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A Study of the Metabolism of Fluorine-18 in Dogs and its Suitability for Bone Scanning[1,2,3]

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Despite great interest in the prevention of dental caries using fluoride and the recent suggestions that fluoride may be of therapeutic value in metabolic bone disease, little information is available on the metabolism of fluoride. Tracer studies using radioisotopes of calcium and strontium have yielded important information which has given rise to some of the current theories of bone metabolism (1). Since fluoride appears to have a different relationship to the hydroxyapatite crystal than calcium or strontium (2) investigation of the behavior of the fluoride ion within the body is necessary for a more complete understanding of bone metabolism. It is the purpose of this presentation to provide information with respect to the dynamic behavior of the fluoride ion in the dog. In a brief study Blau, Nagler and Bender demonstrated that bone and bone lesions will concentrate radiofluoride (3). New data are presented below from 25 dog experiments examining ^{18}F uptake in normal and fractured bone, blood concentration, urinary excretion and tissue distribution. The suitability of ^{18}F as a bone scanning agent is also demonstrated.

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METHODS AND MATERALS

Radiopharmaceutical. The ^{18}F is produced as the carrier free sodium salt by bombarding enriched ^{6}Li carbonate with thermal neutrons in a reactor (Fig. 1). The details have been presented elsewhere (4). The radiopurity of the final product has been established by examining it in a 400 channel analyzer prior to each use. On decay a positron of 0.65 MeV is emitted. Only the 0.51 MeV annihilation peak is seen on gamma spectrometry (see Decay Scheme, Fig. 2). Tritium, which is a byproduct of ^{18}F production, is present in a concentration less than 2×10^{-2} $\mu C^{3}H/\mu C$ ^{18}F at the time of administration. Adequate chemical purity has also been established. Lithium, the target reagent, and lanthanum, used in the purification steps, are less than 0.6 mg/100 ml and 4.5 mg/100 ml respectively. The preparation procedures are conducted under sterile conditions and of 20 batches tested, no pyrogen or bacterial contamination has been detected. The concentration of Na and Cl are about three times greater than that found in serum. The pH is adjusted to 7.4. An average dose of 500 μC of ^{18}F in a volume of approximately 10 ml was given either orally or intravenously at the start of each experiment. No toxic reaction was observed clinically, despite repeated use in the same animal.

Dogs. Seven female mongrel dogs weighing 8-12 kg were used as indicated in Table I. Administration of the nuclide was performed under sodium pentobarbital anesthesia. Animal sacrifice was carried out with "lethal" sodium pentobartital solution.

Equipment. Bone scans were performed using a photoscanner[1] equipped with a 3″ × 2″ NaI (Tl) crystal, 19 hole lead collimator and a spectrometer. Blood, urine and tissue samples were counted in a well counter[2] equipped with a NaI (Tl) crystal and spectrometer.

External point counting was performed with a 1″ × 1½″ NaI (Tl) crystal probe, a spectrometer and a decade scaler. Either a one-inch single bore lead collimator or a seven-hole focusing lead collimator were used with the probe.

Surgical Procedure. Four dogs had their tibiae surgically osteotomized under anesthesia. Sterile technique was employed and the fractured limb was placed in a cast. The cast was removed approximately six weeks postfracture after healing was indicated by clinical and radiographic examination.

Experimental Procedure. All procedures were carried out on anesthetized animals. Those which received the ^{18}F orally (nasogastric tube) had been without food and water for 12 hours. An intravenous saline drip was maintained in order to facilitate adequate urine flow for urine sampling through an indwelling Foley catheter.

Bone Scan: Twenty-three bone scans were performed in five dogs as indicated in Table I. The caudad third of the dog was included in each scan, and where a fractured tibia was present the opposite tibia served as a point of reference. The earliest scan was three hours postfracture and the latest scan 180 days

[1]Picker Magnascanner, Picker Nuclear, 18370 South Miles Road, Cleveland 28, Ohio.
[2]Packard Autogamma, Packard Instrument Sales Corp., Box 428, LaGrange, Illinois.

postfracture. The time of scanning post dose of ^{18}F varied from 30 minutes-to-6 hours. A scan of the lower third of the dog could be completed easily in about 45 minutes.

Blood and urine studies: Blood was collected, at various time intervals following administration of ^{18}F doses, through a venous indwelling plastic catheter.[1] The earliest samples were drawn at 30 seconds post dose and the latest samples at six hours. Urine samples were taken at approximately thirty-minute intervals by permitting the indwelling catheter to drain and then manually compressing the urinary bladder.

External point counting: Five experiments were carried out comparing the accumulation and loss of radioactivity with time, over the fracture and the normal tibia using the probe mentioned above.

Tissue Studies. Two dogs were sacrificed at one and two hours post ^{18}F dose respectively, having had neither previous doses of ^{18}F nor prior surgery. Three other animals were sacrificed one, two, and three and a half hours post ^{18}F dose, having had multiple previous doses of flourine-18. Dog 102B was sacrificed three and one half months postfracture and dogs 106B and 107B were sacrificed five and seven months respectively, postfracture (Table I). Wedge samples, weighing approximately one gram each, were taken from each organ and weighed. Bone samples included a mixture of cortex and trabecular bone.

RESULTS

Bone Scans. Three-to-six hours postfracture no localized concentration of ^{18}F was found at the fracture site. An example of a right tibial fracture performed three hours prior to the scan is shown in Figure 3A. The entire right hind limb appears to have a greater concentration of radioactivity than the left. This may be due to surgical manipulation or the plaster cast. At the third day post-

TABLE I

SUMMARY OF ^{18}F STUDIES IN DOGS

Dog#	*Fracture*	*Bone Scan*	*Blood Studies*	*Urine Studies*	*External Point Counting*	*Tissue Studies*
101-B	—	1	1	0	0	0
102-B	Right Tibia	7	8	8	2	1
103-B	Left Tibia	7	4	4	0	0
104-B	—	0	0	0	0	1
105-B	—	0	0	0	0	1
106-B	Right Tibia	3	3	3	2	1
107-B	Left Tibia	5	5	5	1	1

[1]Intracath, C. R. Bard, Inc., Murray Hill, New Jersey.

fracture, the fracture site demonstrated two times the radioactivity of the control tibia as demonstrated by external counting. After firm union had been observed clinically and by roentgenographic examination, three months postfracture and six weeks after removal of the cast, a three-to-one uptake ratio was observed between the fractured and normal tibia (Fig. 3B). A minimum wait of one hour post dose was necessary in order to achieve a good target-to-nontarget ratio. Joints were often noted to have a greater concentration of ^{18}F than nearby long bones (Fig. 4). Scans performed six hours post dose were satisfactory but slower scanning speeds were required due to the loss of radioactivity from the target. The target-to-nontarget ratios varied considerably but did not change significantly after one hour post dose.

Blood and Urine Studies. Unless otherwise indicated, all data are decay corrected back to the time of administration.

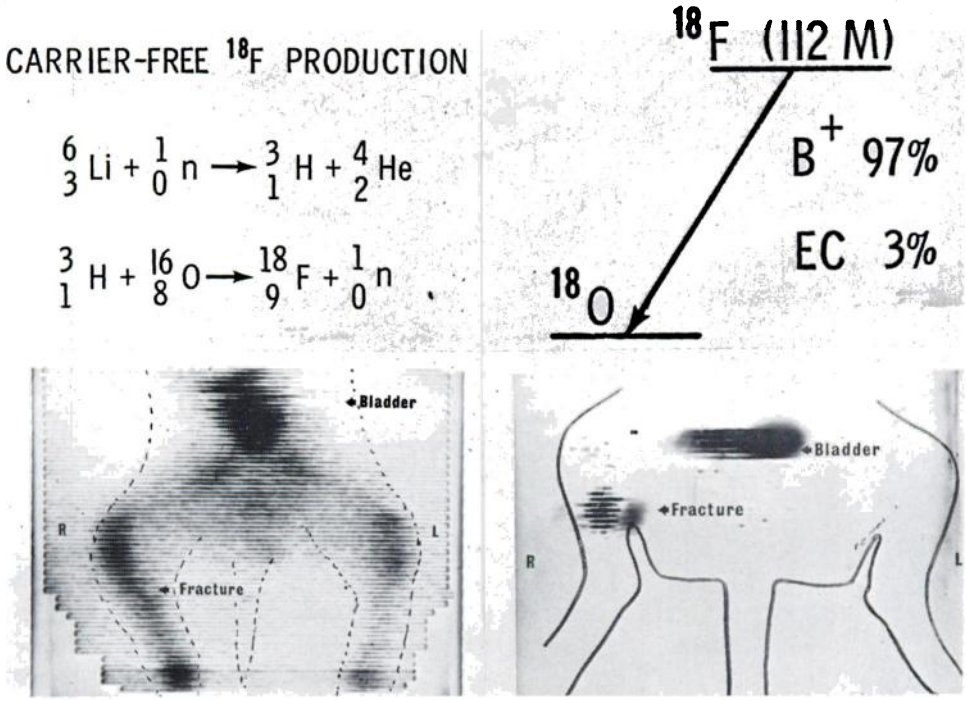


Fig. 1. *Top-Lt.:* **Thermal neutron bombardment of ^{6}Li produces ^{3}H and ^{4}He. The ^{3}H then bombards the oxygen in the lithium carbonate, yielding ^{18}F.**

Fig. 2. *Top-Rt.:* **Decay scheme of ^{18}F (Radiological Health Handbook, Edited by the Division of Radiological Health, United States Public Health Service, rev. ed. 1960).**

Fig. 3A. *Bottom-Lt.:* **Bone scan three hours post right tibial fracture showing no definite concentration of ^{18}F at the fracture site. Note the accumulation of ^{18}F in the urinary bladder (Dog 102B). B.** *Bottom-Rt.:* **Positive bone scan performed on the same dog three months post fracture and one week prior to sacrifice.**

The blood accumulation and disappearance curves for ^{18}F given orally and intravenously are presented in Figure 5. The concentration of radioactivity in the blood reaches a maximum at about one hour post oral administration. The urinary accumulation of ^{18}F given intravenously was somewhat more rapid in the first two hours post dose than that given orally, as shown in Figure 6. However, beyond one and one-half hours the excretion curves did not differ significantly. About 50% of the given dose appears in the urine by six hours.

External Point Counting. The rapidity with which ^{18}F was accumulated in the bone is demonstrated in Figure 7 (not decay corrected). After an intravenous or oral dose of ^{18}F, maximum radioactivity was observed over bone in about one hour or less, and thereafter falls off with a half-time not too dissimilar from the half-life of ^{18}F during the period of observation.

Tissue Studies. The concentration of radiofluorine in bone was at least three times greater than in any soft tissue examined at 1, 2, and 3½ hours with the exception of kidney (on a μC/gm basis). In general, most bones exceeded soft tissue concentration by 5-to-7 fold. Since only five animals were studies at different times, no statistical analysis of the tissue counting studies is attempted. However, the range of magnitude and the relationship among the various tissues examined can be appreciated from the example shown in Figure 8A and B.

Three of the animals sacrificed had previous surgical fractures and the ratio of fractured tibia (Fx) to normal tibia (N) radioactivity is shown in Table II.

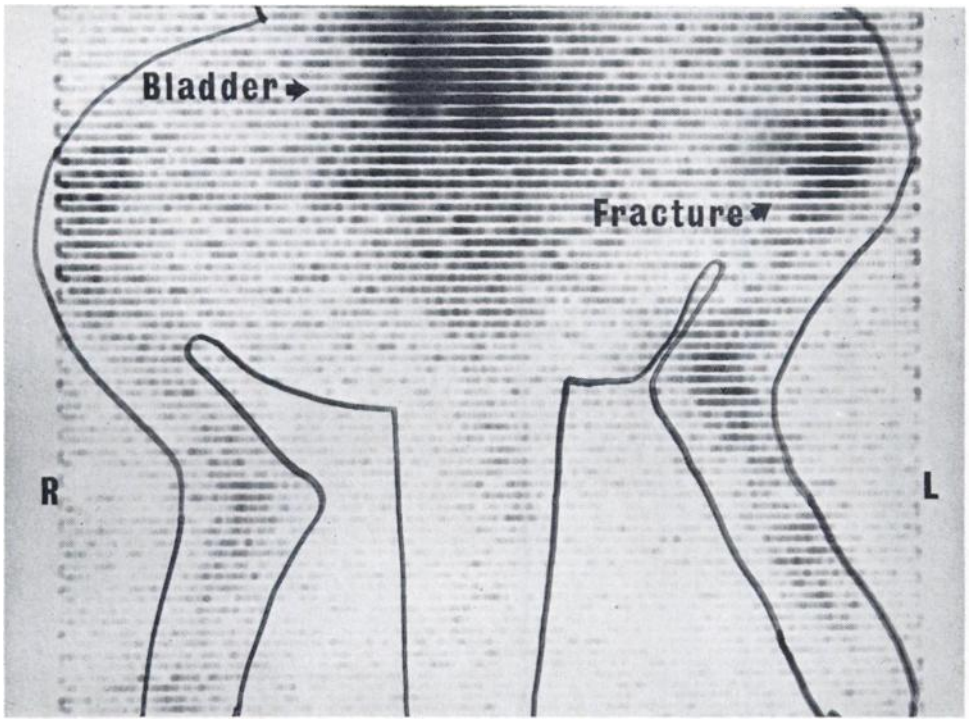
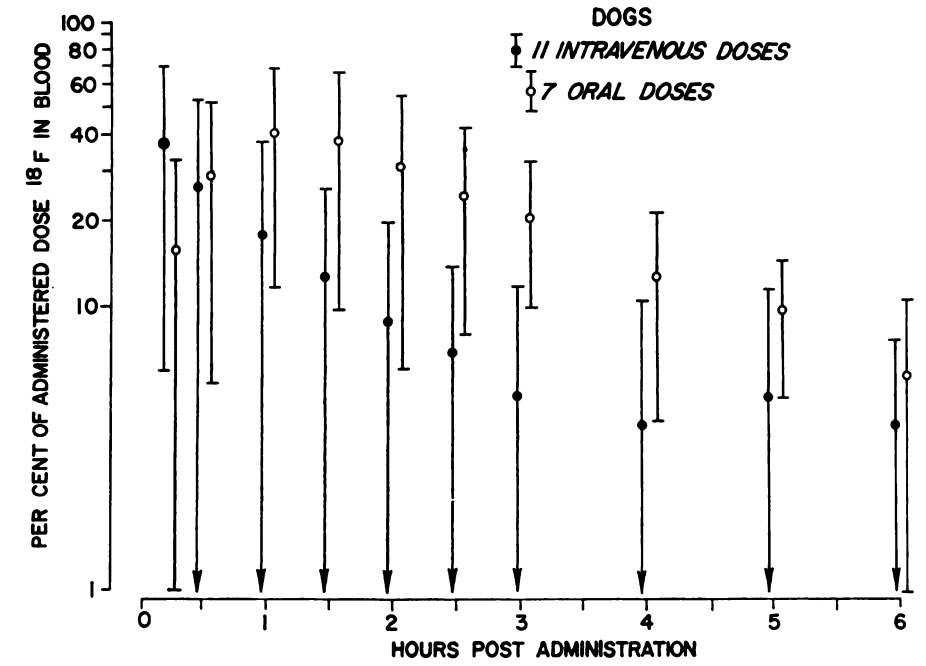


Fig. 4. Positive bone scan three months post left tibial fracture. Note the concentration of ^{18}F in the joints distal and proximal to the fracture.



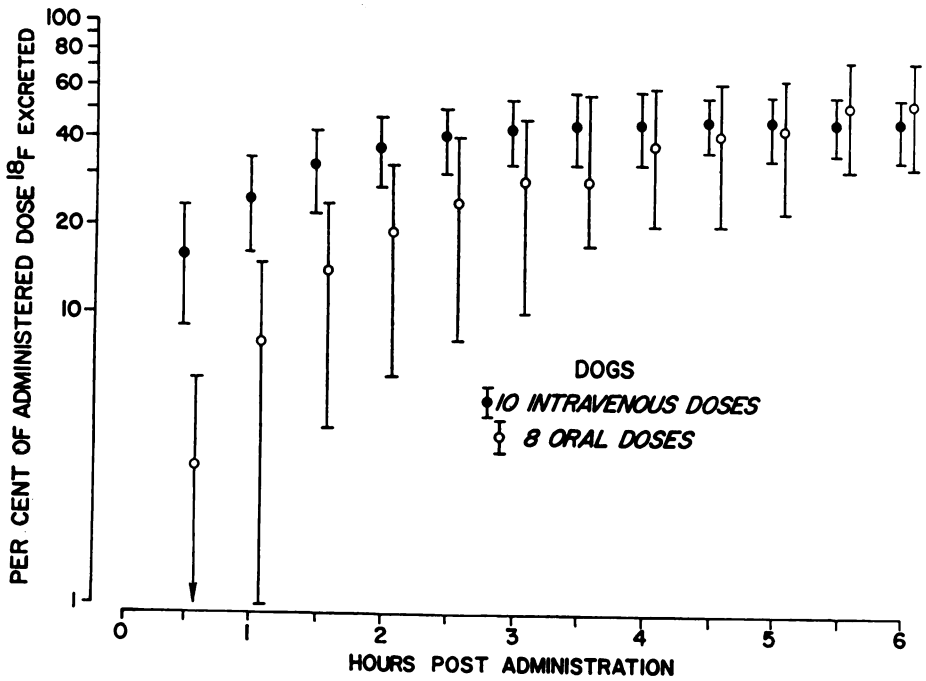


Fig. 5. *Top:* Blood concentration curve of ^{18}F following oral and intravenous administration. One standard deviation is indicated for each mean. The time intervals are 15 and 30 minutes and 1, 1½, 2, 2½, 3, 4, 5 and 6 hours.

Fig. 6. *Bottom:* Urinary excretion curve of ^{18}F following oral and intravenous administration. One standard deviation is indicated for each mean. Half-hourly time intervals are used.

TABLE II
TISSUE CONCENTRATION
RATIO OF FRACTURED (FX): NORMAL (N) BONE

Dog	*Months Post Fracture*	*Hours Post ^{18}F Dose*	*Fx/N*
102-B	3½	3½	2.7
106B	5	1	4.0
107-B	7	2	5.6

Of the normal bones, the greatest concentration of ^{18}F was usually observed in vertebrae and almost as great a concentration was noted in the pelvic bones. As a general rule the more peripherally a bone was located, the less was its ^{18}F concentration. Since bone is a nonhomogenous tissue with respect to ^{18}F accumulation (Fig. 9) and cannot be homogenized rapidly, small variations in sampling techniques could lead to fluctuations in observed activity as great as 50% in the same bone.

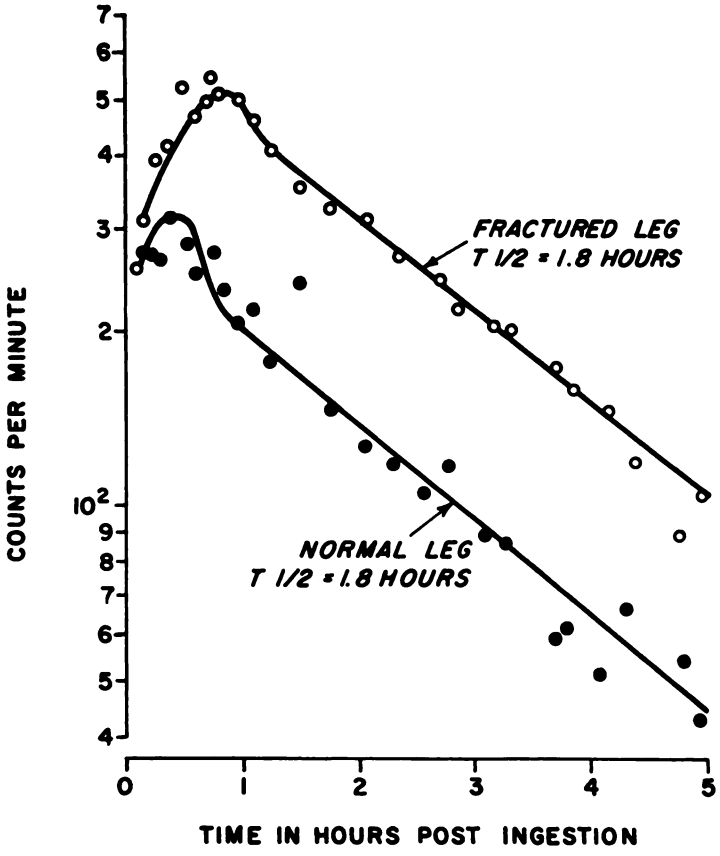


Fig. 7. Fluorine-18 osteogram of fractured and normal tibia using external point counting.

DISCUSSION

The data reported serve to establish the following points:

1. No toxicity of scanning doses of the ^{18}F product were observed when given orally or intravenously to the dog.
2. With the exception of the kidney (and the urine) no significant soft tissue concentrations were found by external counting or tissue sampling that might interfere with interpretation of bone uptakes and scans (5).
3. Scans of good quality may be obtained in a clinically acceptable period of time one hour post administration due to the rapid accumulation of ^{18}F in bone and its rapid disappearance from blood.
4. The uptake of ^{18}F per unit weight of bone varies from one bone to another and within any one bone.

The mechanism of fluorine accretion in bone is thought to differ from that of Ca and Sr although apparently all three are taken up by bone crystal. Fluoride ion has been reported to exchange with the hydroxyl ion on the surface of the hydroxyapatite crystal thus forming a fluoroapatite (2).

Absorbed dose calculations may be performed on the basis of the data collected. The urinary excretion curve (Fig. 6) indicated that about 50% of an administered dose was excreted in six hours (6). Fluorine excretion beyond that time most probably occurred at a much slower rate. The effective half-life for the

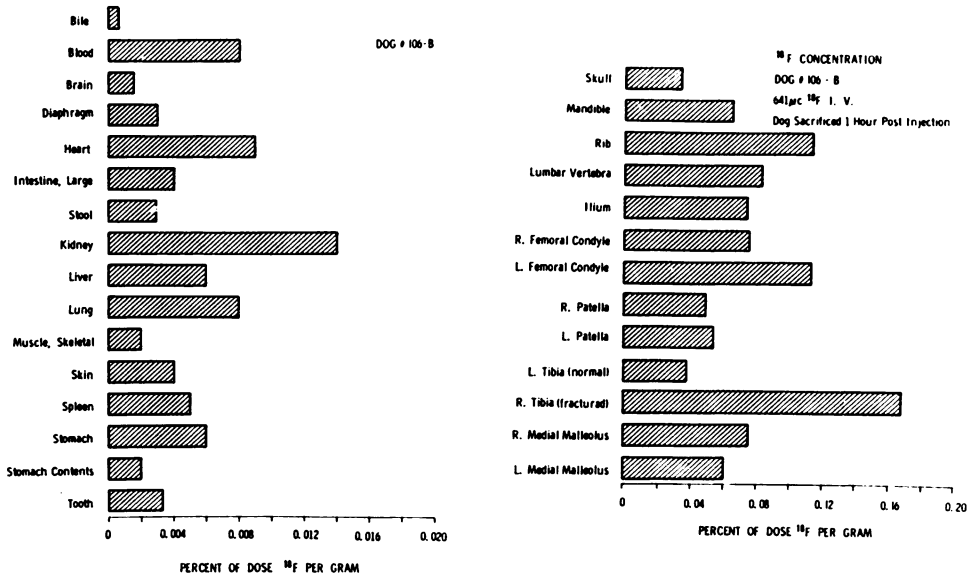


Fig. 8. Fluorine-18 concentration in tissue one hour post intravenous injection of 641 μc, A. *Left:* soft tissues and B. *Right:* bones.

first 50% of the dose was, therefore, about 1.4 hours[1] while the remainder of the ^{18}F will leave the body at an effective half-life approaching the physical half-life of fluorine-18. It becomes obvious that a prolonged (in terms of biologic half-time) careful study of the excretion of a radionuclide, whose total biologic half-time far exceeds its physical half-life, is unnecessary. To assume an effective half-life equal to 1.87 hours, in this particular case (the physical half-life of ^{18}F) offers an error no greater than 10 to 15% over estimation. This is easily within the limits of acceptability for dosimetric calculations when compared to the errors made in assuming uniform distribution within an organ or organism or in selecting a geometry factor.

The problem of selecting the mass of tissue in which the retained ^{18}F is distributed is not simple. The autoradiograph (Fig. 9) shows nonhomogenous distribution of ^{18}F in long bones with little being concentrated in the cortex. Pos-

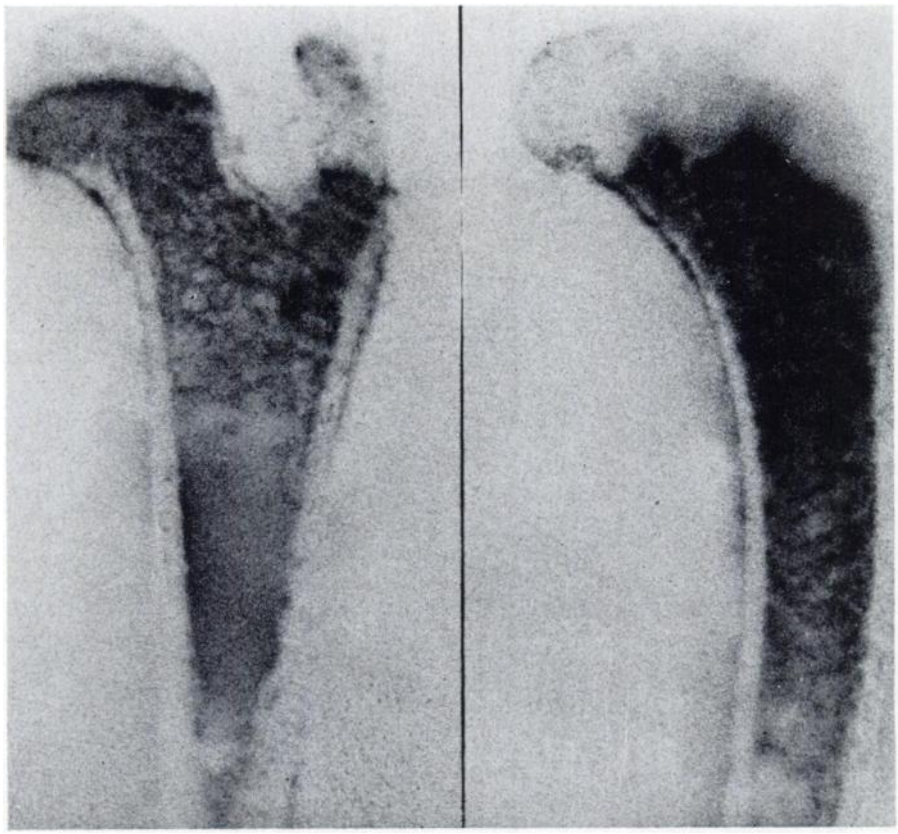


Fig. 9. Fluorine-18 autoradiograph of the proximal (left) and distal (right) normal dog femur. Note the accumulation of radioactivity in the region of the epiphyseal plates of this adult animal and the relative absence of radioactivity in the region of the cortex.

[1] $$T_{eff} = \frac{T\ phys \times T\ biol}{T\ phys + T\ biol} = \frac{1.87 \times 6}{1.87 + 6} = 1.4$$

sibly due to better vascularization, bones placed closer to the central body axis appear to concentrate more ^{18}F, and when uniform distribution is assumed (as we have done and as most others do), larger errors than those normally introduced are incurred. Assuming that the excretion data collected from dogs can be applied to the average human subject, and that the ^{18}F not excreted is in the bone, one obtains an absorbed bone dose[1] of 0.12 rad per millicurie administered (7). This value is an approximation and it approaches the value reported by Blau *et al* (3). It is far less than the absorbed bone dose reported from ^{85}Sr and is of the same magnitude as the reported dose for ^{87m}Sr for equivalent scanning doses (8).

Flourine has been shown to be biologically superior to strontium in certain situations, thus adding to its suitability for scanning human subjects. The rapid disappearance of ^{18}F from blood, high target-to-nontarget ratios and diagnostic bone scans for reticulum cell sarcomas have been reported using ^{18}F but have not been reported with isotopes of strontium (9).

Other advantages to be considered are the high count rates (with a small absorbed radiation dose as compared to ^{85}Sr) thus allowing more rapid scanning. Scanning may be performed as early as one hour after ^{18}F administration.

Certain limitations currently exist. The half-life of ^{18}F is short and proximity to the site of production is necessary. Also cost is high. Both of these factors are relative, however, since if ^{18}F is produced on a commercial basis, the cost will fall and current rapid transportation puts most of the United States within one or two hours travel time of a production site. The rather high energy of the 0.51 MeV photon is not optimal for most collimator systems. This has not severely limited the acceptability and diagnostic accuracy of the bone scans produced with fluorine-18. The rapid collection of ^{18}F in the urinary bladder makes voiding desirable prior to scanning of the pelvic region.

SUMMARY

Twenty-five dog experiments were performed using orally and intravenously administered ^{18}F as carrier free NaF. Bone scans and external point counting indicated that the uptake of ^{18}F by bone reached a maximum within one hour and that scans of good quality could be achieved after that time. A rapid fall in blood radioactivity was found as well as rapid urinary excretion of ^{18}F; 50% of the administered dose was found in the urine within six hours. Bone radioactivity usually was more than five fold that found in soft tissues (except kidney) as determined by well counting. Autoradiographs revealed nonhomogenity of ^{18}F distribution in bone; 0.12 rad/mC is the estimated radiation dose to bone using the usual methods of calculations.

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[1]The values used in the equations taken from reference 7 were:

$E_B = 0.24$ Mev, $g = 44$, $\Gamma = 3$ cm^2R/mC hr., $T_{eff} = 7.8 \times 10^{-2}$ days

$Co = \frac{500\ \mu C}{7000\ gm}$

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