A Model for Local Accumulation of Bone Imaging Radiopharmaceuticals

Michael A. King, Robert W. Kilpper, and David A. Weber

The University of Rochester School of Medicine and Dentistry, Rochester, New York

A simple model, having phenomenological parameters as variables, is developed for predicting local radioactive tracer accumulation in bone. Blood delivering tracer to one gram of bone is treated as a compartment separate from the remainder of the circulation in order to observe the effects produced by variations in both bone blood flow and barrier permeability. Kinetic curves derived by analog computer were obtained for normal and perturbed values of the parameters for F-18 and Ca-47 in a segment of rabbit bone. Apparent confirmation of the predicted influence of decreased blood flow on F-18 deposition was obtained by measuring bone uptake following constriction of the right femoral artery in five rabbits. Such models may prove useful in explaining variations in uptake for different agents, in selecting imaging times, and in correlating uptake patterns with disease.

J Nucl Med 18: 1106–1111, 1977

The primary rate-controlling factors governing the deposition of radiopharmaceuticals in bone are (a) blood flow (*1–13*), (b) capillary or barrier permeability (*1–6*), (c) the volume of the exchangeable bone pool (*1–4,7,13,14*), and (d) bone metabolism (*1–3,8,9,15,16*). While each is conceded to be a contributor, there is considerable disagreement regarding their relative importance in short-term deposition, and the complexity of the system precludes direct, manipulative experimentation. As a consequence, many models have been proposed and analyzed in attempts to increase understanding. The model developed here (*17*) allowed us to separate the effects of each parameter on bone deposition by conceptually isolating a single gram of bone and thus to simulate the effects of local disease on imaging. Using published data (*18*), normal and perturbed deposition curves for F-18 and Ca-47 were determined, and the model's predicted F-18 flow dependence was in good agreement with experimental findings.

MATERIALS AND METHODS

The model. In modeling the in vivo uptake, distribution, and excretion of compounds, it is customary to consider all kinetically similar tissues as comprising a single "compartment." One cannot change the properties of any part of a compartment, however, without changing the corresponding properties of the total compartment. Since we wanted to study the effects of perturbations in the local parameters on bone imaging, our model was designed to isolate a gram of bone and its blood supply from the rest of the body. The "total body" determined the shape of the blood concentration clearance curve, and no attempt was made to find a particular model that would generate that curve. The values of the local parameters are derived to yield the best fit of the model to the experimental blood-clearance data and bone-activity levels in the normal animal. The effects of variations in each of the parameters are then found by selectively changing individual values while exposing the isolated gram of bone to normal blood clearance and noting the corresponding changes in the uptake curve for the bone. This assumes that since only one gram of bone is perturbed by this procedure, the resulting effect on the blood-

Received Dec. 1, 1976; revision accepted June 29, 1977.

For reprints contact: David A. Weber, Div. of Nuclear Medicine, University of Rochester Medical Center, Rochester, NY 14642.

concentration curve is negligible. This is observed in clinical studies demonstrating only local disease (*19*).

The details of the model are given in Fig. 1, where the arrows indicate movement of material between the different compartments. At the right, the radioactive tracer in the circulating blood pool, P, is shown as flowing into a pool of blood in contact with a small segment of bone. This nutrient bone blood pool, BP, communicates directly with an exchangeable bone compartment through a permeability barrier. The exchangeable bone compartment supplies material to the blood, as well as receives material from it. Physiologically, the makeup of this compartment would include bone extracellular fluid and bone surfaces. Some material from this exchangeable bone pool is assumed to go into a nonexchangeable bone compartment, BN, which allows for uptake by accretion and long-term exchange. A very slow return from the nonexchangeable to exchangeable bone compartments will appear to be nonexistent or at least negligible over the time periods of interest to our analysis. After supplying the isolated bone segments, the remainder of the tracer is shown returning to the systemic blood pool.

Assuming that the local volume flow rate of blood into bone, $\dot{Q}$, is the same as that leaving, the equations governing the behavior of the model are:

$$\frac{d}{dt}(BP) = \dot{Q}\left[C_p - \frac{BP}{V_{BP}}\right] - \rho\left[\frac{BP}{V_{BP}} - \alpha\frac{BE}{V_{BE}}\right],$$

$$\frac{d}{dt}(BE) = \rho\left[\frac{BP}{V_{BP}} - \alpha\frac{BE}{V_{BE}}\right] - k\frac{BE}{V_{BE}}, \text{ and}$$

$$\frac{d}{dt}(BN) = k\frac{BE}{V_{BE}},$$

where C_p is the concentration of the radiopharmaceutical in the circulating blood; BP, BE, and BN are the amounts in the local bone blood, exchangeable bone, and nonexchangeable bone compartments respectively; and V_{BP} and V_{BE} are appropriate compartment values. The product of the permeability

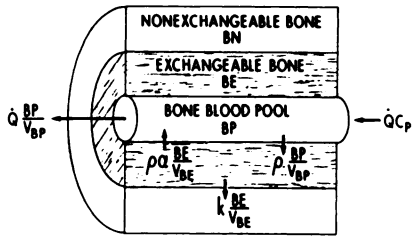

FIG. 1. Model for tracer deposition in bone. Symbols are defined as follows: Q, local blood flow; C_P, systemic blood concentration of tracer; ρ, product of barrier permeability and its surface area; α, partition coefficient; k, constant for accretion and long-term exchange; BP, BE, BN, amount of tracer in respective compartments; V_{BP}, V_{BE}, volume of respective compartments.

of the barrier at the blood/bone interface and its area is denoted by ρ, and α is a partition coefficient that allows for a steady-state concentration difference between exchangeable bone and the blood in contact with it. The accretion or long-term first-order rate constant is designated by k.

These equations were solved on an analog computer. The normal blood-clearance curves, normal curves for the total amount of tracer in a gram of bone, $\dot{Q}$, and V_{BP}, were obtained from Costeas (*18*) (Table 1). The value for the local blood flow was estimated by dividing (a) the uptake of F-18 per gram of bone at 5 min by (b) the time integral of the blood concentration of F-18 between 0 and 5 min. This assumed a 100% clearance of F-18 from the blood in contact with bone, only during the first few minutes post injection (*10*). At different rates of flow or longer times, our model is not constrained to a linear relationship between $\dot{Q}$ and uptake of F-18. The volume of the bone blood pool per gram of bone was taken from the I-131 human serum albumin in rabbit cortical bone at 10 min post injection (*18*). The values for the other parameters of the model were determined from the best fit of the computed curve to the bone-tracer uptake data determined by Costeas. These normal curves are labeled as "initial fit" in Figs. 2 and 3. The values thus determined are shown in Table 2. We assumed $\alpha = 1$ in reporting the values of the parameters because we

TABLE 1. INPUT FACTORS FOR SOLUTION OF MODEL EQUATIONS

Data*	F-18	Ca-47
Whole-blood activity levels (% dose/g)	$C_P = .0796e^{-.0485t} + .0238e^{-.0100t}$	$C_P = .0502e^{-.0556t} + .0423e^{-.00597t}$
Cortical-bone activity levels (% dose/g)	"Initial fit" points (Fig. 2)	"Initial fit" points (Fig. 3)
Bone blood flow ($\dot{Q}$) (ml/g bone)	.095	.095
Volume of bone blood pool (V_{BP}) (ml/g bone)	.03	.03

* Data taken from reference 18.

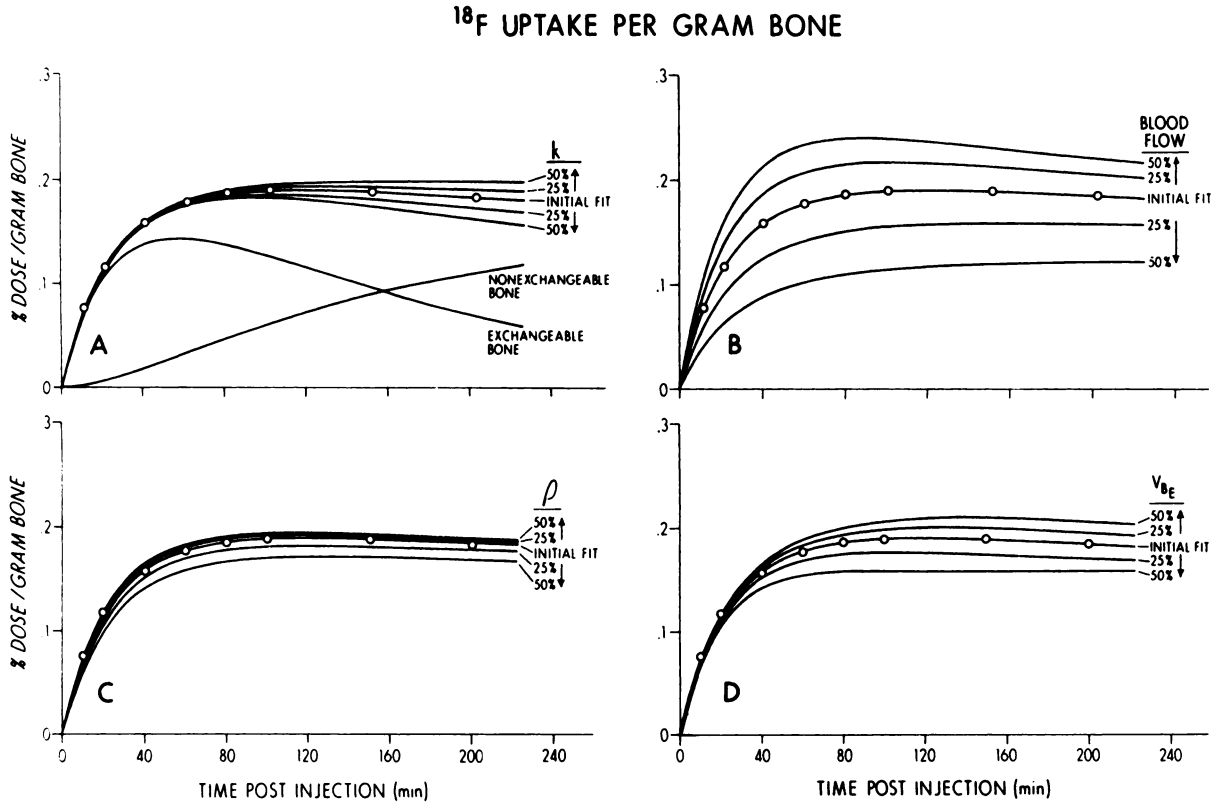

FIG. 2. Changes produced in local accumulation of F-18 as a result of raising or lowering each of the following variables by indicated percentages of their initial value: (A) k, accretion constant; (B) $\dot{Q}$, blood flow per gram bone; (C) ρ, product of barrier permeability and surface area; and (D), V_{BE}, volume of exchangeable bone compartment.

were able to obtain independent values for only 3 of the 4 unknown parameters.

Local blood-flow experiment. The influence of local blood flow was tested experimentally in rabbits. The right femoral arteries of five male New Zealand albino rabbits were constricted with black silk sutures to reduce bone blood flow. Approximately 3 hr later, to allow recovery from sodium pentobarbital anesthesia, the animals were administered 500 μCi of both F-18 and Tc-99m pyrophosphate (PP_i) intravenously. One minute before being sacrificed by an intracardiac injection of 10 ml of saturated KCl solution, the rabbits were administered 400 μCi of Rb-86 intravenously. The bone clearance of the Rb-86 was used as a measure of the relative bone blood flow (*20,21*) between the two legs. With these results permitting an estimate of the alteration in blood flow, the model was used to predict a value for the relative uptake of F-18 at the time of sacrifice. These values were compared with the differential uptake observed for F-18 in the sacrificed animals.

RESULTS

The uptake and clearance curves derived by the analog computer for F-18 and Ca-47 are given in Figs. 2 and 3. The "initial fit" curve was obtained as described previously and is shown in each frame. With the exception of the curves for exchangeable and nonexchangeable bone in Figs. 2A and 3A, the other curves were obtained by changing the indicated parameters.

The results from the experiment to test the predicted influence of local blood flow are given in Table 3. The observed relative blood flow is the ratio of the right (constricted) to left (control) 1-min clearance of Rb-86. The predicted F-18 uptake is given by the model for the observed alteration in local blood flow divided by the "initial fit" value for deposition at the time of killing. The observed uptake is expressed as the ratio of the counts/minute/gram of bone of the ligated to control leg. For the first rabbit, with a relative blood flow of 49% and a time of sacrifice of 2 hr, the model predicted a 60% uptake of F-18 compared to the "initial fit" value. This is in good agreement with the 56% uptake observed in the experiment. The experimental observations in the other rabbits also agree with the model's predictions.

From Table 1, it can also be seen that Tc-99m PP_i has a flow dependence probably less than that for F-18. This might be expected on the basis of the slower clearance of Tc-99m PP_i from blood (*5*).

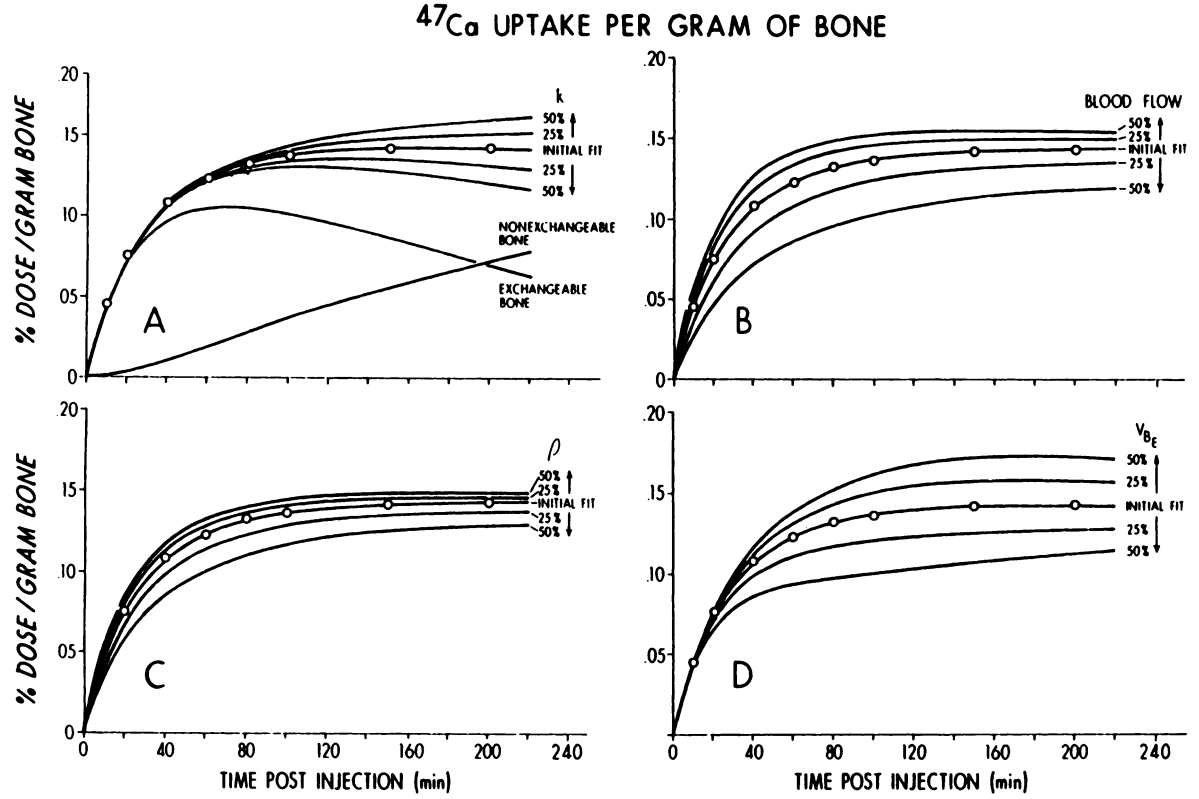

FIG. 3. Changes produced in local accumulation of Ca-47 as a result of raising or lowering each of the following variables by indicated percentages of their initial value: (A) k, accretion constant; (B) $\dot{Q}$, blood flow per gram bone, (C) ρ, product of barrier permeability and surface area; and (D) V_{BE}, volume of exchangeable bone compartment.

DISCUSSION

The proposed model was designed to provide a means by which individual rate-controlling factors could be selectively changed and the resulting imaging characteristics could be predicted. A discussion of the curves generated by the model (Figs. 2 and 3) will demonstrate its potential usefulness. For each parameter, one finds a family of five curves; the "initial fit" curve shows the observed bone uptake in the normal rabbit. Note that the produced effect is not proportional to the fractional change in a parameter, and there is an upper limit for each effect. This is shown explicitly in Fig. 4, where we have plotted fractional change in blood flow in contrast to the resultant fractional change in F-18 uptake predicted by the model at 3 hr post injection. The implication of these observations is that the large changes in uptake seen in patient studies would require simultaneous changes in several parameters. Note also that increased uptake on an image may result from an increase in the amount of bone within the area being imaged.

TABLE 2. VALUES OF MODEL PARAMETERS DETERMINED BY SOLUTION EQUATIONS ON ANALOG COMPUTER

	F-18	Ca-47
Product of permeability and surface area (ρ)	.62 ml/min	.16 ml/min
Volume of exchangeable bone pool (V_{BE})*	13.5 ml	.44 ml
Accretion constant (k)†	.078 ml/min	.019 ml/min

* V_{BE} is calculated assuming $\alpha = 1$. Since F-18 is not protein bound in blood, its apparent solubility will be lower than that of Ca-47 and its value of V_{BE} will be artificially elevated.

† k is calculated by assuming $\alpha = 1$.

A comparison of Figs. 2 and 3 will demonstrate the variation in relative importance in short-term deposition of each of the model parameters between F-18 and Ca-47. These figures demonstrate that V_{BE} was found to have a greater effect than changes in $\dot{Q}$ for Ca-47, which is the opposite of the finding for F-18. This is probably the result of the slower initial blood clearance of Ca-47 (*18*).

Several comments should be made regarding the relationship of Figs. 2 and 3 to clinical interpretations. First, we chose not to let the tracer blood concentration (C_p) be altered by changes in our parameters. This was done by modeling one gram of bone. Our results provide a useful analog to localized

TABLE 3. MEAN RIGHT/LEFT RATIOS

Rabbit No	$\dot{Q}$*	Time post injection	Predicted F-18	F-18 observed	Tc-99m PP_i observed
1	.49 (.46–.53)†	2 hrs	.60	.56 (.53–.58)†	.68 (.65–.74)†
2	.23 (.21–.25)	3.2 hrs	.38	.44 (.41–.46)	.53 (.49–.57)
3	.48 (.40–.61)	2 hrs	.59	.51 (.45–.55)	.59 (.53–.63)
4	.15 (.11–.21)	3 hrs	.25	.27 (.26–.29)	.32 (.31–.32)
5	.26 (.14–.35)	3 hrs	.42	.44 (.43–.47)	.46 (.43–.47)

* Rb-86 measured blood flow ratio.
† Mean and range for three sections of the tibia from each animal.

skeletal conditions, where the blood tracer concentration does not change as a result of local perturbation at a single lesion site or as a result of systemic alterations (*19*). Consideration of systemic changes would require additional information and would be beyond the scope of this paper. Next, we concede that results from the rabbit probably will not be quantitatively the same in the human. Our results should hold true in a general way, however, since local bone blood flow and C_p are similar, thus making the results of our analysis applicable (*18,22,23*).

In applying the data from Costeas (*18*) to our model in order to obtain a value for $\dot{Q}$, the blood flow per gram of bone, we made the assumption of 100% extraction efficiency for the blood exchanging F-18 with bone during the first 5 min after injection. Wootton (*10*) has obtained experimental evidence that this assumption is approximately correct. It still would be of interest to check our value of blood flow against those obtained by others using different techniques as a further confirmation. However, no technique has gained general acceptance yet, and the values obtained by different techniques seldom agree (*23*).

The volume of the bone blood pool was taken as 0.03 ml/g bone (*18*). It was found that this parameter could be tripled or halved with no noticeable effect upon the curves' fit to Costeas' data, indicating that the accuracy of this value is not critical for this study.

Since there is the possibility of two barriers (the capillary and the extracellular fluid/bone) to material exchange between blood and the bone surface, a more complex model was tried. An extracellular fluid compartment was added between the bone/blood and exchangeable bone pools of the original model. The fit to Costeas' data and the predictions made for alterations in uptake due to changes in the parameters were not significantly different between the models; therefore, the simpler model was chosen.

We interpret the predictions made by our model as agreeing generally with the work of Siegel et al. in rats (*12*). Their correlation of treated/contralateral uptake ratios for Sr-85 microspheres (blood flow) and Tc-99m HEDP was interpreted as indicating a linear relationship between blood flow and Tc-99m HEDP deposition. This relationship leads to the conclusion that there is a 40% uptake of Tc-99m HEDP at zero blood flow, which is clearly impossible. A curve of the general form given in Fig. 4 would provide a better fit to their data for decreased blood flow in ligated rats. For fractional flow rates near 1, the linear relationship is approximately valid; as the ratio increases or decreases, however, the nonlinearity becomes more pronounced.

To investigate the effects of increased blood flow, they studied rats with 3-week-old right tibial fractures. In these animals, they observed altered blood flow to have a greater effect on Tc-99m HEDP deposition than one would expect from our model. For rats with a Sr-85 (blood flow) per gram ratio of less than 1.7, they observed a mean Sr-85 ratio of 1.37 and a mean Tc-99m HEDP ratio of 1.38. For all rats with fractures, these ratios were 2.10 and

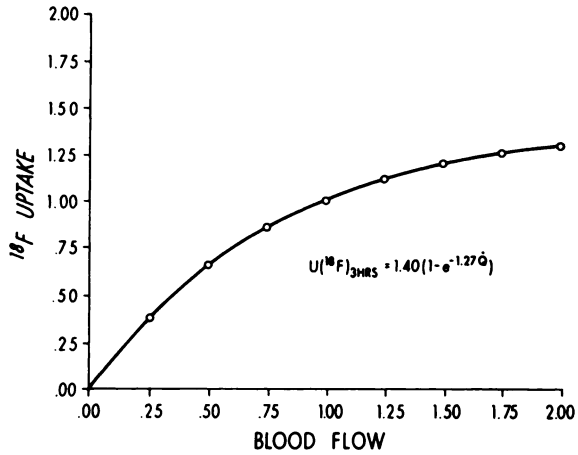

FIG. 4. F-18 uptake in bone at 3 hr as a function of relative blood flow. Relative F-18 uptake is normalized to 1.0 for value of blood flow used in "initial fit" data. Data points were predicted by analog computer; equation was derived from least-squares fit to data points.

1.60, respectively. This discrepancy from the projected results of our model can be accounted for if one recalls that the fractured leg shows an increase in both V_{BE} and k, as well as in $\dot{Q}$. The fact that these two parameters also contribute to the observations of Siegel et al. is demonstrated in their results from fractured and ligated rats. Here they observed a mean depression of the Sr-85 (blood flow) ratio to 0.86, whereas the Tc-99m HEDP uptake ratio remained elevated at 1.29. This clearly shows that local blood flow is not the single cause of the elevated uptake seen in the rats with fractured tibiae.

CONCLUSION

By using a phenomenological approach in constructing our model, we separated that volume of blood exchanging radiopharmaceutical with bone from the rest of the circulating blood. This approach has allowed us to test each parameter of the model for its effect on deposition of radiopharmaceuticals in bone. Local blood flow and the volume of the exchangeable bone pool were observed to exert the greatest influence on local accumulation for the radionuclides studied. None of the parameters, however, was individually able to produce very large changes in uptake. It is necessary to have several parameters change simultaneously in order to have the extremely abnormal uptakes sometimes seen clinically. A similar approach could be adapted to the study of the kinetics and imaging characteristics of radiopharmaceuticals in other organ systems.

ACKNOWLEDGMENTS

The authors would like to thank E. Summer King and Virginia Kubarycz for their assistance in preparation of the manuscript, and E. R. Squibb & Sons for providing the pyrophosphate used in this study. This work was originally presented at the Annual Meeting of the Society of Nuclear Medicine in Dallas, Texas, in June 1976. It was based on work partially performed under contract with the U.S. Energy Research and Development Administration at the University of Rochester Biomedical and Environmental Research Project, and has been assigned Report No. UR-3490-879.

REFERENCES

1. WINCHELL HA: Mechanisms for radiopharmaceutical localization. *J Appl Radiol* 5: 176–177, 206–207, 1976

2. BELL EG: Nuclear medicine and skeletal disease. *Hosp Pract* 7: 49–60, 1972

3. JONES AG, FRANCIS MD, DAVIS MA: Bone scanning: Radionuclidic reaction mechanisms. *Sem Nucl Med* 6: 3–18, 1976

4. COFIELD RH, BASSINGTHWAIGHTE JB, KELLY PJ: Strontium-85 extraction during transcapillary passage in tibial bone. *J Appl Physiol* 39: 596–602, 1975

5. GARNETT ES, BOWEN BM, COATES G, et al: An analysis of factors which influence the local accumulation of bone-seeking radiopharmaceuticals. *Invest Radiol* 10: 564–568, 1975

6. PARADIS GR, KELLY PJ: Blood flow and mineral deposion in canine tibial fractures. *J Bone and Joint Surg* 57-A: 220–226, 1975

7. GENANT HK, BAUTOVICH GJ, SINGH M, et al: Bone-seeking radionuclides: An in vivo study of factors affecting skeletal uptake. *Radiology* 113: 373–382, 1974

8. CHARKES ND, PHILIPS C, MALMUD LS: Bone tracer uptake: Evaluation by a new model. *J Nucl Med* 16: 519, 1975 (Abst)

9. KAYE M, SILVERTON S, ROSENTHALL L: Technetium-99m-pyrophosphate: Studies in vivo and in vitro. *J Nucl Med* 16: 40–45, 1975

10. WOOTTON R: The single-passage extraction of ^{18}F in rabbit bone. *Clin Sci Molec Med* 47: 73–77, 1974

11. VAN DYKE D, ANGER HO, YANO Y, et al: Bone blood flow as shown with F^{18} and the positron camera. *Am J Physiol* 209: 65–70, 1965

12. SIEGEL BA, DONOVAN RL, ALDERSON PO, et al: Skeletal uptake of ^{99m}Tc-diphosphonate in relation to local bone blood flow. *Radiology* 120: 121–123, 1976

13. COSTEAS A, WOODARD HQ, LAUGHLIN JS: Depletion of ^{18}F from blood flowing through bone. *J Nucl Med* 11: 43–45, 1970

14. COSTEAS A, WOODARD HQ, LAUGHLIN JS: Comparative kinetics of calcium and fluoride in rabbit bone. *Radiat Res* 46: 317–333, 1971

15. CITRIN DL, BESSENT RG, MCGINLEY E, et al: Dynamic studies with ^{99m}Tc-HEDP in normal subjects and in patients with bone tumors. *J Nucl Med* 16: 886–890, 1975

16. HAMAMOTO K, YAMAMOTO I, MORITA R, et al: Bone scintigraphy with ^{99m}Tc-pyrophosphate—Its relationship to bone metabolism. *J Nucl Med* 15: 489, 1974 (Abst)

17. KING MA, KILPPER RW, WEBER DA: A model for local accumulation of bone-seeking radiopharmaceuticals. *J Nucl Med* 17: 549, 1976 (Abst)

18. COSTEAS A: Comparative kinetics of calcium and fluoride in rabbit bone. PhD Thesis, Graduate School of Cornell University, New York, NY, 1968

19. COREY KR, WEBER D, MERLINO M, et al: Calcium turnover in man. In *Dynamic Clinical Studies with Radioisotopes*, Knisely RM, Tauxe WN, eds. Oak Ridge, Tenn., Oak Ridge Institute of Nuclear Studies, TID-7678, 1964, pp 519–536

20. SAPIRSTEIN LA: Regional blood flow by fractional distribution of indicators. *Am J Physiol* 193: 161–168, 1958

21. KANE WJ, GRIM E: Blood flow to canine hind-limb bone, muscle, and skin. *J Bone Joint Surg* 51-A: 309–322, 1969

22. WEBER DA, GREENBERG EJ, DIMICH A, et al: Kinetics of radionuclides used for bone studies. *J Nucl Med* 10: 8–17, 1969

23. VAN DYKE D, DOBSON EL, PARKER H, et al: Radiopharmaceutical techniques for the study of bone and marrow blood flow. In *Radiopharmaceuticals*, Subramanian G, Rhodes BA, Cooper JF, et al, eds. New York, The Society of Nuclear Medicine, 1976, pp 329–342