DETECTION OF NEOPLASTIC BONE LESIONS BY QUANTITATIVE SCANNING AND RADIOGRAPHY

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Previous reports by the authors (1–4) have indicated that bone scanning with ^{47}Ca and ^{85}Sr can demonstrate bone lesions before they appear on radiographs. Similar observations have been reported by other investigators (5–8). The usefulness of ^{47}Ca and ^{85}Sr in bone scanning, however, has not been adequately demonstrated in terms of a controlled comparison of the sensitivity of this method with radiographic procedures. Nor have the optimum times for scanning or quantitative measurements of uptake following nuclide administration been adequately studied.

The objectives of this study were:

1. To compare the sensitivity of routine and special radiographic procedures with that of scanning for detecting metastases in bone,
2. To determine the optimal scanning time after injection for bone-lesion detection and
3. To investigate the range of time intervals that elapses between the detection of bone lesions by scanning and their appearance on radiographs.

METHODS

Patient selection. Because all patients had been treated in the past for histologically proven cancer, they presented the clinical problem of localized bone pain and/or hypercalcemia and were suspected of having recurrent cancer. One patient with suspected cancer, severe bone pains and weight loss was investigated extensively without confirmation of malignancy. Skeletal surveys within 2 weeks of the start of the nuclide study revealed no bone lesions or no more than one or two discrete lesions remote from the symptomatic area. If the symptomatic area was sufficiently localized, special views—tomographs or spot views—were taken before the scan study.

Follow-up. Three follow-up studies were carried out:

1. Whenever possible, a needle biopsy of the bone marrow was taken at the symptomatic site within 1 week after scanning.
2. Special or tomographic views were taken of the symptomatic site within 1 month after scanning. Repeat films at the convenience of the patient and within the time requirements essential to answer the questions projected for the study were taken when these special and tomograph views were read as negative.
3. All available pathological specimens and autopsy reports were evaluated to determine whether bone lesions were present and, if so, what their location and extent were.

Radiographic findings. All patients studied were accepted on the basis of negative routine x-ray film readings. In addition to the routine film readings, all radiographs were reviewed by the senior radiologist associated with the scan study. The final radiographic summaries were made after direct comparison with scan findings to eliminate the possibility of missing a lesion that might have been discernible on x-ray if clinical symptomatology had been more specific.

Scan routine. Stationary external counting was done over selected areas on each patient with a cylindrical-bore collimator 4 in. long × 2 in. dia coupled to a 4 × 4-in. NaI(Tl) crystal at 5 hr, 24 hr and 5 days after the intravenous administration of ^{47}Ca-chloride or ^{85}Sr-nitrate. These times were selected because previous work (2) has indicated that: (1) abnormally elevated uptake over lesion-involved bone occurs during the first few hours after the administration of ^{47}Ca and ^{85}Sr, (2) maximum uptake over selected normal bone sites occurs within

the first 36 hr and (3) when an abnormal ratio is found between bone containing a radiologically detectable lesion and normal bone, the ratio frequently continues to increase for at least the first 5 days after injection. Although later measurements may show an increased ratio, 5 days was set as a practical time limit for external counting.

The standard areas counted included the symptomatic area and contralateral or adjoining sites, the tibiae, patellae, femurs, greater trochanters and the vertebrae at 5-cm intervals from 10 cm below the spinous process of the 7th cervical vertebra to the sacrum. A 24-hr total-body search scan (TBSS) was taken covering a minimum area from shoulder to midfemur, and a detailed search scan was run at 5 days over any suspicious area. Two collinearly opposed 4 × 4 in. NaI(Tl) crystals with 4-in. long and 1½-in. dia collimators were used for the TBSS, and various focusing collimators were used with both detectors for the detailed scans.

All scan data were digital in format. Briefly, the data-recording mechanism consists of a computer-compatible punched paper-tape system which records scan direction, length of data collection increment and counts accumulated per increment for one or two channels of data for each of two colinearly opposed detectors. Scan data displays available for clinical interpretation were: (1) a digital record of the counts accumulated per scan increment, (2) a

computer-analyzed scan that presents the digital data in symbols linearly matched with the counting rate, e.g., 0–10% of maximum counting rate recorded in the scan as A, 10–20% as B, etc., with symbol spacing as fine as $\frac{1}{10} \times \frac{1}{6}$ in. by linear interpolation between four adjacent data points and (3) a photoscan.

The computer-analyzed scan display simplifies the reading of the digital scan yet retains a basis for applying statistical criteria to evaluate suspicious areas. The change in symbols for different levels gives the appearance of isocount contours without further data manipulation. More extensive information concerning the data readout features can be found in the literature (4,9–11).

Scan interpretation. External point count readings were evaluated according to:

1. Comparison with contralateral and/or adjacent bone.
2. Comparison with a standard bone in the skeleton (e.g., clinically normal midshaft of the tibia) and
3. The relative percent uptake of dose (i.e., each recorded external point count was expressed as a percent of the counting rate of an aliquot of injected solution measured before and after the scan in a standardized geometry, corrected to the total volume of nuclide administered).

Local uptake was considered abnormal if the ratio to the contralateral area, normal adjoining bone or adjacent vertebrae was greater than 1.2. To avoid artifacts in measurements near the bowel or bladder, laxatives were given to many of the patients before scanning and when adnormal uptake was noted in or adjoining these areas, cleansing enemas were prescribed and repeat readings were taken.

Comparison of each measurement with a standard reference bone in the skeleton (e.g., a normal tibia) and the evaluation of percent uptake ratio provided a control for anatomically symmetrical areas which were both abnormal but which demonstrated comparable radionuclide concentration. This comparison gave an additional index for detecting generalized skeletal changes.

TABLE 1. DIAGNOSTIC GROUPING OF PATIENTS

Primary disease	Number of patients
Breast carcinoma	18
Epidermoid carcinoma (cervix, lung)	2
Malignant melanoma	1
Oat cell carcinoma of the lung	2
Lymphoepithelioma	1
Thyroid carcinoma	1
Unknown etiology	1

TABLE 2. SUMMARY OF SCANNING AND RADIOGRAPHIC RESULTS

No. of patients scanned	Radiological findings before scan		Results of scans	Metastases confirmed
	Negative radiographs of symptomatic areas	Degenerative changes in symptomatic areas		
11	10	1	Abnormal	Yes
13	4	9	Abnormal	No*
2	2	0	Normal	No

* Incomplete followup. See text.

RESULTS

Twenty-six patients satisfied the protocol requirements and were admitted for this study. Table 1 indicates the diagnostic grouping. Twelve patients received [47]Ca and 14 patients received [85]Sr.

Detection of lesions. In 24 out of 26 of the patients selected for study, the scans were interpreted as positive, and the results are summarized in Table 2.

1. In 11 patients with postive scans metastatic bone disease was confirmed at the site which demonstrated abnormal nuclide uptake. Four of these patients received [47]Ca and seven received [85]Sr. These confirmations were based on appearance of the lesion on subsequent radiographic views or demonstration by biopsy or at autopsy. Two of these scan confirmations must be qualified further because they did not fully satisfy the study requirements. One patient with positive radiographs at the positive scan site 40 days postinjection had, in retrospect, a lesion in the radiographs taken just before injection. A second patient accepted in the study with normal skeletal survey was found to have a lesion at the positive scan site when readings of the tomographic views taken just before the study started were reported and reviewed.

2. Of 13 patients with abnormal scans, nine were found to have a nonmalignant lesion at the abnormal site, one was found to have a herniated intervertebral disk on a myelogram performed 25 days after the scan and eight had osteoarthritic changes which included bony spurs and bridging between the vertebrae. These changes were sufficient to account at least in part for the abnormal scans. No definite bone metastases were found in one or more sets of radiographs taken of the abnormal scan sites, with the longest interval extending 149 days after tracer injection. The other four patients had no lesions which could account for the local increase in uptake of the nuclide tracer and were lost to follow-up.

3. Two patients with scans interpreted as negative were confirmed to the extent that each patient remained negative in terms of clinical and radiographic findings up to 1½ years after radionuclide study.

Optimum time for scanning. Abnormal uptake was seen 5 days after radionuclide administration in each of the 11 patients later confirmed to have metastatic bone disease. Two patients who received [85]Sr from this group had normal uptake at the lesion site 5 hr postinjection, and one of these patients also had normal uptake at 24 hr. The nine other patients had abnormal uptake at the lesion site at 5 hr, 24 hr and 5 days. The maximum lesion-to-normal-bone ratio was seen at 5 days in 10 of the 11 patients. On the basis of these findings, with the three periods selected for scanning each patient, the optimum time for scanning appears to be 5 days following injection.

Time lapse. The time lapse between abnormal scan findings and radiographic or histological con-

FIG. 1. Computer analyzed posterior search scan of [85]Sr from patient AR with counting rate information divided into 10% levels of maximum count recorded. Localized site of abnormally elevated counting rate (arrow) is seen in the left hemithorax. Color has been added to accent counting-rate-level transitions, and color code corresponding to different levels of counting rate is indicated beside figure.

firmation of metastatic bone disease varied over an interval ranging from 34 to 146 days.

INDIVIDUAL STUDIES

Patient AR with histologically proven malignant melanoma was studied with [85]Sr. At the time of the scan study, the patient complained of dull pain for the past month in the right lateral chest radiating to the back. A skeletal survey and chest films taken within 2 weeks of the scan revealed a single discrete lesion in the right 6th rib anteriorly; no other lesions were found. In addition to demonstrating this lesion on the anterior scan view, the 24-hr search scan suggested an abnormal contralateral asymmetry of the left to right hemithorax on the posterior scan view (Fig. 1). A focusing-collimator scan run at 5 days (Fig. 2) indicated an abnormal area showing a maximum contralateral left-to-right uptake asymmetry of 4:1 at the approximate level of the left 6th rib posteriorly. Radiographs 4 days before nuclide in-
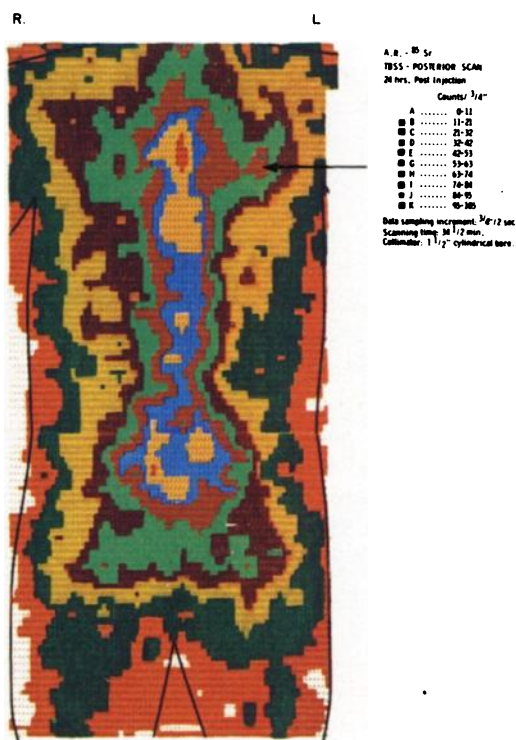
jection and 16 days after are seen in Fig. 3A and B. Each was read as negative for the presence of metastatic lesions to bone. Figure 3C, a radiograph taken 35 days postinjection, indicates a 2 × 1-cm lytic lesion in the left 6th rib posteriorly. Later films showed further destruction of the same rib. All other measurements on this patient were normal. As seen in a number of other confirmed scans, the positive scan site did not always conform with the symptomatic area.

Patient MD, a 65-year-old female with breast carcinoma, complained of back pain. Skeletal survey and tomographic views of the thoracic and lumbar vertebrae were interpreted as showing no evidence of metastatic disease within 2 weeks before scan study. Figure 4 shows the results of point counts taken with the 4-in. long × 2-in. dia cylindrical-hole collimator for three sequential measurements. Uptake is expressed in relative percent of dose. Abnormally high uptake was noted at the level of the lower thoracic vertebrae. Ratios of uptake between this site and adjoining vertebrae varied from 1.1 to 1.5. The highest ratio was seen at 5 days. A collapse of the 10th thoracic vertebra due to metastatic deposits was seen in radiographs taken 50 days after nuclide injection. Slight wedging of the 8th and 12th thoracic vertebrae were also seen for the first time on these radiographs. Earlier films revealed no evidence of destructive lesions in this area.

DISCUSSION

It is evident from these results that some early lesions will go undetected on radiographic views even with careful scrutiny of the radiographs by a radiologist who is aware of the clinical state of the patient

FIG. 2. Focusing collimator search scan taken 4 days postinjection of ⁸⁵Sr over intrascapular region with patient prone reveals presence of area of increased uptake in left upper corner of scan corresponding to left 6th rib. Left-to-right counting-rate ratio of approximately 4 to 1 is seen. Area corresponds to 2 × 1-cm lytic lesion site first detected by radiographs 35 days postinjection.

and the results of the bone scan. This is reasonable in view of the findings quoted in the literature that 30–50% change in bone density is required before visible changes can be detected on routine radiographs (13–15). It is not known how many go undetected by both methods; however, the present study indicates that scanning techniques are more sensitive than radiography for detecting early bone lesions. Research studies with ⁴⁷Ca or ⁸⁵Sr conducted on more than 400 patients since 1958 have indicated similar findings in many instances. This controlled study has verified these observations. The use of periodic bone scans in patients presenting a high risk of bone metastases such as in cancer of the breast or of the prostate would therefore appear to be more useful than serial skeletal surveys.

It must be reemphasized that abnormal scans do not necessarily reflect the presence of a malignant lesion and that some malignant lesions may not result in abnormal scans. Elevated ⁴⁷Ca or ⁸⁵Sr uptakes may be observed in any case in which a pathological process causes an increase in the local turnover rate of calcium. Examples of this include malignant, degenerative, inflammatory or traumatic processes.

Theoretical considerations. When used to detect bone lesions, radiography and radionuclide scanning each aim at evaluating a different basic parameter. In radiography the parameter is the amount and variation in bone calcium content between diseased and neighboring or contralateral areas. This is determined by visual recognition of a significant variation in optical density on the radiograph which corresponds to different degrees of absorption of the incident x-ray beam in these areas. In radionuclide scanning the parameter is the amount and differential of ⁴⁷Ca (or gamma-emitting homologue) incorporated in the lesion area and in neighboring or contralateral bone at various times following intravenous injection as determined by quantitative scanning.

The sensitivity of the radiographic test depends on many factors including the size and location of the lesion, the amount of differential absorption of the incident x-ray beam, and the optimization and reproducibility of physical parameters associated with the equipment and film as well as the experience of the radiologist and the data and time available to him. Several studies reported in the literature indicate that a minimum of 30–50% demineralization must occur in bone before visualization by standard radiographic procedures is possible (13–15). Vose (12) has shown that under very carefully controlled experimental conditions using a densitometer to measure optical density changes of approximately 3% and 5%, mineral content may be detected in the
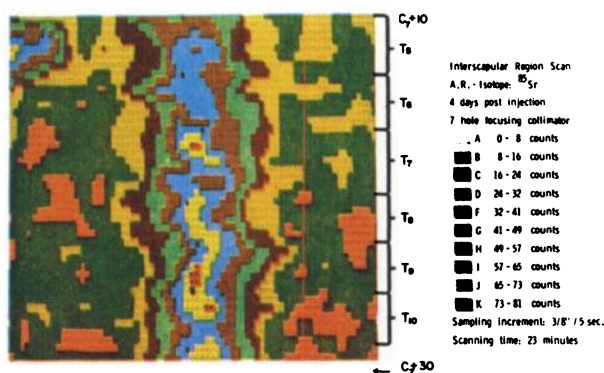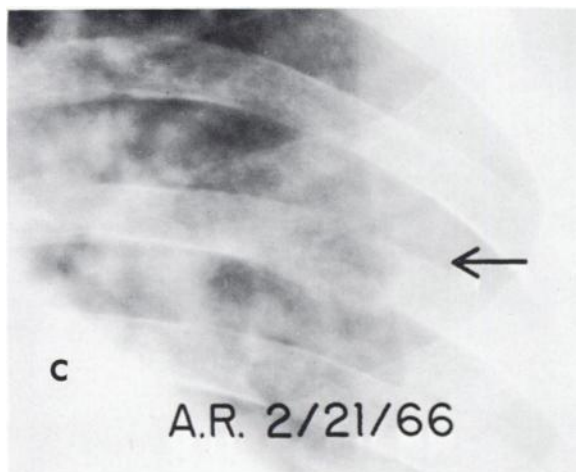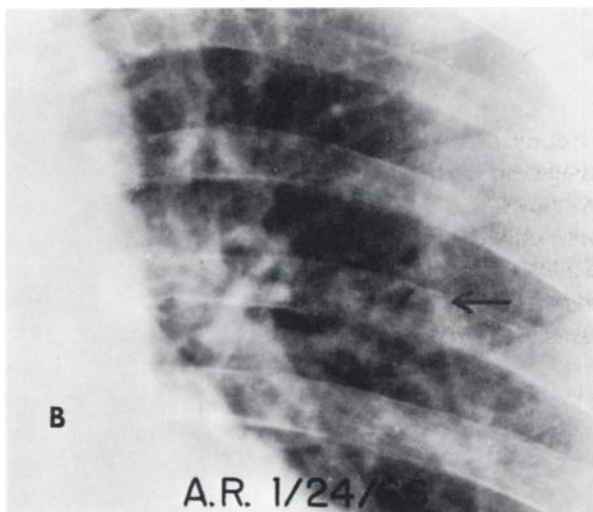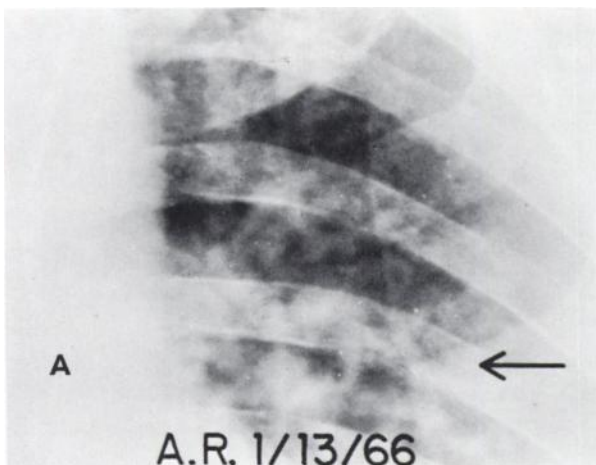
A.R. 1/13/66

A.R. 1/24/

A.R. 2/21/66

FIG. 3. Sequential views (A and B) of left rib cage show no abnormalities in left 6th rib posteriorly (arrow). Films were of good technical quality, and no destructive lesions could be identified even in retrospect. In C there is 2 × 1-cm lytic lesion involving posterior aspect of left 6th rib (arrow) where none was seen previously.
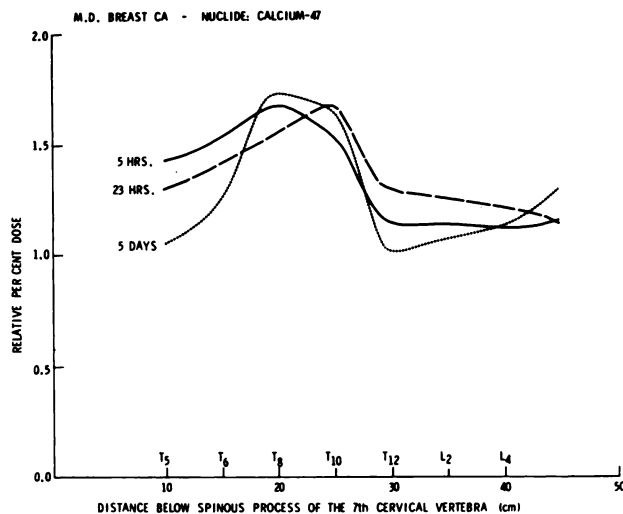

M.D. BREAST CA - NUCLIDE: CALCIUM-47

FIG. 4. Profile curves expressed in relative percent dose for patient MD for sequential point count measurements of ⁴⁷Ca taken over thoracic and lumbar vertebrae. Radiographs taken 50 days after nuclide injection revealed metastatic disease in 10th thoracic vertebra. No destructive lesions were seen in this area on previous films taken just before injection and during first month post-injection.

adult femoral neck and third lumbar vertebra, respectively, in serial films. These figures are equivalent to approximately 80 mg and 170 mg, respectively, of calcium in the study quoted.

The sensitivity of the radionuclide test and its rationale derive from the following considerations: It has been shown by Bauer et al (16,17) that there is a normal range of turnover rates of calcium in healthy bone and that this turnover rate is increased in areas where bone damage has occurred and where an attempt at healing is taking place. In the normal adult in whom the accretion and resorption rates of calcium are approximately equal, measurements according to Bauer's method yield a turnover rate of the order of 400 mg of calcium per day in the whole skeleton. In the vicinity of a bone lesion, the local accretion and resorption rates are generally both elevated to varying degrees depending on the rate of growth or repair of the lesion. The balance between these two rates indicates whether the lesion is lytic or blastic, but even in the case of lytic lesions, the accretion rate is generally elevated above normal unless growth has been completely arrested and no healing is taking place. A few cases of multiple myeloma have been seen in which there was no detectable increase in the local accretion rate.

The uptake of radionuclide in a particular area in bone after time t (days) is the product of the local accretion rate in milligrams stable calcium per day, and the average specific activity of the serum in microcuries per milligram of stable calcium in

the time period 0–t. This relation assumes that no significant resorption of the radioactive calcium occurs in time t, which is generally considered true if t is 5 days or less. It does not take into account the additional amount of radionuclide taken up in the rapidly exchanging fraction of the bone. The average value of the serum specific activity for the first 24 hr after intravenous injection of 100 μCi of ^{47}Ca in an adult is of the order of 0.02 μCi/mg calcium, and the amount of calcium accreted in the third lumbar vertebra (L3), for example, in the same period is of the order of 10 mg. Thus the amount of radionuclide taken up in this interval in L3 is about 0.2 μCi. The scintillation detector used for point counting in this study has a sensitivity of the order of 4,000 cpm/μCi for ^{47}Ca when used with a 4-in. long $\times$ 2-in. dia cylindrical collimator. Differentials in uptake of as low as 20% between the vertebrae, corresponding to approximately 2 mg of calcium, can easily be measured in a few minutes counting time 24 hr after intravenous injection of 100 μCi of ^{47}Ca. In practice, the observed counting rate over L3 24 hr after injection of 100 μCi of ^{47}Ca is about 4,000 cpm with the 2-in. collimator. Only about 20% of this figure is accounted for by ^{47}Ca accreted in L3 in the 24-hr period. The remainder is due to uptake of rapidly exchangeable calcium in L3 and activity in tissues outside the vertebrae. A differential of 20% in accreted ^{47}Ca between a normal neighboring vertebra and L3 would thus appear as a difference in counting rate of 4,000 compared to 4,160 cpm with this collimator which could be detected as a 2 standard-deviation difference in a 3-min count over each vertebra. A slow linear scan along the spine with a specially designed 7-hole tungsten focusing collimator provides greatly enhanced sensitivity over the figures quoted above for detecting spine lesions. These figures indicate the order of sensitivity of the radionuclide test. A differential gain or loss of 2 mg calcium/day between L3 and a neighboring vertebra would require a minimum of 85 days to reach the 170-mg differential detectable by the most sensitive radiographic method using densitometry, or 510 days by standard radiographic techniques.

Therefore, it appears that the sensitivity of the radionuclide test for determining changes in bone mineral content is approximately two orders of magnitude greater than that of radiographic methods. The experimental results appear to confirm the theoretical calculations of increased sensitivity offered by the radionuclide test.

Experimental considerations. Localized abnormal uptake can have a variety of causes other than malignant bone lesions. Inflammatory as well as trau-

matic or degenerative bone lesions can give increased local turnover rates of bone-seeking nuclides (11, 18). Such lesions, however, can usually be defined radiographically.

The following results of this study are mentioned briefly as potential guidelines for further investigation to refine the interpretation of scan data.

1. Comparison of the counting rates at serial times after injection on paired bones which were clinically and radiographically normal indicate that generally two contralateral bones differ by less than 2½ times the standard deviation (s.d.) of the mean of the two counting rates. The s.d. for each external point count is routinely kept to less than ± 5%. As an example, 1,500 and 1,800 net counts were measured, each in 0.5 min, over the left and right midfemurs. The mean is 1,650 and its s.d. is 41. The difference between the two measurements is thus 7.3 times the s.d. of the mean, which is well outside the normal allowable difference of 2½ s.d. Three serial readings tended to minimize errors in positioning. In 10 out of the 11 confirmed cases, the highest uptake ratios of lesion involved to normal bone occurred at the latest reading—5 days.

2. There is strong indication that the relative uptake values at selected times and for selected areas in adult subjects are sufficiently grouped about a mean to predict that a normal pattern could be obtained from a study of a larger number of patients. Such a library of values in a particular clinic or laboratory using its own scanners and standardizing procedures could serve as a useful internal reference for normal uptake ranges.

The values of relative percent dose calculated for external counts taken over various bones showed a grouping for each of the two nuclides used in this study. Table 3 gives the values taken from clinically normal areas— which remained negative during radiographic followup—of the patients included in this study. Patients had an age range of 25–65 years and a weight range of 100–200 lb. Values were excluded from symptomatic or isolated lesion-involved bone, from patients with previous or coexistent hormone therapy and from patients when readings were taken at a time which deviated more than ± 1 hr from the 5-hr measurements and ± 3 hr from the 24-hr and 5-day postinjection measurements. The arithmetic mean and root-mean-square standard deviation (RMS σ) are given for

TABLE 3. MEAN AND PERCENT ROOT-MEAN-SQUARE DEVIATION OF MEAN FOR RELATIVE PERCENT DOSE MEASUREMENTS RECORDED OVER CLINICALLY NORMAL BONE

Location	Nuclide	5 hr			24 hr			5 days		
		No. of cases	Mean	RMS σ as % of mean	No. of cases	Mean	RMS σ as % of mean	No. of cases	Mean	RMS σ as % of mean
Tibia	^{47}Ca	5	0.453	9.1	6	0.433	13.8	4	0.313	22.6
	^{85}Sr	13	0.325	13.6	13	0.291	22.7	7	0.224	27.3
Femur	^{47}Ca	4	0.501	6.8	6	0.464	9.0	1	0.319	——
	^{85}Sr	13	0.338	10.8	13	0.262	20.6	10	0.159	27.2
Patella	^{47}Ca	3	0.904	6.8	5	1.002	10.4	3	0.821	20.3
	^{85}Sr	8	0.658	10.6	14	0.778	15.9	9	0.506	22.7
Trochanter	^{47}Ca	4	1.322	7.8	3	1.341	13.9	3	1.317	11.6
	^{85}Sr	12	0.933	17.2	9	0.826	14.2	10	0.507	17.3

each of the areas evaluated. The grouping of values for each nuclide indicates that laboratories can develop internal reference uptake values for comparing patient studies and interpreting radionuclide data.

Cataloging uptake ranges for measurements over various skeletal sites according to the patients clinical diagnosis, age, past treatment, known skeletal involvement, etc. should lead to an improvement in the diagnostic usefulness of bone tracer studies. This study, as well as previous ones, revealed patients in whom comparison of uptake between contralateral bones were well within the normal range of 2.5 standard deviations, while their uptake levels were higher than normal. These patients were frequently found to have generalized skeletal disturbances previously not diagnosed or to have active bone metastases at sites missed by previous clinical tests. Evaluating external counting data from tracer studies in this manner parallels findings observed in kinetic studies (2).

SUMMARY

This controlled study has shown that bone scanning after the administration of ^{47}Ca or ^{85}Sr is a definite complement to radiological techniques for the diagnosis of bone lesions. Changes incident to early malignant bone lesions can be demonstrated before their detection by standard and special radiographic techniques. Bone lesions were detected by scanning 34–146 days before their appearance on radiographs in this study.

Further investigation of the local uptake patterns of normal and abnormal bone as a function of time may lead to the development of scan procedures that might possibly differentiate between malignant and certain nonmalignant lesions in bone, something that is currently not possible. The fact that 2 out of 11 confirmed malignant bone lesions detected by scanning in this study showed abnormal uptake only at

times greater than 5 hr after injection of the nuclide stresses the importance of sequential scans up to 5 days. The additional observation of an increasing lesion-to-normal bone ratio in 10 of 11 patients for the serial readings over 5 days emphasizes that the time factor plays an important role in nuclide scanning for bone-lesion detection.

REFERENCES

1. GREENBERG, E., PAZIANOS, A., COREY, K. R., KENNY, P., LAUGHLIN, J. S. AND PEARSON, O.: Radioactive calcium (Ca-47) and tracer studies in patients with bone lesions. *Proc. Conf. Res. Radiotherapy Cancer*, American Cancer Soc., 1961, p. 158.

2. COREY, K. R., KENNY, P., GREENBERG, E., PAZIANOS, A., PEARSON, O. AND LAUGHLIN, J. S.: The use of calcium-47 in diagnostic studies of patients with bone lesions. *Am. J. Roentgenol.* 85:955, 1961.

3. COREY, K. R., KENNY, P., GREENBERG, E. AND LAUGHLIN, J. S.: Detection of bone metastases in scanning studies with Ca-47 and Sr-85. *J. Nucl. Med.* 3:454, 1962.

4. KENNY, P., LAUGHLIN, J. S., WEBER, D. A., COREY, K. R. AND GREENBERG, E.: High-energy gamma ray scanner, in *Progress in Medical Radioisotope Scanning*. TID 7673, USAEC, Washington, D.C., 1963, p. 236.

5. GYNNING, I., LANGELAND, P., LINDBERG, S. AND WALDESKOG, B.: Localization with Sr-85 of spinal metastases in mammary cancer and changes in uptake after hormone and roentgen therapy. *Acta Radiol.* 55:119, 1961.

6. CHARKES, N. AND SKLAROFF, D.: Studies of metastatic bone lesions with strontium-85. *Radiology* 80:270, 1963.

7. ROSENTHALL, L.: The role of Sr-85 in the detection of bone disease, *Radiology* 84:75, 1965.

8. SIMPSON, W. J. AND ORANGE, R. P.: Total body scanning with strontium-85 in the diagnosis of metastatic bone lesions. *Can. Med. Assoc. J.* 93:1,237, 1965.

9. LAUGHLIN, J. S., BEATTIE, J. W., COREY, K. R., ISAACSON, A. AND KENNY, P.: Total body scanner for high energy gamma rays. *Radiology* 74:No. 1, 108, 1960.

10. BENUA, R. S., WEBER, D. A., KENNY, P. AND LAUGHLIN, J. S.: Digital scanning compared with photoscanning in liver examination. *J. Nucl. Med.* 9:135, 1968.

11. LAUGHLIN, J. S., KENNY, P., COREY, K. R., GREENBERG, E. AND WEBER, D. A.: Localization and total body

high energy gamma-ray scanning studies in cancer patients, in *Medical Radioisotope Scanning,* IAEA, Vienna, 1964, p. 253.

12. VOSE, G. P.: Factors affecting the precision of radiographic densitometry of the lumbar spine and femoral neck. *Progress in Development of Methods in Bone Densitometry.* NASA SP-64, 1965.

13. BABAIANTZ, L.: Les osteoporoses. *Radiol. Clin.* **16:** 291, 1947.

14. FUSI, G.: Saggio sperimentale sulle prime manifestazioni radiologiche di osteoporosi. *Radiol. Clin.* **22:**123, 1953.

15. LACHMAN, E.: Osteoporosis: the potentialities and limitations of its roentgenologic diagnosis. *Am. J. Roentgenol.* **74:**712, 1955.

16. BAUER, G. C. H., CARLSSON, A. AND LINDQUIST, B.: Bone salt metabolism in humans studied by means of radiocalcium. *Acta. Med. Scand.* **158:**143, 1957.

17. BAUER, G. C. H. AND WENDEBERG, G.: External counting of ⁴⁷Ca and ⁸⁵Sr in studies of localized skeletal lesions in man. *J. Bone Joint Surg.* **41B:**558, 1959.

18. FLEMMING, W. H., MCILRAITH, J. D. AND KING, E. R.: Photoscanning of bone lesions utilizing Sr-85. *Radiology* **77:**635, 1961.