Studies of Skeletal Tracer Kinetics: II. Evaluation of a Five-Compartment Model of [^{18}F]fluoride Kinetics in Rats

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We have evaluated a five-compartment model of [^{18}F]fluoride kinetics in rats. The initial fluoride distribution was found to be similar to that of [^{77}Br]bromide, a known extracellular-fluid (ECF) tracer, in agreement with the hypothesis underlying the model, and the measured uptake rate in rat bones compared well with the digital computer solution. Simpler models did not give a better fit. In dead rats, fluoride movement was found within the skeleton, presumably from bone ECF to bone substance, although not as rapidly as predicted or found in the live animal. Evaluation of the rate constants permitted estimates to be made of cardiac output, skeletal blood flow, and bone ECF volume, all in accord with independent measurements. It is suggested that skeletal blood flow at rest is a constant fraction of body weight, and probably subserves a hematopoietic as well as a mineralization function.

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We have recently described a five-compartment model of [^{18}F]fluoride kinetics in humans that appears to account satisfactorily for the movement of this ion in the body in the first few hours following i.v. administration (*1*) (Fig. 1). The model assumes rapid, free diffusion of fluoride ion out of the blood and into the extravascular, extracellular space of the body (ECF), including that portion of the ECF located in bone (*2–4*); fluoride is then assumed to pass from bone ECF into bone substance ("exchangeable bone"). The model provides for urinary excretion, and first-order bidirectional exchange is assumed between all compartments, since there is no evidence to the contrary. The model was initially solved on an analog computer (*5*) and, more recently, by digital computer techniques using the SAAM-25 program (*1*), which provides a least-squares best fit to the blood and urine input data. Perturbation analysis revealed the bone uptake to be markedly nonproportional with respect to changes in systemic and skeletal blood flow, which permitted certain inferences to be drawn concerning bone-scan interpretation.

The purpose of this study was to test, in rats, the assumptions underlying the model, using digital computer methods. The experimental findings showed a good fit of the proposed five-compartment model to the data, lending credence to the validity of the underlying assumptions. From the calculations, values were derived for cardiac output and skeletal blood flow that are in good agreement with results obtained by other methods.

MATERIALS AND METHODS

The kinetics of [^{18}F]fluoride and a known ECF-tracer, [^{77}Br]bromide (*6*), were investigated in 57 male Wistar rats, 10–12 wk of age and weighing 250–320 g (mean weight 289 ± 26 s.d.). Under ether anesthesia, each animal was injected intravenously with a mixture of cyclotron-produced [^{77}Br]bromide and [^{18}F]fluoride in a weighed syringe. [Since the chemical form of the F-18 supplied by the manufacturer (MRC Cyclotron Unit, Hammersmith Hospital, London) is uncertain (*7*), the

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F-18 was diluted in stable sodium fluoride to 2 ppm before injection, to convert it to fluoride form.] The animals were killed by abdominal hemisection at 0.5, 1, 2, 3, 5, 7.5, 10, 15, 20, 30, 45, 60, and 120 min after injection, and the mixed arterial and venous blood was collected. Ten minutes before killing, each rat was also injected with Cr-51-labeled red cells suspended in heparinized saline in a weighed syringe, for determination of the red-cell volume. One femur and tibia, the stomach, kidneys, and urinary bladder were dissected free from surrounding soft tissue and weighed, and aliquots of whole blood and plasma were prepared in duplicate. Microhematocrit measurements were also made, again in duplicate, and corrected by 0.96 for trapped plasma. Samples were counted in a well scintillation counter equipped with a multichannel analyzer, immediately after the experiment and 24 hr later; the Br-77, Cr-51, and F-18 concentrations were determined by differential decay and the method of Veall and Vetter for two emitters (*8*). One month later, when the Br-77 had decayed to less than 0.1% of its original value, the samples were recounted for Cr-51.

The volumes of distribution of fluoride and bromide (corrected for urinary, gastric, and red-cell losses) were determined by standard methods (*6*), modified for the Donnan-Gibbs equilibrium ratio and plasma-protein concentration by a factor of

$$\frac{0.96}{1.04} = 0.92:$$

$$V(t) = \frac{W}{r} \cdot \left[\frac{D - \int U(t) - \int G(t) - R(t)}{P(t)} - L\right] + L,$$

where V(t) is the volume of distribution at time t, P(t) is the plasma F-18 or Br-77 concentration at time t, D is the administered tracer dose in cpm, $\int U(t)$ is the cumulative urinary loss of tracer (cpm) at time t, $\int G(t)$ is the cumulative gastric loss (cpm) at time t, R(t) is the amount in red cells (cpm) at time (t), L is the plasma volume (40.4 ml/kg) (*9*), r is the Donnan-Gibbs equilibrium ratio [calculated (*10*) to be 1.04, assuming plasma chloride = 96 mEq/liter (*11*) and plasma-protein concentration = 5.7% (*12*)], and W is the concentration of water in plasma (corrected for protein concentration (*6*) = 1 − (0.01)(5.7)(0.73) = 0.96.

In another experiment, three rats were killed by hemisection 30 sec after Br-77/F-18 injection and the left tibia rapidly dissected out, cleaned, shattered into hundreds of shards by multiple blows with a hammer, weighed, and washed five times with 4 ml of water. This entire process took about 3.5 min. The combined washings and the bone shards were then counted. The other tibia was treated in the same manner 60 min after the animal was killed. Three control rats were killed 60 min after Br-77/F-18 injection and both tibias were processed in the same manner. The purpose of this experiment was to determine whether fluoride moved from bone ECF to bone substance in the dead rat (i.e., in the absence of blood flow) as predicted by computer solution of such a perturbed model. The washing step removed most but not all of the fluoride in bone blood and bone ECF; the efficiency of extraction was calculated from the residual Br-77 counts in the bone shards and in the wash volume (approximately 85% of the Br-77 was washed out). The F-18 counts lost in washing were therefore divided by the Br-77 extraction efficiency (simultaneously determined)to give the total non-bone-substance counts. These counts were then subtracted from the summed F-18 counts in shards plus washings to give the total counts in bone substance, and thus gave the fluoride partition between bone substance and bone ECF plus bone blood.

Data were processed for further analysis by a minicomputer. Means and standard deviations of blood values (expressed as fractions of the administered dose) and cumulative urinary excretions were then entered in the SAAM-25 program on a digital computer.* This program generates the intercompartmental rate constants by an iterative least-squares method, and also gives an estimate of the error for each parameter. The final value for each rate constant was assumed when successive fits differed by no more than 0.01%. The fraction of the administered dose present in every compartment at time t for 15-sec increments was then calculated on the minicomputer, using these rate constants.

Four different models (Figs. 1 and 2) were evaluated. "Goodness of fit" was determined visually by comparing the computer-predicted curve for fluoride in the entire skeleton (bone substance plus bone ECF) with the experimentally measured values, having first subtracted the amount of [^{18}F]fluoride present in the blood in each bone from the measured F-18 counts using the formula: $^{18}F_s = {}^{51}Cr_s \cdot {}^{18}F_b$ where $^{18}F_s$ = fraction of F-18 dose in

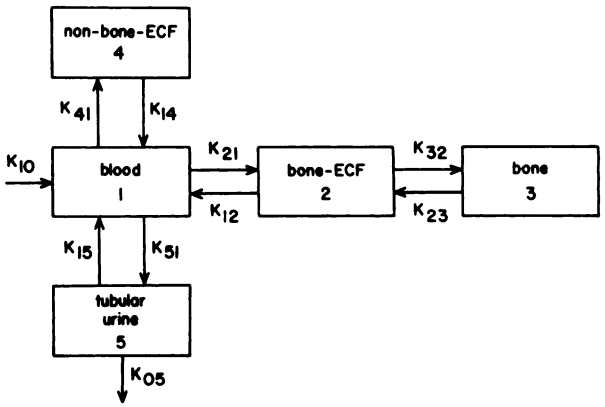

FIG. 1. Five-compartment model of fluoride kinetics. Values for rate constants are given in Table 1. Reproduced with permission of *J Nucl Med* (19: 1301–1309, 1978) and the authors.

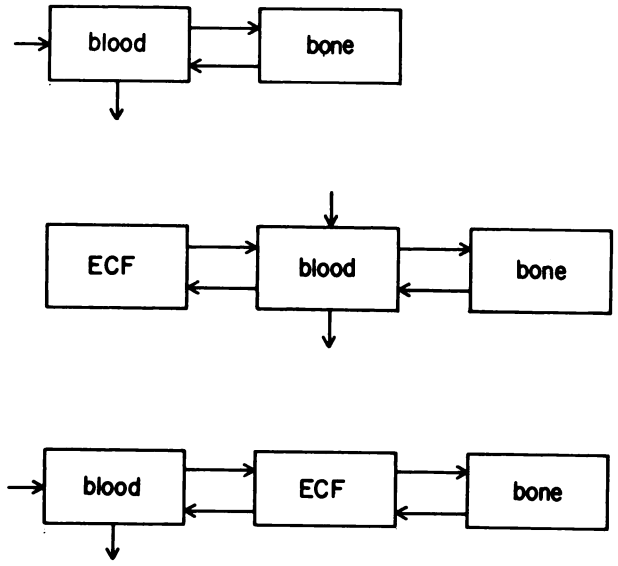

FIG. 2. Other models of fluoride kinetics that were tested.

the blood in a bone (tibia or femur), $^{51}Cr_s$ = fraction of Cr-51 dose in the same bone, $^{18}F_b$ = fraction of F-18 dose in whole blood. In these computations, total skeletal uptake for each rat was estimated by multiplying the mean fraction of the administered F-18 dose per tibia (or femur) by a conversion factor (48.31 for tibia, 34.44 for femur). The conversion factor is the reciprocal of the mean fractional weight of the tibia (or femur) per skeleton, previously determined on 40 boiled (defatted) rat skeletons by one of us (Brookes, unpublished). The rats of the latter group were of the same strain, age, sex, and weight as those used for the current experiments. The estimated skeletal uptakes for the "tibial standard" and "femoral standard" were then averaged to give the mean estimated total skeletal F-18 uptake for each rat (bone substance plus bone ECF).

All F-18 counts were decay-corrected to the time of dose administration so that the results could be expressed in terms of the biological behavior of the fluoride ion.

Additional information of physiologic interest was obtained as follows: the cardiac output can be shown to be equal to the blood volume multipled by the sum of the rate constants of fluoride exit from blood†; absolute skeletal blood flow equals the blood volume multiplied by the rate constant to bone ECF from blood; and fractional skeletal blood flow equals the ratio of the rate constant to bone ECF from blood to the sum of the exit rate constants from blood (*13*). In these calculations, blood volume was taken to be the sum of the measured mean red cell volume‡ for all 57 rats (22.5 ml/kg) and the plasma volume (40.4 ml/kg) (*9*). Absolute skeletal blood flow was expressed per 100 g skeletal weight by dividing the skeletal blood flow value obtained as above by estimated skeletal weight per kilogram body weight using these formulas:

$$\frac{\text{skeletal wt. (T)}}{\text{body wt.}} = \frac{1}{57} \cdot \frac{\text{skeletal wt. (T)}}{\text{tibial wt.}} \cdot \sum_{n=1}^{57} \frac{\text{tibial wt.}}{\text{body wt.}}(n)$$

$$\frac{\text{skeletal wt. (F)}}{\text{body wt.}} = \frac{1}{57} \cdot \frac{\text{skeletal wt. (F)}}{\text{femoral wt.}} \cdot \sum_{n=1}^{57} \frac{\text{femoral wt.}}{\text{body wt.}}(n)$$

$$\frac{\text{mean skeletal wt.}}{\text{body wt.}} = \frac{1}{2}\left[\frac{\text{skeletal wt. (T)}}{\text{body wt.}} + \frac{\text{skeletal wt. (F)}}{\text{body wt.}}\right]$$

where the ratio of skeletal weight to tibial (or femoral) weight is the measured conversion factor given above.

RESULTS

Distribution volume. The ratios of the distribution volumes of bromide to fluoride are plotted in Fig. 3. The ratio constantly decreases, as a result of progressive fluoride losses to bone and urine, and could be approximated in the first 20 min by a straight line on a semilogarithmic plot. When the correlation line was ex-

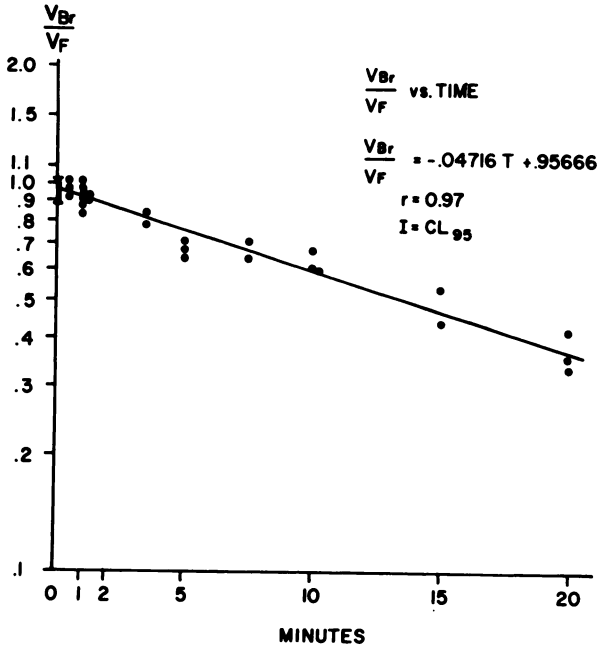

FIG. 3. Semilogarithmic plot of ratios of distribution volumes of bromide to those of fluoride, simultaneously determined in each of 26 rats up to 20 min after injection. Zero intercept of regression line is not significantly different from unity.

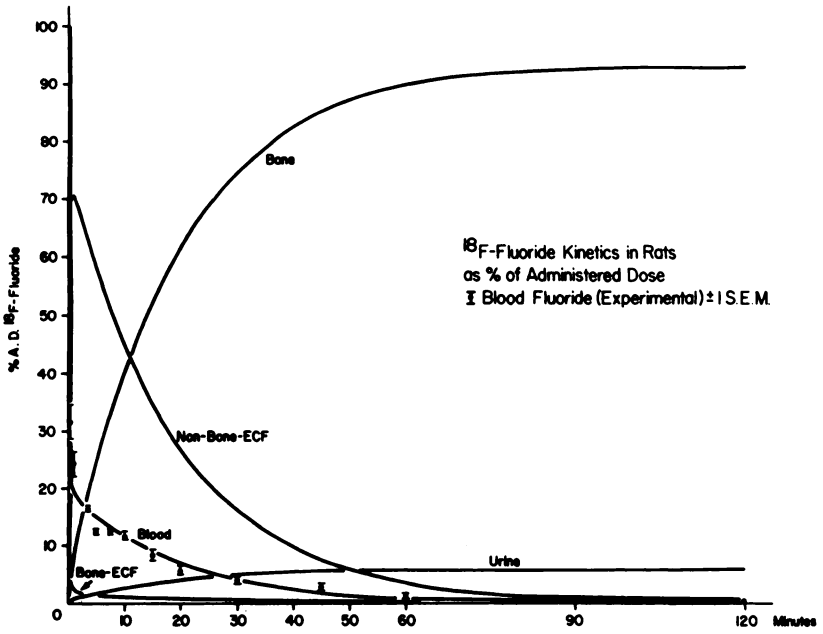

FIG. 4. Computer-generated curves of fluoride kinetics for five-compartment model of Fig. 1, using rate constants of Table 1. Curves have been corrected for F-18 decay. Mean blood values are shown as solid circles ± 1 s.e.m.

trapolated to zero (time), the ratio was within the 95% confidence limits of 1.0, i.e., the initial distribution volumes of fluoride and bromide were not significantly different.

Model fitting. The computer-generated curves for the five-compartment model are shown in Fig. 4. Uptake in bone substance is seen to reach about 90% of the administered dose 90–120 min after injection. The rate constants for the model are given in Table 1, including estimates of minimum transfer rates between plasma and erythrocytes.

Since fluoride partition between bone ECF and bone substance was not determined separately for each rat, the sum of the two compartments was lumped as a single curve and plotted against the experimental values (corrected for bone-blood content) in Fig. 5. A good fit was observed. The three-compartment models of Fig. 2 also gave good fits, but the fit to the two-compartment model was poor.

Bone fluoride uptake in dead rats. The results of this experiment are shown in Fig. 6. There was good agreement between the predicted and measured values for fluoride partition between bone substance and bone ECF plus bone-blood, both in the rats killed 30 sec after injection and in the control rats killed 1 hr after injection. In the dead rats, fluoride appeared to move from the bone ECF to bone substance, although not as much as predicted from the live model or found in the living animals.

Physiological data. These are summarized in Table 2. Good agreement was found between the distribution volumes calculated by the rate-constant method (*13*) and measured with [^{77}Br]bromide. The calculated skeletal blood flow was 19.3 ± 0.6 ml/100 g bone-min; cardiac output 201 ± 4 ml/kg-min, and the fraction of the cardiac output delivered to the skeleton 9.6 ± 0.2%.

TABLE 1. COMPUTER-GENERATED RATE CONSTANTS FOR FIVE-COMPARTMENT MODEL OF FLUORIDE KINETICS IN MIN^{-1}*

k_{12}	0.640	± 0.08†
k_{21}	0.307	± 0.01
k_{14}	0.781	± 0.03
k_{41}	2.852	± 0.06
k_{15}	0.454‡	—
k_{51}	0.033‡	—
k_{23}	0.0016	± 0.0002
k_{32}	2.335	± 0.17
k_{05}	0.015‡	—
$k_{plasma} \rightarrow RBC$‖	0.326	—
$k_{RBC} \rightarrow plasma$‖	1.053	—

* See Fig. 1.
† ± 1 s. d.
‡ Assumes GFR 1.7 ml/kg-min.
‖ Other rate constants must be proportionally increased when compartment 1 is plasma.

DISCUSSION

Bromide ion is known to distribute within the extravascular space of the body (6), and the results of our bromide/fluoride simultaneous injection study indicate that fluoride ion does so also. Fluoride is freely diffusible through collodion membranes (*14*), and its rapid passage into the ECF (*15*) undoubtedly accounts for the marked fall in plasma fluoride concentration that we noted im-

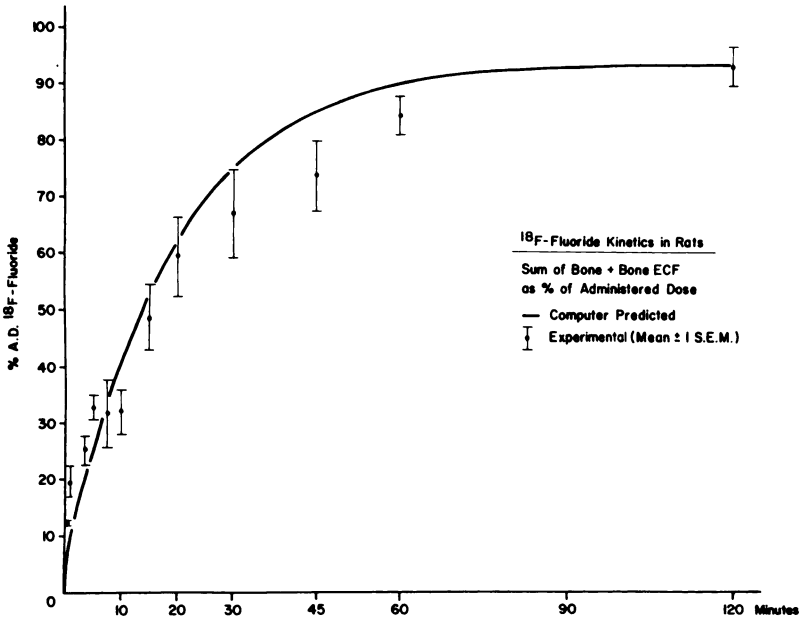

FIG. 5. Computer-generated curve of fluoride kinetics, for sum of bone ECF and bone compartments of five-compartment model, derived from blood and urine values only. Experimental measurements are shown as solid circles ± 1 s.e.m.

mediately following i.v. injection. As with other halogens, some intracellular penetration is found; our value for RBC:plasma concentration, 0.54, is identical to that noted by previous investigators (*15*). The blood levels and long-bone concentrations that we obtained were very close to those reported for female rats of the same age injected with cyclotron-produced F-18 of similar specific activity (*15*).

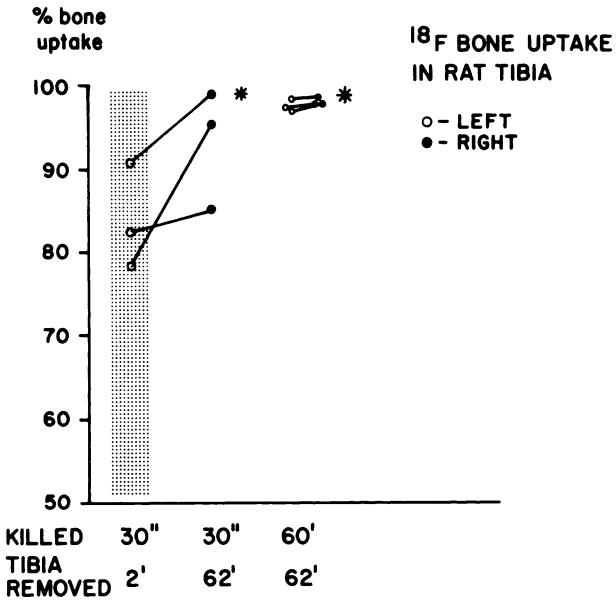

FIG. 6. Left-hand panel shows fraction whole tibial [^{18}F]fluoride in bone substance of animals killed 30 sec after injection, as open circles. Stippled background is range of values predicted by the model between 30 sec and 2 min after dose, when tibias were removed for processing. Middle panel shows values for contralateral tibia in same animals, removed 1 hr after death. Computer-predicted value for such a perturbation is shown as an asterisk. In right-hand panel are values for both tibias from control animals killed 1 hr after injection, with computer-predicted value for perturbation shown as an asterisk.

The estimate we obtained for bone ECF volume using the rate-constant ratio method (*13*)—0.59 plasma volumes, corrected by 0.92 for Donnan-Gibbs equilibrium effects and plasma water concentration—was very close to the figure of 0.63 that we found by direct measurement with [^{77}Br]bromide. These measurements support light and electron microscopy findings of a large extravascular, extracellular space in bone (*2–4*). Since plasma volume in rats is about 4% of body weight, bone ECF therefore accounts for ~2.6% of body weight and 26% of total bone weight; this value is similar to the ratio of ECF to body weight measured by bromide dilution (27.8%).

Extravascular fluid volume estimated by the rate-constant method came to 5.1 plasma volumes (also corrected for Donnan-Gibbs equilibrium and plasma water), not significantly different from the value of 5.9 ± 0.5 obtained with bromide ($p < 0.05$). We note that the ratio of fluoride-to-bromide distribution volumes calculated directly from the plasma concentration data of the two tracers also appeared to show a slightly (but not significantly) lower value for fluoride distribution volume. Although both ions are halogens, they ultimately behave quite differently in the body: fluoride is incorporated into hydroxyapatite crystals and is excreted into the urine in significant amounts, whereas bromide, like iodide, penetrates into the stomach, thyroid gland, and cerebrospinal fluid. Erythrocyte penetration of bromide is greater than that of fluoride, as shown in Table 2. It is quite possible, therefore, that the slightly lesser distribution volume of fluoride ion compared with bromide ion suggested by our findings might prove real if more

TABLE 2. MEASUREMENTS OF PHYSIOLOGICAL INTEREST IN THE RAT

	Methods		
	Fluoride rate constants	Bromide distribution	Other (ref.)
Cardiac output (ml/kg-min)	201 ± 4*	—	173–280, range of 10 reports (*18*) 210 ± 45, ether anesthesia (*20*) 204 ± 18, Fick principle (*18*) 205, K-42 or Rb-86 dilution (*19*)
Skeletal blood flow (% C.O.)	9.6 ± 0.2	—	3–27. arteriolar blockade (*25,34*)
(ml/100 g bone-min)	19.3 ± 0.6	—	20, Cr-51-RBC washout (*23*)
Distribution volume (% body wt)‡	24.5†	27.8 ± 2.33	25–31, bromide (*40*)
Bone ECF volume (% body wt)	2.36†	2.55 ± 0.24	—
(per plasma volume)	0.59†	0.63 ± 0.06	—
Extravascular volume (% body wt)	20.5†	23.8 ± 2.0	21–27, bromide (*40*)
(per plasma volume)	5.1†	5.9 ± 0.5	5.6–6.2, bromide (*40*)
Mean RBC:plasma concentration	0.54	0.82	0.54, fluoride (*15*)

* ± 1 s. d.
† Difference not significant ($p > 0.05$) in comparison with bromide value.
‡ Does not include losses to RBC volume, urine, bone, or stomach.

animals had been tested.

We observed a good fit of the projected "summing compartment" (bone substance plus bone ECF) curve to the experimental data, but this was no better than the projections made for the other models tested (not shown). In other words, a choice of model cannot be made on mathematical grounds alone. By measuring bone ECF and nonbone ECF with bromide ion, and relating them to known anatomic evidence for these spaces, it becomes possible to reject those models that do not include these compartments as being less satisfactory than the five-compartment model for explaining fluoride behavior.

Our model does not include a compartment for incorporation of fluoride into hydroxyapatite from exchangeable bone, since the rate constant for this transfer is not known at present. If it is as slow in comparison with the bone ECF to bone transfer as is the calcium system, it would not appreciably affect the kinetic analysis during the first few hours with respect to total bone accumulation. In vitro studies in our laboratory (unpublished) suggest that this transfer rate is an order of magnitude slower than the bone ECF to bone transfer rate, and can therefore be neglected in short-term studies.

Our experimental estimate of fluoride partition between bone substance and bone ECF was well within the range predicted by the model solution for 0.5–2 min after injection, at which time the tibias were removed, and agrees closely with the predicted value for animals killed 1 hr after dose. Fluoride movement into bone substance appeared to occur in the dead rats, although not as much as predicted from the live model, which suggests that this transfer process is partially dependent on the living state and is not solely a passive physicochemical process. Such a requirement for free, passive ionic diffusion has been postulated by others (*16*), and our findings are in keeping with the "living membrane" hypothesis.

Tothill and MacPherson have recently reported migration of F-18, Sr-85, and Ca-47 ions into bone from soft tissue after death (*17*). The femurs and tibias of all the animals in our study were removed within 10 min of death, so that spuriously elevated bone concentrations were not produced.

Our estimate of the cardiac output in these rats, 201 ± 4 ml/kg-min, using the rate constant method (*13*), is well within the range of 173–280 ml/kg-min reported in ten different studies summarized by Popovic and Kent, in which the Fick principle or Stewart-Hamilton method was used (*18*). Sapirstein found a value of 205 ml/kg-min using another freely diffusible tracer, K-42 (*19*), and Bullard reported 210 ± 45 ml/kg-min by dye dilution in ether-anesthetized rats (*20*). We note in passing that the cardiac index of the anesthetized rat is approximately double that of larger mammals ranging in size from the rabbit (*21*) to the giraffe (*22*), including man (*1,22*).

Using the same rate-constant method, we estimated skeletal blood flow to be 19.3 ± 0.6 ml/100 g bone-min, not significantly different from the value of 20 ml/100 g-min obtained by Brookes (*23*) with the Cr-51-labeled red-cell washout technique. Frederickson et al. reported a range of 10–30 ml/100g-min by the Ca-45 clearance method. All of these values are significantly greater than

skeletal tracer clearance measurements reported by Van Dyke et al. (8.7 ml/100 g-min) (*24*) and Tothill and McCormick (10.0 ml/100g-min) (*25*). In their method, tracer uptake by bone during a time period, Δt, is divided by the product of Δt and the mean arterial tracer concentration during that time, giving clearance. Flow is proportional to clearance, and if extraction is 100%, the two are identical. If extraction is less than 100%, the calculated value for blood flow is a minimum value. According to Van Dyke et al., the two basic assumptions on which the method rests are "no loss of F-18 from the bone and no saturation effects." Shim et al. (*26*) and Ray et al. (*27*) found a rapid and progressive fall in extraction of the skeletal tracer Sr-85 during the first few minutes after injection, as did Wootton (*28*), Bosch (*29*), and Costeas et al. (*30*), who used Ca-45, Ca-47, and F-18 over 120 min. A significant return flux of fluoride is a feature of the five-compartment model, in agreement with earlier models of calcium kinetics (*31*). Thus, the first assumption (no return of fluoride to blood) is incorrect, and estimates of skeletal blood flow by this method are, at best, minimum values.

With respect to the second assumption (no saturation effect), perturbation analysis of the five-compartment model (*1*) reveals the system to be markedly nonproportional with respect to skeletal blood flow, and *apparent* saturation is in fact a feature of the system ("diffusion-limited"). Experimental deviations from a simple linear relationship between skeletal tracer uptake and skeletal blood flow have been found by other investigators (*25,29,32,33*) using other methods, in accord with our results. A single inverse exponential equation will not fit the data (*29*), but a sum of exponentials (derived from the intercompartmental rate constants) gives an excellent fit (*33*). Such a system displays marked nonproportionality with respect to flow if the intercompartmental fluxes are widely disparate, which is the case with fluoride transport.

Under these circumstances, the relatively slow skeletal extraction rate is the rate-limiting step, and *apparent* saturation is the result. It appears, therefore, that the skeletal tracer clearance technique is not a suitable method for measuring bone blood flow.

From our estimates of cardiac output (201 ± 4 ml/kg-min), skeletal blood flow (19.3 ± 0.6 ml/100 g bone-min), and measured skeletal weight as 10% of body weight, we find that skeletal blood flow is approximately 9.6 ± 0.2% of the cardiac output in ether-anesthetized rats. Values ranging from 3 to 27% have been reported using arteriolar blockade methods (*25,34*). In larger mammals, with proportionally lower cardiac outputs (about half that of the rat), fractional skeletal blood flow is approximately double that of the rat. In man, for example, we found this fraction to be 16.8% (*1*), and in monkeys it is 19% (*35*).

The product (fractional cardiac output to bone) × (cardiac output)—i.e., absolute skeletal blood flow—may be species-independent, but is masked by the progressively greater skeletal bulk in larger animals. When skeletal blood flow is expressed in terms of volume of perfusate per 100 g bone per min, representative values are: rat 19 (this study), rabbit 16 (*36*), and man 12 (*1*). Skeletal weight as a fraction of body weight, however, progressively increases with size: rat 10% (Brookes, unpublished), rabbit 11% (*21*), and man 15% (*37*). The product of these two variables appears to be very similar among these species (rat 1.9, rabbit 1.7, man 1.8 ml per 100 g body weight). This may be a biologic constant, like many other physiologic functions. It is very likely that this apparent constancy of skeletal blood flow relative to body weight among species serves a hematopoietic need as well as a mineralization function. Skeletal blood flow is known to be dependent upon erythropoietic activity (*38*), and most of the blood flow to long bones traverses the marrow rather than the cortex (*39*). Under these circumstances, bone extracellular fluid appears to serve a valuable purpose as a buffer zone, providing a necessary milieu for mineral homeostasis.

FOOTNOTES

* IBM 370

† This relationship is valid under normal circumstances where unidirectional F-18 efflux from blood is 100% (*28*), but at high flow rates of diffusion-limited flow (*33*), unidirectional efflux declines and cardiac output is thereby underestimated.

‡ In calculating the red-cell volumes, the volume of the injected Cr-51-labeled red cells was subtracted from the measured value.

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