KINETICS OF RADIONUCLIDES USED FOR BONE STUDIES

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In this paper we report our investigation to study the kinetics of five bone-seeking nuclides and to compare their local bone and plasma kinetics and urinary excretion rates in order to establish their relative usefulness for detecting and following up the course of metastatic bone lesions. The studies were quantitative, and they used quantitative and computerized scanning methods previously developed in this laboratory (*1–3*).

Radionuclide scanning of bone with ^{47}Ca and ^{85}Sr is a sensitive diagnostic technique (*4–9*) which can frequently indicate the presence and extent of lesions before they are visible on routine or special radiographs or tomograms (*10*). Experience in our laboratory and in others indicates that the short-lived nuclides ^{18}F (*11–15*), ^{87m}Sr (*14–19*) and ^{68}Ga (*20,21*) can also be used for bone scanning to determine and outline the probable site of lesion-involved bone. No intercomparison studies of all five nuclides have been reported, however, and this has made nuclide selection somewhat subjective in diagnostic situations where a short-lived nuclide would be desirable.

Improved methods of cyclotron and reactor production of the short-lived nuclides (*22,23*) and the ease of obtaining ^{87m}Sr and ^{68}Ga by generator elution (*24–26*) have recently made these nuclides available for routine use. Serious consideration should therefore be given to their use if evidence can be found that any of them has as well-defined characteristics of concentrating in bone, clearing rapidly from the soft tissues and blood and demonstrating comparable differential uptake between lesion-involved and normal bone as has been demonstrated for ^{47}Ca or ^{85}Sr. The half-life and decay mode of each of these three short-lived nuclides are attractive. Each potentially offers (1) reduced radiation dose to the patient, (2) suitable gamma-ray energies for *in vivo* scanning and (3) sufficiently short half-life to allow sequential follow-up studies or other radiopharmaceutical studies within a period of days.

A comparison of the kinetics of intravenously administered doses of ^{47}Ca (chloride), ^{85}Sr (nitrate), ^{87m}Sr (chloride) and ^{18}F (sodium fluoride) was made in man. Results of serial serum and external point-count measurements, short-term excretion data and general quantitative scan distribution characteristics are described.

The possibility of metal toxicity (*27*) and the additional chemical preparation procedures related to the use of ^{68}Ga (citrate) restricted our initial evaluation of this tracer to animal studies. Results of both scanning and *in vitro* specimen counting of rats following the intravenous administration of ^{47}Ca, ^{85}Sr, ^{18}F and ^{68}Ga are given.

MATERIALS AND METHODS

Instrumentation. The scanning facility used for all *in vivo* counting was the Sloan-Kettering Institute high-energy gamma-ray scanner (*1*). This scanner uses two co-linearly opposed detectors, each containing a 4 × 4-in. NaI(Tl) scintillation crystal (*28*). *In vitro* counting was carried out with a well-type gamma-ray detector system using a 3 × 3-in. CsI(Tl) crystal.

Nuclides. Table 1 shows the basic physical characteristics and the chemical form of each nuclide that was injected for bone scanning. ^{47}Ca and ^{85}Sr are the longer-lived nuclides with half-lives of 4.5 and 65 days, respectively; ^{87m}Sr, ^{18}F and ^{68}Ga are the contrasting short-lived nuclides with half-lives of 2.8 hr and less. Each nuclide gives a high photon

Received Jan. 29, 1968; revision accepted June 14, 1968.

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TABLE 1. PHYSICAL AND CHEMICAL CHARACTERISTICS OF TRACERS USED IN THIS STUDY

Nuclide	^{47}Ca	^{85}Sr	^{87m}Sr	^{18}F	^{68}Ga
Physical half-life	4.5 days	65 days	2.8 hr	110 min	68 min
Primary gamma energy (No./100 disintegrations)	1.31 MeV (76)	0.513 MeV (100)	0.388 MeV (78)	0.511 MeV (97, $\beta+$)	0.511 MeV (87, $\beta+$)
Chemical form	Chloride	Nitrate	Chloride	Sodium fluoride	Citrate + carrier Ga
Specific activity*	>140 mCi/gm Ca	>7 Ci/gm Sr	>5 Ci/gm Sr	Carrier free	Carrier free
Admin. activity	100 μCi	100 μCi	1 mCi	1 mCi	1 mCi†
Counts/min/μCi in std geom‡	4.3×10^3	1.01×10^4	9.5×10^3	1.96×10^4	1.76×10^4
Dose-to-bone (rads)	6.3**	5.2	0.14	0.26	0.38

* Specific activities listed refer to the time of injection.
† Proposed dose.
‡ 2-in.-diameter × 4-in.-long cylindrical bore collimator: Channel width = 100 keV, fixed source-to-crystal distance.
** Includes dose from 5% contaminant of ^{45}Ca and ^{47}Sc daughter product of ^{47}Ca consequent on injecting 3 days post 7-day irradiation of ^{46}Ca.

yield for the major gamma-ray energy; a range of 0.76–1.94 photons per disintegration is available from these five nuclides. The primary gamma-ray energies are of the same order of magnitude with the exception of ^{47}Ca. The latter is considered a high-energy gamma-ray nuclide in terms of diagnostic tracer studies (*28*).

The gamma-ray emitting isotopes of calcium, strontium and fluorine were obtained from commercial suppliers in the chemical form and specific activities listed in Table 1. ^{68}Ga as the EDTA complex was obtained from a commercially available ^{68}Ge–^{68}Ga generator by elution with 0.005 *M* EDTA. ^{68}Ga-citrate with stable carrier gallium was prepared by the ^{68}Ga-EDTA-Ga(III) exchange method suggested by Hayes (*21*). "Carrier-free" ^{68}Ga-citrate was prepared by evaporating the ^{68}Ga-EDTA generator eluate to dryness in a platinum crucible under an infrared lamp, ashing at about 400°C for 20 min and dissolving the ash in 2% (W/V) citric acid. Aluminum content in the eluate was estimated to be in microgram amounts by the generator supplier. Columns are normally washed with water and 0.005 *M* EDTA (pH 7) to remove fines from the alumina before shipment. ^{68}Ge leakage was verified experimentally to be less than 0.01% of its total activity in the column.

Patient studies. Eleven patients with radiographic evidence of localized active cancer involving bone were included in this study. The primary diagnoses for these patients are shown in the box at the right.

Each patient received two nuclides intravenously: six patients received ^{18}F and ^{47}Ca; three, ^{18}F and ^{85}Sr; and two, ^{87m}Sr and ^{85}Sr. One millicurie of ^{18}F or ^{87m}Sr was given on the first day of the study, and 100 μCi of ^{47}Ca or ^{85}Sr was given from 24 to 72 hr later. Heparinized blood samples were taken four times during the first hour and then hourly until 5 hr after each injection. The 5-hr urine excretion also was collected and measured. Local uptake or point-count measurements over both normal and lesion-involved bone were carried out at 30 min and 1 hr and then at hourly intervals until 5 hr. Continuous scans were run at selected times between point count measurements. For the longer-lived nuclides, additional external point counts were taken at 24 hr and 5 days after injection.

Animal studies. Each of the nuclides studied in man was also studied in Sprague-Dawley rats. In addition ^{68}Ga citrate, both with and without carrier, was also studied in rats. Relative distribution characteristics were studied between soft tissue and bone and also between normal bone and repairing bone. Tracer studies were carried out on rats 11 days after the fracture of a single tibia. Published studies indicate that bone-healing processes are well underway by 11 days after fracture (*29,30*). While

Patient	Primary diagnosis
IG, IL, MS, JT, RC, VS	Breast carcinoma
CM	Thyroid carcinoma
GW, EC	Chondrosarcoma
JB	Prostatic carcinoma
DM	Lung carcinoma

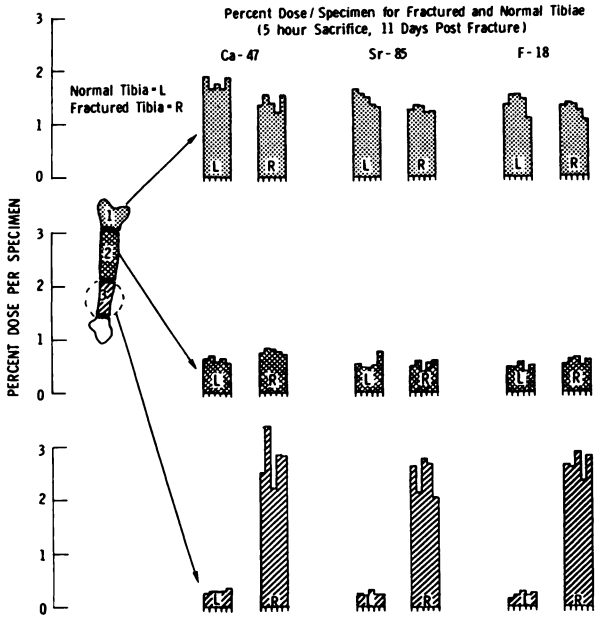


FIG. 1. Comparison of activities in different regions of normal and fractured rat tibiae for calcium, strontium and fluorine tracers. Five rats were studied with each tracer. (^{47}Ca rats: 233–294 gm, 56 days old; ^{85}Sr rats: 273–340 gm, 66 days old; ^{18}F rats: 262–295 gm, 60 days old.)

under light ether anesthesia, the rats were given one of the five tracer solutions intravenously into the tail vein. The animals were sacrificed by excess ether 5 hr later.

In the first series of experiments, a total of 20 rats was studied. Following sacrifice, radiographs were taken to verify the position of fracture, scans were run and specimens were dissected for *in vitro* counting and for determinations of percent dose/gram tissue (wet weight). The specimens included the left and right tibiae and femora, and samples of the calvarium, rib, vertebrae, thigh muscle, kidney, pancreas, lung, spleen, heart, liver, testes, whole blood and fat.

Fifteen additional rats were injected and then sacrificed to evaluate specifically the different regions of the normal and fractured tibiae. ^{18}F, ^{85}Sr and ^{47}Ca were each studied in five rats. The fractured and normal tibiae were each divided into three specimens for counting: (1) the proximal head, including the epiphysis; (2) the shaft extending to the proximal edge of the callus; and (3) the portion of the shaft containing the callus and the contralateral distal portion of the shaft (Fig. 1). The specimens were counted separately.

RESULTS

Counting efficiency. Counting-rate sensitivity for a standardized geometry with a constant 100-keV window setting centered on the primary gamma-ray energy varied by more than a factor of four for the five nuclides on a microcurie-to-microcurie comparison. Table 1 shows ^{18}F > ^{68}Ga > ^{85}Sr > ^{87m}Sr > ^{47}Ca.

Patient studies. The radiation dose to bone calculated for each of the five nuclides in a 70-kg man is listed in Table 1. Conservative assumptions were made: the total administered dose was assumed to be distributed homogeneously in bone, and the effective half-life was taken to be equal to the physical half-life for each nuclide. For the proposed administered activity of 100 μCi of ^{47}Ca or ^{85}Sr and 1 mCi of ^{18}F, ^{87m}Sr or ^{68}Ga, the radiation dose for the short-lived nuclides is less than 10% of that received from ^{47}Ca or ^{85}Sr.

Figure 2 shows the mean plasma concentration curves expressed as percent dose per liter for the patients during the first 5 hr postinjection for ^{47}Ca, ^{85}Sr and ^{18}F. The mean curve for ^{87m}Sr is not indicated because it had the same characteristic slopes and amplitudes as that for ^{85}Sr. ^{18}F disappeared from the plasma much more rapidly than did ^{47}Ca, ^{85}Sr and ^{87m}Sr. The second rate constant of the ^{18}F

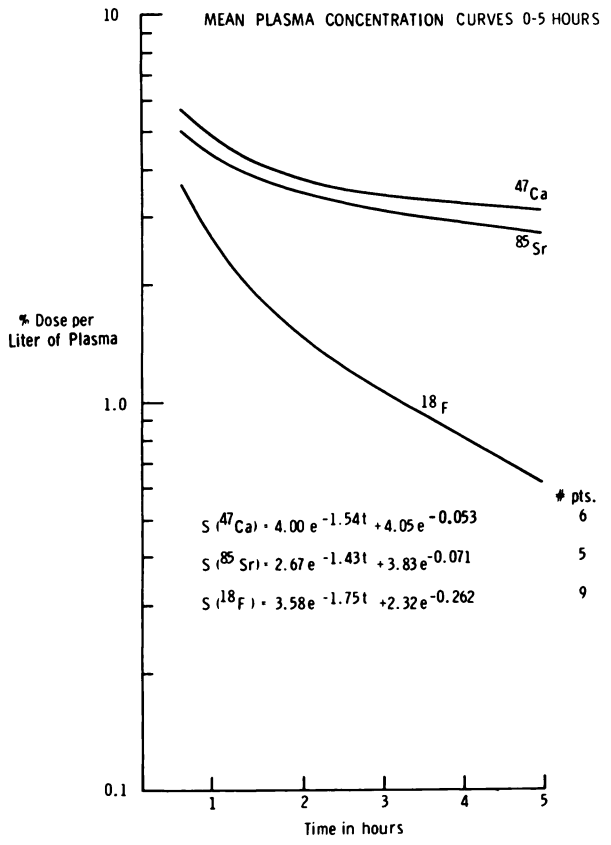


FIG. 2. Variation of mean plasma concentration with time for ^{47}Ca, ^{85}Sr and ^{18}F. (^{47}Ca, six patients; ^{85}Sr, five patients; ^{18}F, nine patients.)

TABLE 2. COMPARISON OF CUMULATIVE 5-HR URINE EXCRETIONS OF CALCIUM, STRONTIUM AND FLUORINE TRACERS

	Cumulative 5-hr urine excretion (% of injected dose)				
Patient	^{47}Ca	^{18}F	Patient	^{85}Sr	^{18}F
IG	0.2	7.4	JB	8.9	23.5
IL	1.6	17.9	EC	4.1	24.8
CM	1.4	11.9	DM	5.1	22.3
MS	4.3	22.0	Patient	^{85}Sr	^{87m}Sr
JT	2.2	22.4	RC	5.2	5.3
GW	—	—	VS	3.0	2.7

TABLE 3. COMPARISON OF UPTAKES OF CALCIUM, STRONTIUM AND FLUORINE TRACERS 4-5 HR POSTINJECTION IN MIDSHAFTS OF NORMAL TIBIAE*

Patient	Relative percent of injected dose			Relative percent of retained dose		
	^{47}Ca	^{18}F	Ca/F	^{47}Ca	^{18}F	Ca/F
IG	0.30	0.15	2.0	0.30	0.16	1.9
IL	0.49	0.22	2.2	0.50	0.27	1.9
CM	0.31	0.25	1.2	0.31	0.28	1.1
MS	0.30	0.13	2.4	0.31	0.16	1.9
JT	0.40	0.28	1.5	0.41	0.36	1.2
GW	0.44	0.29	1.5	—	—	—
	^{85}Sr	^{18}F	Sr/F	^{85}Sr	^{18}F	Sr/F
JB	0.30	0.22	1.3	0.32	0.29	1.1
EC	0.29	0.18	1.6	0.30	0.24	1.2
DM	0.30	0.18	1.6	0.31	0.23	1.3

* Measured by external counting with a 2-in.-diameter × 4-in.-long collimator at contact. Results are expressed both in terms of percent of injected dose and percent of retained dose, relative to counting rate of aliquot of injected dose measured in standard geometry and scaled up to counting rate of whole injected dose.

curve shows the plasma clearance to be four to five times faster than that for the other nuclides. For the different patients included in the paired studies, the resultant mean plasma concentrations calculated from the activity integrated over 5 hr varied from 1.1 to 2.6% of dose/liter for ^{18}F, 3.4 to 6.2 for ^{47}Ca and 3.3 to 4.9 for ^{85}Sr and ^{87m}Sr.

Table 2 summarizes the 5-hr cumulative urine-excretion measurements for the four nuclides. The urine excretion of ^{18}F was consistently greater than that for the other nuclides in paired studies: the range of injected dose that was excreted in eight patients was 7.4–24.8%. Within experimental variation, the excretion of ^{85}Sr and of ^{87m}Sr in urine was observed to be the same. The urinary excretion of strontium varied from 2.7% to 8.9% of the injected dose in five patients. ^{47}Ca showed the lowest 5-hr excretion in urine: 0.2% to 4.3% of injected dose in five patients.

Serial external point counts over both normal and lesion-involved bone of the skeleton were measured with a cylindrical collimator with a bore 2 in. in diameter and 4 in. long. The data revealed considerable differences in the relative percent of administered activity present at different times following injection for each nuclide. The measured values over normal compact bone, such as the shafts of the tibiae or femora, generally indicated greatest uptake for ^{47}Ca per unit dose, less for ^{85}Sr and ^{87m}Sr isotopes and least for ^{18}F. Relative percent of administered dose measured for ^{47}Ca or ^{85}Sr over these areas tended to remain constant or to increase slightly during the period from 30 min to 5 hr. The same measurements for ^{18}F show continuously decreasing values during the same interval.

TABLE 4. COMPARISON OF UPTAKES OF CALCIUM, STRONTIUM AND FLUORINE TRACERS AT 4-5 HR POSTINJECTION IN BONE LESION SITES*

Patient	Location of lesion	Relative percent of injected dose			Relative percent of retained dose		
		^{47}Ca	^{18}F	Ca/F	^{47}Ca	^{18}F	Ca/F
IG	Greater trochanter	1.77	1.48	1.2	1.77	1.60	1.1
IL	Femur	0.77	0.65	1.2	0.78	0.80	1.0
CM	Femur	0.79	0.31	2.5	0.80	0.36	2.2
MS	Humerus	0.54	0.33	1.6	0.56	0.43	1.3
JT	Femur	0.95	1.44	0.7	0.97	1.85	0.5
GW	Tibia	0.94	0.87	1.1	—	—	—
		^{85}Sr	^{18}F	Sr/F	^{85}Sr	^{18}F	Sr/F
JB	Lumbar vertebrae	1.35	1.98	0.7	1.48	2.59	0.6
EC	Femur	0.87	1.00	0.9	0.91	1.33	0.7
DM	Femur	1.11	1.04	1.1	1.17	1.34	0.9
		^{85}Sr	^{87m}Sr	$^{85}Sr/^{87m}Sr$	^{85}Sr	^{87m}Sr	$^{85}Sr/^{87m}Sr$
RC	Thoracic vertebrae	0.73	0.67	1.1	0.77	0.71	1.1
VS	Humerus	0.40	0.37	1.1	0.41	0.38	1.1

* Measured by external counting with 2-in.-diameter × 4-in.-long collimator at contact. Results are expressed both in terms of percent of injected dose and percent of retained dose, relative to counting rate of aliquot of injected dose measured in standard geometry and scaled up to counting rate of whole injected dose.

This may be due in part to differences in soft tissue and blood clearance of the different nuclides.

Calculation of relative percent retained dose did not compensate for the differences in uptake seen by external counting. Table 3 illustrates the results of measurements over the tibial shafts between 4 and 5 hr postinjection. The uptake gradient among the different nuclides retains the same order when expressed as local uptake relative to dose injected or as local uptake relative to percent dose retained in the body.

The same correlation for external point counts recorded over the lesion site between 4 and 5 hr is shown in Table 4. The data indicate that ^{47}Ca has the greatest uptake with respect to administered dose while ^{18}F is somewhat less and ^{85}Sr and ^{87m}Sr is the least. For calculations of local relative percent retained dose, three out of five patients showed an uptake of ^{18}F equal to or greater than that of ^{47}Ca. All three paired Sr/F studies showed considerably greater values for the local relative percent of the retained dose with ^{18}F. As expected, the uptake of ^{85}Sr and ^{87m}Sr are almost identical. The differential of relative percent of the retained dose obtained with ^{18}F compared with ^{47}Ca or ^{85}Sr (^{87m}Sr) indicates that the specificity for uptake of ^{18}F in the bone-lesion area at 5 hr is similar to that for ^{47}Ca and probably is greater than that for ^{85}Sr or ^{87m}Sr. This is indirectly supported by the observation that the plasma concentration of ^{18}F at 5 hr was 12–34% of the values found with ^{47}Ca or ^{85}Sr. Consequently, the percent dose measurements for ^{47}Ca and ^{85}Sr presumably have a proportionately greater contribution from the nontarget soft tissue and blood than do the measurements for ^{18}F.

In eight of the nine patients studied with ^{18}F, the maximum ratio of counts over lesion-involved bone to either contralateral, adjoining or other normal bone was determined between 3 and 5 hr postinjection. Table 5 shows these ratios for seven patients who had either normal contralateral or adjoining bone. In six of these seven patients, the maximum ratio seen for ^{18}F between 3 and 5 hr was equal to or greater than that seen for ^{47}Ca or ^{85}Sr. The one exception was patient CM.

Additional measurements at 24 hr and at 5 days were taken with the longer-lived nuclides, and the ratio was greatest for the latest measurement in five out of six patients. In two of these cases, however, the ratio with ^{18}F was still greater at 5 hr than was the ratio with ^{47}Ca or ^{85}Sr at 5 days. The remaining subjects had a lesion-to-normal bone ratio of ≥ 2 at 5 hr with ^{18}F.

The short-lived nuclides gave better counting statistics than the longer-lived ones during the early period following injection. Table 6 shows the improvement in statistics at 3 and 5 hr for measurements taken over normal tibia with the 2-in.-diameter by 4-in.-long cylindrical bore collimator. The data are normalized to 100 μCi doses of ^{47}Ca and ^{85}Sr and 1 mCi doses of ^{18}F and ^{87m}Sr. The improvement is marked at 3 hr and is still present at 5 hr despite the considerable decay of ^{18}F and ^{87m}Sr.

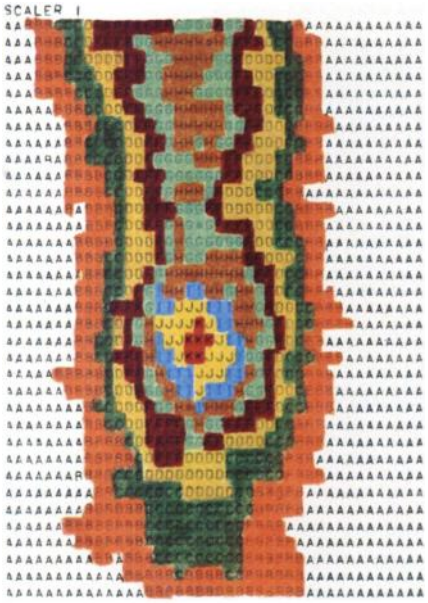
Figures 3A and B and 4A and B show scans from paired nuclide studies with ^{47}Ca and ^{18}F and with ^{85}Sr and ^{18}F, respectively. Figures 3A and B are computer-analyzed scans from punched paper tape with net counting-rate information printed out in 10 equally spaced levels, each an integral multiple of 10% of the maximum counting rate. Both are focusing-collimator* scans taken over the proximal one third of the shaft of the right tibia in patient GW who had sustained a pathological fracture at the site of recurrent chondrosarcoma. This site is located in the central area of each scan. Localization of the lesion is seen with each nuclide. Improved contrast between bone and soft tissue is seen in the ^{18}F scan. Counting statistics are also improved with ^{18}F. The maximum counting rate over the lesion (red or K level) was 132 counts/1.25 sec with ^{18}F; for ^{47}Ca the same position gave 67 counts/5 sec.

TABLE 5. RATIOS OF COUNTING RATES OVER BONE LESIONS TO THOSE OVER NORMAL CONTRALATERAL OR ADJACENT (FOR VERTEBRAE) BONE*

		Time after injection			
		½–5 hr			
Patient	Nuclide	Range of values	Time of max. (hr)	1 day	5 days
IL	^{18}F	1.5–2.0	5	—	—
	^{47}Ca	1.2–1.3	5	1.3	1.7
CM	^{18}F	1.1–2.0	¾	—	—
	^{47}Ca	1.7–2.0	3	1.3	1.0
MS	^{18}F	1.7–2.2	4¾	—	—
	^{47}Ca	1.8–2.2	5	2.8	5.1
GW	^{18}F	3.5–4.8	5	—	—
	^{47}Ca	2.8–3.1	¾	3.0	3.4†
JB	^{18}F	1.9–2.6	3	—	—
	^{85}Sr	1.7–2.2	2	2.3	3.0
EC	^{18}F	3.6–4.4	4½	—	—
	^{85}Sr	2.5–3.0	1	—	—
DM	^{18}F	3.1–5.0	4	—	—
	^{85}Sr	2.1–2.5	2	3.5	6.1‡

* Measured by external counting with 2 in.-diameter × 4 in.-long collimator at contact.
† 3 day value.
‡ 6 day value.

* Tungsten 7-hole focusing collimator; FWHM for ^{60}Co in air is 2.8 cm.



RIGHT TIBIA SCAN
G.W. - Isotope: ^{18}F
149 Min. Post Injection

	A	0 - 13
▬	B	13 - 26
▬	C	26 - 40
▬	D	40 - 53
▬	F	53 - 66
▬	G	66 - 79
▬	H	79 - 92
▬	I	92 - 106
▬	J	106 - 119
▬	K	119 - 132

Sampling Increment:
3/16"/11/4 sec.
Scanning Time: 19 min. **A**

RIGHT TIBIA SCAN
G.W. - Isotope: ^{47}Ca
166 Min. Post Injection

	A	0 - 7
▬	B	7 - 13
▬	C	13 - 20
▬	D	20 - 27
▬	F	27 - 34
▬	G	34 - 40
▬	H	40 - 47
▬	I	47 - 54
▬	J	54 - 60
▬	K	60 - 67

Sampling Increment:
3/8"/5 sec.
Scanning Time: 25 min.
B

FIG. 3. A is scan of proximal third of right tibia with 7-hole tungsten focusing collimator 166 min after injection of ^{47}Ca. Counts were summed for every ⅜-in. increment of distance travelled by the scanner. Scan speed was ⅜ in./5 sec or 4.5 in./min. B is scan of same area after injection of ^{18}F. Counts were summed for every 3/16-in. increment of distance travelled by the scanner. Scan speed was 3/16 in./1¼ sec or 9 in./min.

The patient had first received 407 μCi of ^{18}F and then 73 μCi of ^{47}Ca. Both scans were taken at approximately equal times postinjection.

Figure 4A and B are scans with a 1.5-in.-diameter cylindrical-bore collimator on a patient (JB) who had received 568 μCi of ^{18}F first and then 107 μCi of ^{85}Sr. The scans extend from the level of the suprasternal notch to the patella. Counting-rate-level transitions are purposely coarse, and each color transition represents four standard deviations. The scans are computer corrected for background subtraction and for physical decay of the nuclides. The known lesion sites include metastatic involvement of the 4th lumbar vertebra and the right wing of the ilium. The lesion sites are seen with each nuclide; however, much better definition of the bony skeleton is seen with ^{18}F. The counting rates for ^{18}F over bony areas were more than twice those of ^{85}Sr. Both scans were carried out approximately 4.5 hr postinjection.

Animal studies. The main purpose of these studies was to evaluate the localization of ^{68}Ga-citrate in comparison with the other nuclides for normal and healing bone and for soft tissue before use in humans. Recent studies by Hayes *et al* (*20,21*) indicate that ^{68}Ga may be used as a bone-scanning agent when injected as the citrate with stable gallium carrier added. The chemical toxicity of stable gallium has not been studied thoroughly, but the estimated LD_{10} for man is 20 mg Ga^{3+}/kg body weight (*27*). Hence, we restricted our ^{68}Ga studies to rats

TABLE 6. AVERAGE COUNTING RATES FOR 4 NUCLIDES*

Nuclide	No. of patients	Av. counting rate at 3 hr	Av. counting rate at 5 hr	1 s.d. (% net counting rate) for counting times: ½ min at 3 hr	1 min at 3 hr	½ min at 5 hr	1 min at 5 hr
^{47}Ca	6	1,546	1,585	3.6	2.6	3.6	2.5
^{85}Sr	5	2,831	2,841	2.7	1.9	2.7	1.9
^{18}F	9	15,184	6,354	1.1	0.8	1.8	1.3
^{87m}Sr	2	12,441	7,883	1.3	0.9	1.6	1.1

* Measured with 2-in-diameter × 4-in.-long collimator in contact with midshaft of tibia. Rates are normalized to 100 μCi doses of ^{47}Ca and ^{85}Sr, and to 1 mCi doses of ^{18}F and ^{87m}Sr. Background rates were measured for 5 min.

with 11-day-old fractures. In each of these animals, radiographs and specimen dissection revealed healing fractures along the distal shaft of the fractured tibia.

Definition of the bony skeleton was detailed best with ^{18}F. ^{47}Ca and ^{85}Sr gave somewhat poorer contrast between bone and soft tissue. ^{68}Ga gave the least contrast. The same relationships among these nuclides were seen for decreasing degrees of contrast of fracture site with adjoining and contralateral normal bones.

The ratio of fractured to normal contralateral tibia determined by the ratio of the percent dose/gram wet weight of whole tibia specimens varied by less than a factor of two for all scan agents for the 20 rats included in Table 7. To evaluate more closely the differential available for *in vivo* scan procedures, the ratios of normal tibiae to muscle were calculated. Table 7 shows that this ratio for ^{18}F is more than an order of magnitude greater than for the other nuclides. ^{68}Ga showed minimum contrast between bone and muscle.

The activity level of all soft tissues averaged considerably less with ^{18}F than with the other nuclides

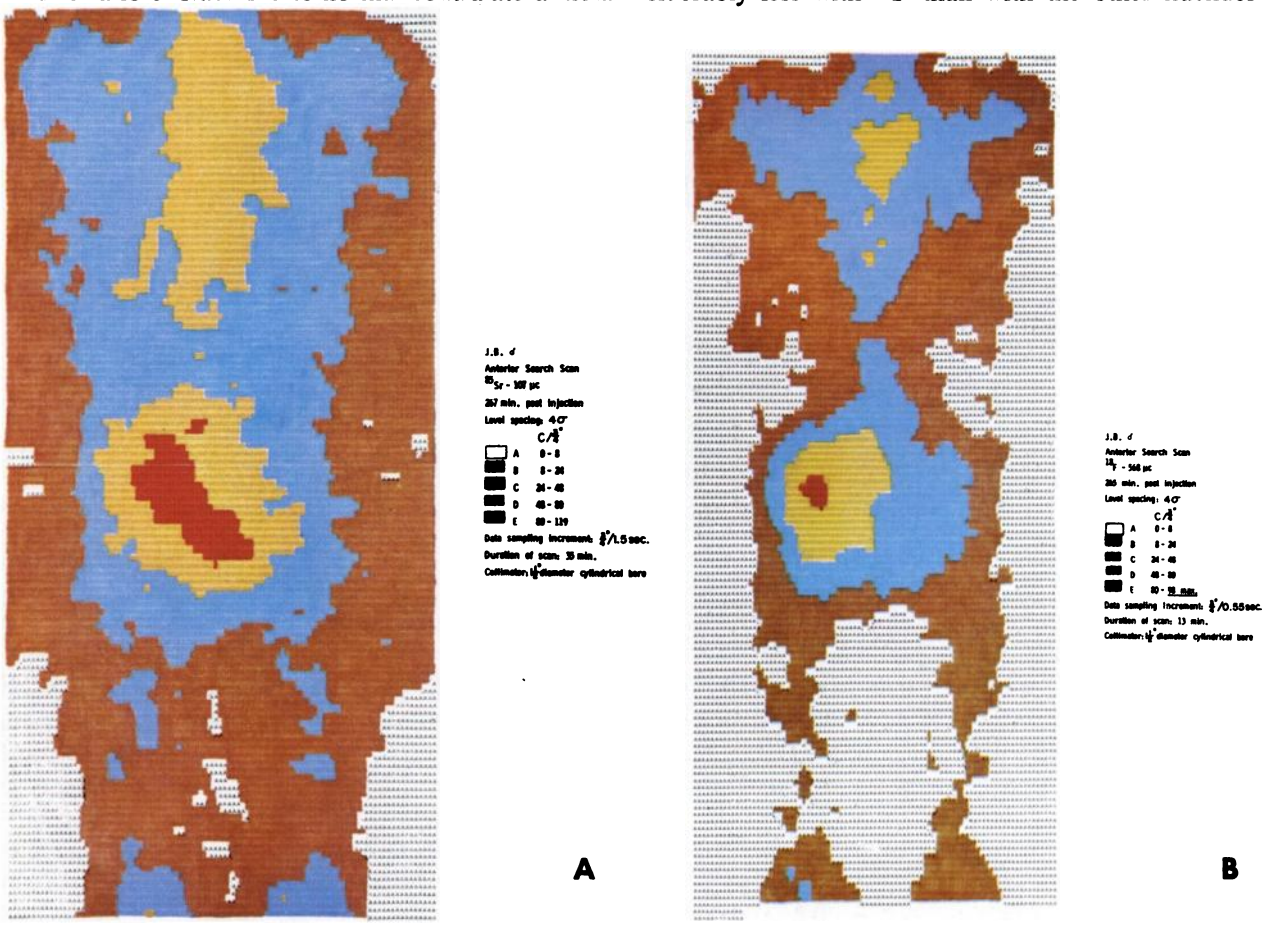


FIG. 4. A is scan extending from suprasternal notch to level of patella with a 1.5-in.-diameter × 4-in.-long cylindrical-bore collimator after injection of ^{85}Sr. Counts were summed for every ¾-in. increment of distance travelled by the scanner. Scan speed was ¾ in./1.5 sec or 30 in./min. B is scan of same area after injection of ^{18}F. Counts were summed for every ¾-in. increment of distance travelled by the scanner. Scan speed was ¾ in./0.55 sec or 82 in./min.

(see Table 7). The normal tibia is compared with the lowest- and highest-activity soft-tissue specimens (per gram wet weight) for each individual rat and averaged for a series with each radionuclide. ^{18}F showed the greatest contrast between bone and soft tissue, and ^{68}Ga showed the poorest contrast.

Fifteen additional rats were injected similarly and then sacrified specifically to evaluate sections of the normal and fractured tibia. ^{18}F, ^{85}Sr and ^{47}Ca were each studied in five rats. Figure 1 contains a sketch of the dissected sections and compares graphically the percent dose/specimen for each section.

The ratio of fractured to contralateral normal bone was calculated from the values of percent dose/specimen for each rat. ^{18}F showed an average ratio of 12.6 compared to 9.4 for ^{47}Ca and 9.9 for ^{85}Sr. The average ratio in terms of percent dose/gram wet weight was 2.6 for ^{18}F, 2.1 for ^{85}Sr and 1.7 for ^{47}Ca.

DISCUSSION

The deposition of bone tracer nuclides is generally thought to be the result of cellular activity causing the deposition of mineral in bone formation and exchange, both rapid ion exchange in and/or on the crystal surfaces and slow incorporation of ions within the crystal by intracrystalline ion exchange (*31,32*).

The mechanism of deposition varies with the element used as a tracer. For example, ^{18}F is injected in the chemical form of NaF and is available for exchange as a monovalent anion. Exchange deposition in bone of this anion is considered to be a heteroionic exchange for hydroxyl groups and perhaps for other anions in the surfaces of the mineral phase. Fluoride can also be incorporated in the hydroxyapatite crystals of bone mineral as they are being laid down and can exchange with hydroxyl ions within crystals previously formed. These mechanisms, while important in long-term biological processes, are too slow to be demonstrated with an isotope with the short 110-min half-life of ^{18}F. ^{47}Ca, ^{85}Sr and ^{87m}Sr are injected as $CaCl_2$, $SrCl_2$ or $Sr(NO_3)_2$. Each is available for exchange as a divalent cation for Ca^{2+} ions in bone crystal and for primary incorporation into new crystals. The possible ion interactions for these elements are discussed in detail in Ref. *32*. ^{68}Ga is administered as gallium citrate with added stable carrier. The mechanism of apatite crystal interaction with gallium has not been fully investigated. The availability for exchange on bone surfaces of either trivalent ^{68}Ga ions or the ^{68}Ga citrate complex apparently depends, however, on competition with binding sites on serum proteins (*33*). At a dose of 2 mg/kg body weight of carrier gallium, the number of stable gallium atoms far exceeds the number of ^{68}Ga atoms. More ^{68}Ga is thus made available for bone and other tissues by the administration of stable carrier gallium.

The deposition of the different nuclides used in tracer work in bone is not necessarily affected in the same way by hormones known to affect bone metabolism. For example, Rodan (*34*) investigated ^{18}F and ^{47}Ca deposition in the rat skeleton after the administration of pharmacologic doses of cortisone, estrogen, testosterone, vitamin D and parathyroid hormone. The rates of deposition of both nuclides were observed to be altered qualitatively in the same way by each agent. Quantitatively, however, more marked changes in uptake following hormone treatment were observed in the animals receiving ^{18}F.

These and other variations in the *in vivo* handling of different tracers such as different renal resorption rates may explain the observations made in this study. The data obtained from this investigation illustrate some baseline criteria which may be used to select the appropriate scanning agent for *in vivo* studies of bone.

In general, the "uptake" of ^{47}Ca, ^{85}Sr, ^{87m}Sr and ^{18}F during the first 5 hr after injection is sufficiently large to make each useful as a bone tracer in diagnosis (Tables 3, 4, 6). The reduced radiation dose to the patient from the short-lived nuclides, however, makes their use advisable when possible. The suggested microcurie doses in Table 1 gives better

TABLE 7. RATIO OF BONE TO MUSCLE AND SOFT TISSUE ACTIVITY CONTENT*

Ratio	Nuclide	Number of rats	Minimum ratio	Maximum ratio	Average ratio
Normal Right Tibia/ Muscle	^{18}F	5	800	13,350	4,800
	^{47}Ca	5	50	120	90
	^{85}Sr	5	60	180	130
	^{68}Ga(I)	3	40	60	50
	^{68}Ga(II)	2	10	20	15
Normal Right Tibia/Soft Tissue	^{18}F	5	490	5,130	—
	^{47}Ca	5	55	180	—
	^{85}Sr	5	70	230	—
	^{68}Ga(I)	3	3	50	—
	^{68}Ga(II)	2	2	10	—

^{68}Ga(I): Hayes (21) preparation of ^{68}Ga-citrate with stable carrier gallium, using 2.7–3.2 mg stable Ga carrier/kg rat.
^{68}Ga(II): "Carrier free" preparation.
Soft tissues included: Thigh muscle, kidney, pancreas, lung, spleen, heart, liver, testes, whole blood and fat.
* Calculated from determinations of percent administered dose per gram. Activity of specimens was measured by well counting. (20 rats studied, 2–4 months old, 125–365 gm, 5 hr sacrifice.)

counting statistics for both ^{18}F and for ^{87m}Sr compared with ^{47}Ca and ^{85}Sr during the first 5 hr after injection. The improved statistics gained with ^{18}F have even more significance because of the more rapid clearance of this material from blood and soft tissues. Greater counting rates are available in conjunction with an improved target-to-background ratio. A similar improvement in counting rates is seen with ^{87m}Sr; however, this is due only to its favorable decay scheme which permits a larger dose to be administered than is the case for ^{85}Sr. The ratio of bone to blood and soft tissues, or the target-to-background ratio duplicates that of ^{85}Sr.

One disadvantage of ^{18}F, however, should not be disregarded. The high urine activity of ^{18}F, which frequently accumulates rapidly in the bladder, can confuse scan interpretation in the area of the lower vertebrae and pelvis. Having the patient void prior to scan reduces the possibility of a false positive reading. Should abnormal uptake be seen in this area, repeating the same procedure is helpful.

Specificity of ^{18}F to areas of lesion-involved bone during the first 5 hr following injection was observed by external scanning to be similar to ^{47}Ca in terms of relative percent retained dose. ^{85}Sr and ^{87m}Sr showed less specificity for these areas. Taken with respect to normal bone uptake of each tracer as measured by external point counting (Table 3) ^{18}F provides the greatest contrast between the lesion involved and normal bone.

For ^{18}F the optimum time for scanning (the time period over which maximum contrast was seen between lesion-involved and normal contralateral bone) was between 3 and 5 hr (Table 5). Even at 5 hr the counting rates for ^{18}F are adequate for satisfactory scanning (Table 6).

The choice of the optimum time of scanning and the preference for ^{18}F over ^{87m}Sr in the present study is not in agreement with recent results obtained by Spencer *et al* (*15*). It is suggested that in the quantitative measurements in this study of *in vivo* distribution, serum disappearance rates and excretion rates as a function of time provided more adequate data for comparison of these different nuclides.

In the majority of patients ^{47}Ca and ^{85}Sr showed higher lesion-involved-to-normal bone ratios at 5 days than did ^{18}F at 5 hr. These nuclides are therefor useful when short-term scan results with ^{18}F are equivocal. Also these nuclides will still be required for studies of calcium kinetics (*35*).

The decay-mode characteristics of ^{68}Ga are favorable for the short-term study. However, the necessity for preparation of the citrate with added carrier, the relatively unexplored problem of the toxicity of gallium in amounts as great as those added as carrier and the higher soft-tissue concentration seen in our animal studies have indicated that use of ^{68}Ga in its current form has no advantage over ^{18}F. The bone-to-tissue ratios in this study agree with data found in the extensive investigation by Hayes *et al* (*21, 36*) in which a wide range of stable gallium carrier was added to the preparation that was injected. The addition of 0–10 mg gallium carrier per kilogram body weight to ^{68}Ga-citrate with sacrifice after 2 hr and 5 mg/kg with sacrifice after 0–18 hr (using ^{72}Ga) by these investigators gave bone-to-soft-tissue and blood ratios which were less than were observed in this study with ^{18}F when sacrifice was at 5 hr.

The uptake data obtained for various regions of rat tibiae when sacrifice occurred at 5 hr generally showed that ^{18}F gives the greatest differential compared with the healing fracture site and contralateral normal site (Fig. 1). In contrast to the lesion-to-normal bone ratios in the studies in patients, both ^{47}Ca and ^{85}Sr showed smaller ratios for the comparison of regenerating or healing fractured bone to normal bone than did ^{18}F.

CONCLUSION

Quantitative comparisons of the kinetics of ^{47}Ca, ^{18}F, ^{85}Sr and ^{87m}Sr were made in humans. In addition to these nuclides, the uptake of ^{68}Ga in rat bone has been studied. The results of studies both in patients and in animals indicate that ^{18}F is the most suitable of the three short-lived nuclides for bone scanning. This is so despite the fact that greater precautions are needed to avoid confusion due to high radioactivity in the urine. Results with ^{68}Ga show poorer localization characteristics for applications in bone scanning.

In contrast to the other nuclides investigated, ^{18}F:

1. has the highest lesion-to-normal bone differential between 3 and 5 hr after injection,
2. shows the most rapid plasma clearance and the greatest short-term excretion, giving better scans of the skeleton,
3. gives low radiation dose to the patient while providing good counting-rate statistics,
4. localizes rapidly at bony sites,
5. decays rapidly to permit sequential studies and
6. decays by positron emission and thus provides unique physical detection characteristics.

ACKNOWLEDGMENT

This work was supported in part by Atomic Energy Commission Research Contract AT(30-1)-910 and NCI Grants CA-08748 and CA-07303.

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