Dental Association 11; 802-805.

Borak J. (1942)
Relationship between the clinical and roentgenological findings in bone metastases. Surgery, Gynaecology and Obstetrics 75: 599-604.

Bronner F, Harris R S, Maletskos J, Benda C E. (1956)
Studies in calcium metabolism. The fate of intravenously injected radiocalcium in human beings. Journal of Clinical Investigation 35: 78-88.

Campbell W W, Greenberg D M. (1940)
Studies in calcium metabolism with the aid of its induced radioactive isotope. Proceedings of the National Academy of Sciences of the United States of America 26: 176-180.

Carlsson A. (1951)
Metabolism of radiocalcium in relation to calcium intake in young rats. Acta Pharmacologica et Toxicologica 7: supplementum 1. pp. 1-74.

Castronovo F P, Callahan R J. (1972)
New bone scanning agent: ^{99m}Tc-labeled 1-hydroxy-ethylidene-1, 1-disodium phosphonate. Journal of Nuclear Medicine 13: 823-827.

Charkes N D, Sklaroff D M. (1964)
Early diagnosis of metastatic bone cancer by photo-scanning with strontium-85. Journal of Nuclear Medicine 5: 168-179.

Charkes N D, Sklaroff D M, Bierly J. (1964)
Detection of metastatic cancer to bone by scintiscanning with strontium 87m. American Journal of Roentgenology Radium Therapy and Nuclear Medicine 91: 1121-1127.

Charkes N D, Sklaroff D M, Young I. (1966)
A critical analysis of strontium bone scanning for detection of metastatic cancer. American Journal of Roentgenology Radium Therapy and Nuclear Medicine 96: 647-656.

Charkes N D, Young I, Sklaroff D M. (1968)
The pathologic basis of the strontium bone scan. Journal of the American Medical Association 206: 2482-2488.

Charkes N D. (1969)
Some differences between bone scans made with ^{87m}Sr and ^{85}Sr. Journal of Nuclear Medicine 10: 491-494.

Charkes N D. (1970)
Bone scanning: principles, technique and interpretation. Radiologic Clinics of North America 8: 259-270.

Chiewitz O, Hevesy G. (1935)
Radioactive indicators in the study of phosphorus metabolism in rats (letter). Nature 136: 754-755.

Christensen S B, Krogsgaard O W. (1981)
Localization of Tc-99m MDP in epiphyseal growth plates of rats. Journal of Nuclear Medicine 22: 237-245.

Christiansen C, Christensen M S, Transbol I. (1981)
Bone mass in postmenopausal women after withdrawal of oestrogen/gestagen replacement therapy. Lancet 1: 459-461.

Citrin D L, Bessent R G, Greig W R. (1974)
Clinical evaluation of ^{99m}Tc-labeled monofluoro-phosphate: A comparison with ethane-hydroxy-diphosphonate. Journal of Nuclear Medicine 15: 1110-1112.

Citrin D L, Bessent R G, Tuohy J B, Elms S T, McGinley E, Greig W R, Blumgart L H. (1975)
A comparison of phosphate bone-scanning agents in normal subjects and patients with malignant disease. British Journal of Radiology 48: 118-121.

Citrin D L, McKillop J H. (1978)
Atlas of technetium bone scans. (Citrin D L, McKillop J H, eds.). Bohn, Scheltema and Holkema, Utrecht.

Citrin D L. (1979)
"Personal Communication".

Cohen Y, Perez R, Henry R, Bardy A, Panneciere C. (1972)
Utilisation du pyrophosphate de sodium marque par le technetium 99m dans la scintigraphie du squelette. Comptes Rendus Hebomadaires Des Seances De L'Academie Des Sciences; D: Sciences Naturelles (Paris), t 275: 1719-1721.

Comar C L, Wasserman R H, Ullberg S, Andrews G A. (1957)
Strontium metabolism and strontium-calcium discrimination in man. Proceedings of the Society for Experimental Biology and Medicine 95: 386-391.

Cooke M B D, Kaplan E. (1972)
Whole-body imaging and count profiling with a modified Anger camera. 1. Principles and application. Journal of Nuclear Medicine 13; 899-907.

Cox PH. (1974)

Abnormalities in skeletal uptake of $^{99}Tc^{m}$ polyphosphate complexes in areas of bone associated with tissues which have been subjected to radiation therapy. British Journal of Radiology 47: 851-856.

Davis A G, Jones A G. (1976)

Comparison of ^{99m}Tc-labeled phosphate and phosphonate agents for skeletal imaging. Seminars in Nuclear Medicine 6: 19-31.

De Nardo G L. (1966)

The ^{85}Sr scintiscan in bone disease. Annals of Internal Medicine 65: 44-53.

De Nardo G L, Volpe J A, Captain M C. (1966)

Detection of bone lesions with the strontium-85 scintiscan. Journal of Nuclear Medicine 7: 219-236.

De Nardo G L. (1968)

Clinical application of bone scintiscans. Clinical Medicine 75: 22-32.

De Nardo G L, Jacobson S J, Raventos A. (1972)

^{85}Sr bone scan in neoplastic disease. Seminars in Nuclear Medicine 2: 18-30.

Deutsch E, Barnett B L. (1980)

Synthetic and structural aspects of technetium chemistry as related to nuclear medicine. In: Inorganic Chemistry in Biology and Medicine. A C S Symposium Series, No 140 (Martell A E ed.). pp. 103-119.

Dow E C, Stanbury J B. (1960)

Strontium and calcium metabolism in metabolic bone diseases. Journal of Clinical Investigation 39: 885-903.

Doyle F, Brown J, Lachance C. (1970)

Relation between bone mass and muscle weight. Lancet 1: 391-393.

Dunson G L, Stevenson J S, Cole C M, Mellor M K, Hosain F. (197:

Preparation and comparison of technetium-99m diphosphonate, polyphosphate and pyrophosphate in nuclear bone imaging radiopharmaceuticals. Drug Intelligence and Clinical Pharmacy 7: 470-474.

Dymling J F. (1962)

Accretion and excretory clearance rates and exchangeable spaces measured in man with Ca^{47} and Sr^{85} under normal and pathological conditions. In: Medical Uses of Ca^{47} Technical Reports Series No 10. International Atomic Energy Agency, Vienna. pp. 73-76.

Dymling J. (1971)

Studies of calcium absorption and metabolism. In: Radioisotopes in Medical Diagnosis. (Belcher E H, Vetter H, eds.). Butterworths, London. pp. 298-318.

Eckelman W, Richards P. (1970)

Instant ^{99m}Tc- DTPA. Journal of Nuclear Medicine 11: 761.

Edelstyn G A, Gillespie P J, Grebell F S. (1967)
The radiological demonstration of osseous metastases: experimental observations. Clinical Radiology 18: 158-162.

Edwards C L, Hayes R, Ahumada J, Kniseley R M. (1966)
Gallium-68 citrate: A clinically useful skeletal scanning agent (abstract). Journal of Nuclear Medicine 7: 363-364.

Eisenberg E, Gordan G S. (1961)
Skeletal dynamics in man measured by nonradioactive strontium. Journal of Clinical Investigation 40: 1809-1825.

Espinasse D, Mathieu L, Alexandre C, Chapuy M C, Meunier P J, Berger M. (1981)
The kinetics of ^{99m}Tc labelled EHDP in Paget's disease before and after dichloromethylene-diphosphonate treatment. Metabolic Bone Disease and Related Research 2: 321-324.

Fels I G, Kaplan E, Greco J, Veatch R. (1959)
Incorporation in vivo of P^{32} from condensed phosphates. Proceedings of the Society for Experimental Biology and Medicine 100: 53-55.

Fink S, Laszlo D. (1957)
A metabolic study following oral $calcium^{45}$ administration in a patient with non-tropical sprue. Gastroenterology 32: 689-703.

Fleisch H, Russell R G G, Francis M D. (1969)
Diphosphonates inhibit hydroxyapatite dissolution in vitro and bone resorption in tissue culture and in vivo. Science 165: 1262-1264.

Fleisch H, Russell R G G. (1970)
Pyrophosphate and polyphosphate. In: International Encyclopedia of Pharmacology and Therapeutics. Section 51, Volume 1. (Rasmussen H, ed.). Pergamon Press, Oxford. pp. 61-100.

Fleisch H, Russell R G G. (1972)
A review of the physiological and pharmacological effects of pyrophosphate and diphosphonates on bones and teeth. Journal of Dental Research, 51: supplement 324-332.

Fleming W H, McIlraith J D, King E R. (1961)
Photoscanning of bone lesions utilising strontium-85. Radiology 77: 635-636.

Fletcher J W, Solaric-George E, Henry R E, Donati R M. (1973)
Evaluation of ^{99m}Tc-pyrophosphate as a bone imaging agent. Radiology 109: 467-469.

Fogelman I, McKillop J H, Citrin D L. (1977)
A clinical comparison of ^{99m}Tc-hydroxyethylidene diphosphonate (HEDP) and ^{99m}Tc-pyrophosphate in the detection of bone metastases. Clinical Nuclear Medicine 2: 364-367.

Fordham E W, Ramachandran P C. (1974)

Radionuclide imaging of osseous trauma. Seminars in Nuclear Medicine 4: 411-429.

Francis M D. (1969)

The inhibition of calcium hydroxyapatite crystal growth by polyphosphonates and polyphosphates. Calcified Tissue Research 3: 151-162.

Francis M D, Russell R G G, Fleisch H. (1969)

Diphosphonates inhibit formation of calcium phosphate crystals in vitro and pathological calcification in vivo. Science 165: 1264-1266.

Francis M D, Ferguson D L, Tofe A J, Bevan J A, Michaels S E. (1980)

Comparative evaluation of three diphosphonates: In vitro adsorption (C-14 labeled) and in vivo osteogenic uptake (Tc-99m complexed). Journal of Nuclear Medicine 21: 1185-1189.

Francis M D, Horn P A, Tofe A J. (1981)

Controversial mechanism of technetium-99m deposition on bone (abstract). Journal of Nuclear Medicine 22: 72.

Fraser R, Harrison M, Ibbertson K. (1960)

The rate of calcium turnover in bone measurement by a tracer test using stable strontium. Quarterly Journal of Medicine 29: 85-111.

French R J , McCready V R. (1967)
The use of ^{18}F for bone scanning. British Journal of Radiology 40: 655-661.

Frohman L A. (1981)
Diseases of the anterior pituitary. In: Endocrinology and Metabolism. (Felig P, Baxter J D, Broadus A E, Frohman L A. eds.). McGraw-Hill, New York. pp. 151-231.

Frost H M. (1963)
Bone remodelling dynamics. Charles C Thomas, Springfield USA.

Frost H M. (1973)
Bone Remodeling and its Relationship to Metabolic Bone Diseases. Charles C Thomas, Springfield, USA.

Goergen T, Halpern S, Alazraki N, Heath V, Taketa R, Ashburn W. (1974)
The "photon deficient" area: a new concept in bone scanning (abstract). Journal of Nuclear Medicine 15: 495.

Goldman R, Bassett S H. (1954).
Effect of intravenous calcium gluconate upon the excretion of calcium and phosphorus in patients with idiopathic hypoparathyroidism. Journal of Clinical Endocrinology and Metabolism 14: 278-286.

Harper P V, Lathrop K A, Jiminez F, Fink R, Gottschalk A. (1965)
Technetium 99m as a scanning agent. Radiology 85: 101-109.

Harris W H, Heaney R P. (1969)

Skeletal renewal and metabolic bone disease.

New England Journal of Medicine 280: 253-259.

Hayes R L, Carlton J E, Byrd B L. (1965)

Bone scanning with gallium-68: A carrier effect.

Journal of Nuclear Medicine 6: 605-609.

Haymovitz A, Horwith M. (1964)

The miscible calcium pool in metabolic bone disease - in particular, acromegaly. Journal of Clinical Endocrinology and Metabolism 24: 4-14.

Heaney R P. (1963)

Evaluation and interpretation of calcium-kinetic data in man. Clinical Orthopaedics 31: 153-183.

Heaney R P. (1976)

Calcium kinetics in plasma: As they apply to the measurements of bone formation and resorption rates. In: The Biochemistry and Physiology of Bone. (Bourne GH, ed.). Academic Press, New York. pp. 105-133.

Hoffman F L. (1924)

Radium (Mesothorium) necrosis. Journal of the American Medical Association 85: 961-965.

Holmes R A. (1978)

Quantification of skeletal Tc-99m labeled phosphates to detect metabolic bone disease. Journal of Nuclear Medicine 19: 330-331.

Horsman A, Nordin B E C, Crilly R G. (1979)
Effect on bone of withdrawal of oestrogen therapy (letter). Lancet 2: 33.

Hosain F, Hosain P, Wagner H N, Dunson G L, Stevenson J S. (1973)
Comparison of ^{18}F, ^{87m}Sr, and ^{99m}Tc-labeled polyphosphate, diphosphonate, and pyrophosphate for bone scanning (abstract). Journal of Nuclear Medicine 14: 410.

Howard J E, Hopkins T R, Connor T B. (1953)
On certain physiologic responses to intravenous injection of calcium salts into normal, hyperparathyroid and hypoparathyroid persons. Journal of Clinical Endocrinology and Metabolism 13: 1-19.

Huberty J P, Hattner R S, Powell M R. (1974)
A ^{99m}Tc-pyrophosphate kit: a convenient, economical, and high quality skeletal-imaging agent. Journal of Nuclear Medicine 15: 124-126.

Isaksson B, Sjogren B. (1967)
A critical evaluation of the mineral and nitrogen balances in man. Proceedings of The Nutrition Society 26: 106-116.

Jeffcoat M K, Kaplan M L, Goldhaber P. (1980)
Predicting alveolar bone loss in beagles using bone-seeking radiopharmaceutical uptake. Journal of Dental Research 59: 844-848.

Jowsey J, Rayner B, Tutt M, Vaughan J. (1953)
The deposition of ^{90}Sr in rabbit bones following intravenous injection. British Journal of Experimental Pathology 34: 384-391.

Kaplan E, Fels I G, Kotlowski B R, Greco J, Walsh W S. (1960)
Therapy of carcinoma of the prostate metastatic to bone with P^{32} labeled condensed phosphate. Journal of Nuclear Medicine 1: 1-13.

Khairi M R A, Altman R D, De Rosa G P, Zimmermann J, Shenk R K, Johnston C C. (1977)
Sodium etidronate in the treatment of Paget's disease of bone A study of long-term results. Annals of Internal Medicine 87: 656-663.

Krane S M, Brownell G L, Stanbury J B, Corrigan H. (1956)
The effect of thyroid disease on calcium metabolism in man. Journal of Clinical Investigation 35: 874-887.

Krishnamurthy G T, Tubis M, Endow J S, Singhi V, Walsh C F, Blahd W H. (1974)
Clinical comparison of the kinetics of ^{99m}Tc-labeled polyphosphate and diphosphonate. Journal of Nuclear Medicine 15: 848-855.

Kyle L H, Schaaf M, Erdman L A. (1954)
The metabolic effects of intravenous administration of calcium. Journal of Laboratory and Clinical Medicine 43: 123-133.

Lacroix P. (1952)

Autoradiographies du tissu osseux spongieux.

Experientia 8: 426.

Lange R C, Treves S, Spencer R P. (1970)

^{135}Ba and ^{131}Ba as bone scanning agents (abstract)

Journal of Nuclear Medicine 11: 340-341.

Lengemann F W. (1957)

Comparative metabolism of Sr^{89} and Ca^{45} by bone grown in vitro. Proceedings of the Society for Experimental Biology and Medicine 94: 64-66.

Leonard R C F, Owen J P, Proctor S J, Hamilton P J. (1981)

Multiple myeloma: Radiology or bone scanning?

Clinical Radiology 32: 291-295.

Lien J W K, Wiegmann T, Rosenthall L, Kaye M. (1976)

Abnormal ^{99m}Technetium-tin-pyrophosphate bone scans in chronic renal failure. Clinical Nephrology 6: 509-512.

Lindsay R, Hart D M, MacLean A, Clark A C, Kraszewski A, Garwood J. (1978)

Bone response to termination of oestrogen treatment.

Lancet 1: 1325-1327.

Lundell G, Marell E, Backstrom A, Casseborn S, Ruden B-I. (1975)

Bone scanning with $^{99}Tc^{m}$ compounds in metastasizing mammary carcinoma. Acta Radiologica Therapy Physics Biology 14: 333-336.

McAfee J G, Subramanian G. (1975)
Radioactive agents for imaging. In: Clinical Scintillation Imaging. (Freeman L M, Johnson P M. eds.). Grune and Stratton, New York. pp. 55-59.

McCance R A, Widdowson E M. (1939)
The fate of calcium and magnesium after intravenous administration to normal persons. Biochemical Journal 33: 523-529.

McDougall I R. (1979)
Skeletal scintigraphy. Western Journal of Medicine 130: 503-514.

Marshall J H. (1964)
Theory of alkaline earth metabolism. In: Medical Uses of Ca-47: Second Panel Report International Atomic Energy Agency, Vienna. pp. 21-33.

Martland H S. (1926)
Microscopic changes of certain anemias due to radioactivity. Archives of Pathology and Laboratory Medicine 2: 465-472.

Mazzuoli G, Samachson J, Laszlo D. (1958)
Interrelationship between serum calcium levels: calcium^{45} and strontium^{85} metabolism in man. Journal of Laboratory and Clinical Medicine 52: 522-532.

Meunier P J, Courpron P, Edouard C, Alexandre C, Bressot C, Lips P, Boyce B F. (1979)
Bone histomorphometry in osteoporotic states. In: Osteoporosis II. (Barzel U S. ed.). Grune and Stratton, New York. pp. 27-47.

Milch R A, Changus G W. (1956)

Response of bone to tumour invasion. Cancer 9: 340-351.

Nadarajah A, Hartog M, Redfern B, Thalassinos N, Wright A D, Joplin G F, Fraser T R. (1968)

Calcium metabolism in acromegaly. British Medical Journal 4: 797-801.

Nelson M F, Melton R E, Van Wazer J R. (1975)

Sodium trimetaphosphate as a bone-imaging agent. 1. Animal studies. Journal of Nuclear Medicine 16: 1043-1048.

Neuman W F, Neuman M W. (1953)

The nature of the mineral phase of bone. Chemical Reviews 53: 1-45.

Neuman W F, Neuman M W. (1957)

Emerging concepts of the structure and metabolic functions of bone. American Journal of Medicine 22: 123-131.

Nordin B E C, Fraser R. (1956)

A calcium-infusion test. 1. Urinary excretion data for recognition of osteomalacia. Lancet 1: 823-826.

Nordin B E C. (1967)

Diagnostic uses of radioisotopes - the study of calcium metabolism. Hospital Medicine 2: 211-214.

Nordin B E C, Horsman A, Aaron J. (1976)
Diagnostic procedures. In: Calcium, Phosphate and Magnesium Metabolism. (Nordin B E C, ed.). Churchill Livingstone, Edinburgh. pp. 469-524.

Norris W P, Kisieleski W. (1948)
Comparative metabolism of radium, strontium, and calcium. Symposia on Quantitative Biology 13: 164-172.

O'Mara R E, McAfee J G, Subramanian G. (1969)
Rare earth nuclides as potential agents for skeletal imaging. Journal of Nuclear Medicine 10: 49-51.

Pauwels E K J. (1982)
"Personal communication".

Pendergrass H P, Potsaid M S, Castronovo F P. (1973)
The clinical use of ^{99m}Tc-diphosphonate (HEDSPA). Radiology 107: 557-562.

Perez R, Cohen Y, Henry R, Panneciere C. (1972)
A new radiopharmaceutical for ^{99m}Tc bone scanning (abstract). Journal of Nuclear Medicine 13: 788-789.

Reifenstein E C, Albright F, Wells S L . (1945)
The accumulation, interpretation and presentation of data pertaining to metabolic balances, notably those of calcium, phosphorus, and nitrogen. Journal of Clinical Endocrinology 5: 367-395.

Rich C, Ensinck J, Fellows H. (1961)
The use of continuous infusions of Calcium^{45} and Strontium^{85} to study skeletal function. Journal of Clinical Endocrinology and Metabolism 21: 611-623

Riggs B L, Randall R V, Wahner H W, Jowsey J, Kelly P J, Singh M. (1972)
The nature of the metabolic bone disorder in acromegaly. Journal of Clinical Endocrinology and Metabolism 34: 911-918.

Russell R G G, Smith R. (1973)
Diphosphonates experimental and clinical aspects. Journal of Bone and Joint Surgery 55B: 66-86

Russell R G G, Smith R, Preston C, Walton R J, Woods C G. (1974)
Diphosphonates in Paget's disease. Lancet 1: 894-898.

Schilling A, Laszlo D. (1951)
Rate of urinary calcium excretion following its intravenous administration as an indicator of bone metabolism. Proceedings of the Society for Experimental Biology and Medicine 78: 286-289.

Serafini A N, Watson D D, Nelson J P, Smoak W. M. (1974)
Bone scintigraphy - comparison of ^{99m}Tc-polyphosphate and ^{99m}Tc-diphosphonate. Journal of Nuclear Medicine 15: 1101-1104.

Shackman R, Harrison C V. (1948)
Occult bone metastases. British Journal of Surgery 35: 385-389.

Sharma S M, Quinn J L. (1972)
Sensitivity of ^{18}F bone scans in the search for metastases. Surgery, Gynecology and Obstetrics 135: 536-540.

Shirazi P H, Rayudu G V S, Fordham E W. (1974)
^{18}F bone scanning: Review of indications and results of 1500 scans. Radiology 112: 361-368.

Silberstein E B, Saenger E L, Tofe A J, Alexander G W, Park H-M. (1973)
Imaging of bone metastases with ^{99m}Tc-Sn- EHDP (Diphosphonate), ^{18}F, and skeletal radiography. A comparison of sensitivity. Radiology 107: 551-555.

Silberstein E B, Maxon H R, Alexander G W, Rauf C, Bahr G K. (1978)
Clinical comparison of Technetium-99m diphosphonate and pyrophosphate in bone scintigraphy: Concise communication. Journal of Nuclear Medicine 19: 161-163.

Sklaroff D M, Charkes N D. (1964)
Diagnosis of bone metastasis by photoscanning with strontium 85. Journal of the American Medical Association 188: 1-4.

Sklaroff D M , Charkes N D. (1968)
Bone metastases from breast cancer at the time of radical mastectomy. Surgery, Gynecology and Obstetrics 127: 763-768.

Smith R, Russell R G G, Bishop M. (1971)
Diphosphonates and Paget's disease of bone. Lancet 1: 945-947.

Spencer H, Hausinger A, Laszlo D. (1954)
The calcium tolerance test in senile osteoporosis. Journal of the American Geriatrics Society 2: 19-25.

Spencer H, Laszlo D, Brothers M. (1957)
Strontium^{85} and calcium^{45} metabolism in man. Journal of Clinical Investigation 36: 680-688.

Spencer H, Li M, Samachson J, Laszlo D. (1960)
Metabolism of strontium-85 and calcium-45 in man. Metabolism 9: 916-925.

Spencer R P, Lange R C, Treves S. (1970)
^{131}Ba: an intermediate-lived radionuclide for bone scanning. Journal of Nuclear Medicine 11: 95-96.

Subramanian G. (1970)
^{135m}Ba: Preliminary evaluation of a new radionuclide for skeletal imaging. (abstract) Journal of Nuclear Medicine 11: 650-651.

Subramanian G, McAfee J G. (1971)

A new complex of ^{99m}Tc for skeletal imaging.

Radiology 99: 192-196.

Subramanian G, McAfee J G, Blair R J, O'Mara R E,

Greene M W, Lebowitz E. (1971)

^{157}Dy-HEDTA for skeletal imaging. Journal of Nuclear Medicine 12: 558-561.

Subramanian G, McAfee J G, Bell E G, Blair R J, O'Mara R E,

Ralston P H. (1972a)

^{99m}Tc-labeled polyphosphate as a skeletal imaging agent. Radiology 102, 701-704.

Subramanian G, McAfee J G, Blair R J, Mehter A, Connor T. (1972b)

^{99m}Tc-EHDP: a potential radiopharmaceutical for skeletal imaging. Journal of Nuclear Medicine 13: 947-950.

Subramanian G, McAfee J G, Blair R J, Rosenstreich M,

Coco M, Duxbury C E. (1975a)

Technetium-99m-labeled stannous imidodiphosphate, a new radiodiagnostic agent for bone scanning: Comparison with other ^{99m}Tc complexes. Journal of Nuclear Medicine 16: 1137-1143.

Subramanian G, McAfee J G, Blair R J, Kallfelz F A, Thomas F D. (1975b).

Technetium-99m-methylene diphosphonate - a superior agent for skeletal imaging: Comparison with other technetium complexes. Journal of Nuclear Medicine 16: 744-755.

Subramanian G, McAfee J G, Thomas F D, Feld T, Zapf-Longo C, Palladino E. (in press)

Localization of new Tc-99m labeled diphosphonates in experimental bone lesions. In: Proceedings of 19th International Annual Meeting of the Society of Nuclear Medicine Europe.

Sy W M. (1981)

Gamma Images in Benign and Metabolic Bone Diseases. (Sy W M, ed.). CRC Press, Boca Raton, Florida.

Teitelbaum S L, Nichols S H. (1977)

Tetracycline-based morphometric analysis of trabecular bone kinetics. In: Bone Histomorphometry (Meunier P J, ed.). Société de la Nouvelle Imprimerie Fournié Toulouse-France. pp. 311-319.

Thalassinos N C, Wicht S, Joplin G F. (1970)

Secondary hyperparathyroidism in osteomalacia. British Medical Journal 1: 76-79.

Tofe A J, Francis M D. (1972)

In vitro optimization and organ distribution studies in animals with the bone scanning agent ^{99m}Tc-Sn-EHDP. (abstract) Journal of Nuclear Medicine 13: 472.

Tow D E, Wagner H N. (1967)

Scanning for tumors of brain and bone. Journal of the American Medical Association 199: 610-614.

Tutt M, Kidman B, Rayner B, Vaughan J. (1952)

The deposition of Sr^{89} in rabbit bones following intravenous injection. British Journal of Experimental Pathology 33: 207-215.

Vattimo A, Cantalupi D, Righi G, Martini G, Nuti R, Turchetti V. (1981).

Whole-body retention of ^{99m}Tc-MPD in Paget's disease. Journal of Nuclear Medicine and Allied Sciences 25: 5-10.

Volpe J A. (1971)

The radioisotope skeletal survey. Journal of Surgical Oncology 3: 43-51.

Walke H. (1940)

The radioactive isotopes of calcium and their suitability as indicators in biological investigations. Physical Review 57: 177-184.

Weber D A, Greenberg E J, Dimich A, Kenny P J, Rothschild E O, Myers W P L, Laughlin J S. (1969)

Kinetics of radionuclides used for bone studies. Journal of Nuclear Medicine 10: 8-17.

Weinstein M C. (1980)

Estrogen use in postmenopausal women - costs, risks, and benefits. New England Journal of Medicine 303: 308-316.

Wendeberg B. (1965)

Bone salt accretion and exchangeable calcium spaces in man measured with Ca-47 and Sr-85. Clinical Orthopaedics and Related Research 40: 162-183.

Wiegmann T, Kirsh J, Rosenthall L, Kaye M. (1976)

Relationship between bone uptake of ^{99m}Tc-pyrophosphate and hydroxyproline in blood and urine. Journal of Nuclear Medicine 17: 711-714.

Wiegmann T, Rosenthall L, Kaye M. (1977)

Technetium-99m-pyrophosphate bone scans in hyperparathyroidism. Journal of Nuclear Medicine 18: 231-235.

Yano Y, Van Dyke D C, Verdon T A, Anger H O. (1971)

Cyclotron-produced ^{157}Dy compared with ^{18}F for bone scanning using the whole body scanner and scintillation counter. Journal of Nuclear Medicine 12: 815-821.

Yano Y, McRae J, Van Dyke D C, Anger H O. (1973)

Technetium-99m-labeled stannous ethane-1-hydroxy-1 1-diphosphonate: A new bone scanning agent. Journal of Nuclear Medicine 14: 73-78.

A P P E N D I X

SHADOW-SHIELD WHOLE-BODY MONITOR

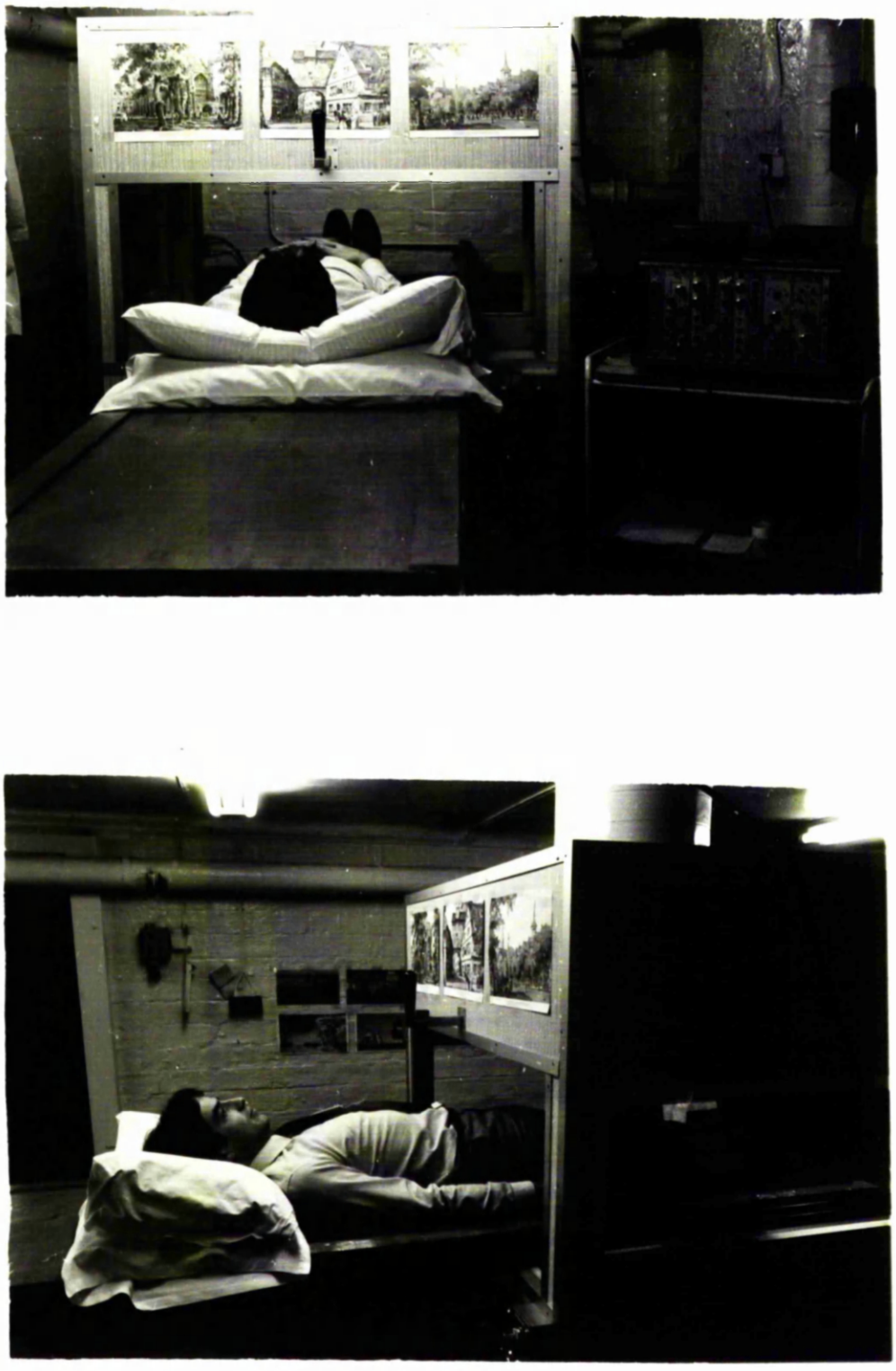

Figure 4

Shadow-shield whole-body monitor.

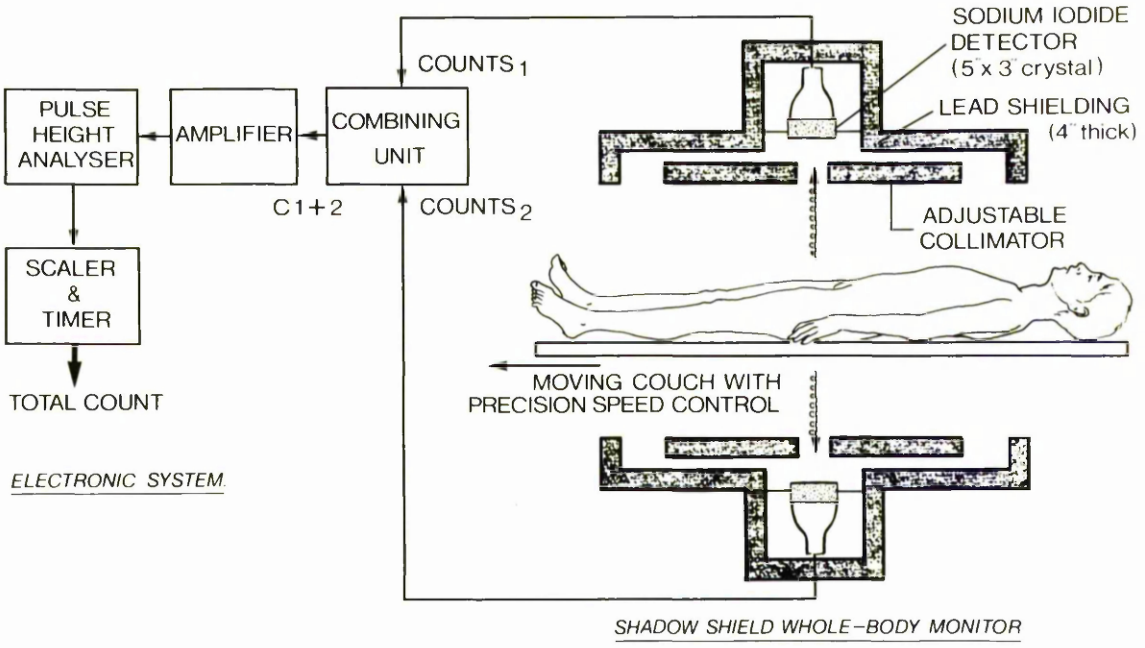

Figure 5