Studies of Skeletal Tracer Kinetics. I. Digital-Computer Solution of a Five-Compartment Model of [^{18}F] Fluoride Kinetics in Humans

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We have developed a new model of short-term fluoride kinetics in humans and have solved the model on a digital computer using the SAAM-25 program. The solution accords well with available data. About 60% of intravenously administered [^{18}F] fluoride is taken up by bone. Evaluation of the rate constants of tracer egress from blood indicates that about 17% of the cardiac output is distributed to the skeleton. When the model was perturbed to simulate changes in systemic or skeletal blood flow, we found that the system behaves in a nonlinear manner; even a five-fold increase in systemic or skeletal blood flow did not appreciably increase the amount of fluoride taken up by bone 1–2 hr later, the time when scans are usually made. A simulated increase in bone extraction rate, however, had a marked effect on bone-fluoride uptake. These findings suggest an important homeostatic role for bone in the regulation of blood calcium concentration and have considerable bearing on the interpretation of bone scans.

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The mechanism of skeletal mineralization is poorly understood. Factors that are thought to be of major significance include the quantity of mineralizable bone, the rate and amount of bone blood flow, capillary permeability, local acid/base relationships, fluid pressure within bone, and the modulating influence of parathyroid hormone and vitamin D metabolites (*1*). The quantitative contributions of each of these factors to both normal and abnormal states of bone formation are not known, and study has been hampered by lack of an acceptable model of ion transport from blood to bone. In this paper we report on a computer-generated solution of a new model of short-term fluoride kinetics that appears to describe adequately the movements of this anion in the first few hours following i.v. injection.

Fluoride was chosen as the prototype ion for this study—rather than calcium and its alkaline earth congeners, or the diphosphonates—because of a large body of published data on fluoride kinetics both in animals and man, lack of protein binding, and the purported dependence of skeletal fluoride uptake on bone blood flow (*2*). Perturbations of the model to simulate alterations in cardiac output, skeletal blood flow, and bone extraction rate have allowed us to evaluate the role of these processes in bone mineralization and to relate these changes to the interpretation of bone scans made with radioactive fluorine-18 as fluoride ion (F-18).

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Additional information was obtained with respect to the fraction of the cardiac output delivered to the skeleton.

METHODS AND MATERIALS

In order to simulate the kinetics of F-18 in humans, all published data relating to blood and urinary excretion measurements made with this ion were collected and analyzed. We found nine such studies in the literature (*3-11*). Many of the individuals studied were normal, but not all. Blood concentrations were first normalized to 7% of body weight, if not reported directly as such, and were expressed as the percentage of administered dose per total blood volume (4900 ml) for intercomparison. In those studies in which F-18 concentration was expressed in terms of plasma volume, the data were converted to whole-blood concentrations using the red-cell/plasma partition ratios determined by Hosking and Chamberlain (*12*). Values at selected times after i.v. injection were then averaged and weighted for the number of patients studied at that time. If the number of patients in a study was not explicitly given we assumed the number four, and 95% confidence limits (CL_{95}) about the mean were then calculated. Blood contents were not always determined at the same time by different authors; the implicit patient total that we used at any given time therefore varied but never exceeded 60 patients. The means, standard deviations, and patient numbers for different sample collection times, as well as urinary excretion rates, are given in Table 1.

In analyzing kinetic information compartmentally, the preferred approach is to fit a postulated model to the observed data, rather than "curve stripping" (*13,14*). Initially we employed an analog computer for this purpose. (*15*). To achieve greater accuracy for the analysis, we used the SAAM-25 program (*16*) and a digital computer,* which provide an iterative least-squares best fit to the measured blood and urine data points. Assuming first-order kinetics of fluoride transfer between compartments, the program generates the desired rate constants. These constants were then used in potentiometer settings on the analog computer in order to display continuous curves of fluoride content within each compartment as a function of time. The system behaves as a hybrid computer.

Model construction. The minimum number of permissible compartments in this system must be two—blood and bone—with the forcing function (bolus i.v. injection) into blood and egress from blood into urine. However, inspection of the published blood values (Fig. 1) showed a rapid and profound fall in fluoride concentration, immediately following injection, to about 30% of the initial levels within 2 min, suggesting rapid dispersion of the ion into a larger compartment adjacent to the blood. Such an anatomic compartment is the body's extracellular, extravascular space (ECF). This seemed reasonable, since the halogen congeners bromide and chloride are known to distribute within this space (*17*). In testing various compartmental arrangements on the analog computer, we found that the best fit occurred when ECF was interposed between blood and bone, suggesting the requirement for a bone-ECF space also. Such a space has been described by electron microscopy (*18*) and autoradiography (*19*) and its approximate volume and composition measured (*20-22*). Since the ECF space of the body includes a considerable volume

TABLE 1. FLUORINE-18 BLOOD CONTENT* AND URINARY EXCRETION DATA IN HUMAN SUBJECTS

No. of subjects	Ref.	Minutes after injection										Cumulative urinary excretion
		1	5	10	15	20	30	45	60	90	120	
4	7	—	18.2	16.1	15.1	13.3	10.9	8.4	7.0	5.3	4.6	18-32% @ 3 hr
(4)†	3	—	—	—	18.0	—	12.0	—	7.5	5.0	4.0	—
15	5	35.0‡	—	25.0	20.7	—	14.7	—	9.5	6.9	5.4	20-60% @ 2 hr
9	6	—	—	—	—	—	14.4	11.6	9.4	7.0	5.3	7-25% @ 5 hr
4	4	25.0	20.8	15.9	12.7	—	9.4	7.0	6.3	4.8	3.8	14-24% @ 3 hr
4	8	—	—	—	18.0	—	11.5	—	7.4	—	4.9	—
(4)†	10	—	26.3	—	—	—	12.5	—	9.0	—	5.3	20% @ 2 hr
(4)†	11	—	—	—	—	13.1	11.5	9.0	6.8	4.6	3.3	11% @ 1 hr 19% @ 2 hr
12	9	—	—	18.6	—	—	—	—	7.4	—	6.1	—
No. of subjects		4	12	35	31	8	48	21	60	40	60	
Group mean		25.0	21.8	20.8	18.3	13.2	12.9	9.6	8.2	6.1	5.1	
± 1 S.D.		5.0	3.5	3.9	2.9	0.1	1.8	1.9	1.2	1.0	0.8	

* In percentage of dose, assuming 4.9-liter volume.
† Estimated
‡ 2-min value

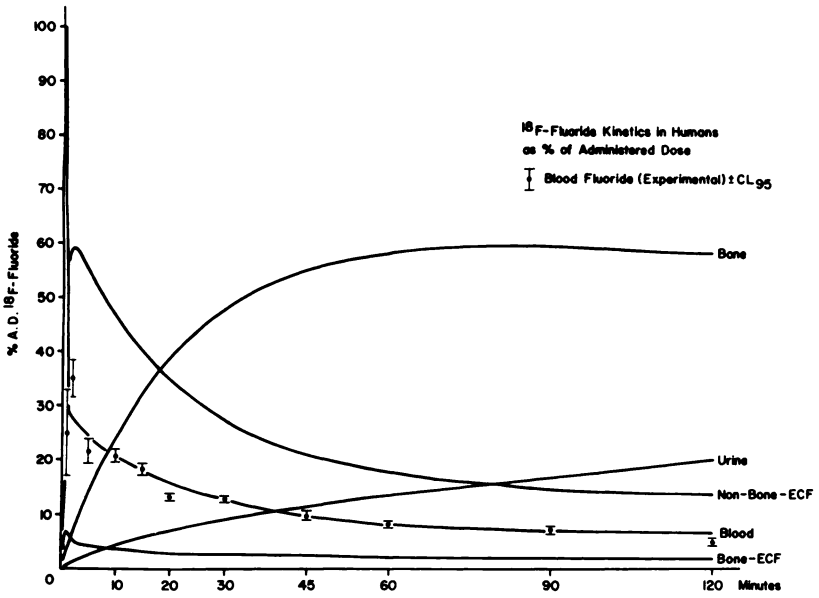

FIG. 1. Computer-generated curves (corrected for F-18 decay) for the five-compartment model in humans, showing percentage of administered dose of [^{18}F] fluoride as a function of time. Means of blood-data points (see Table 1) are shown in solid circles ± 95% confidence limits.

not in contiguity with bone, we provided separate bone-ECF and nonbone-ECF compartments in a mammillary relationship to the blood. Inasmuch as the renal clearance of fluoride ion is less than that of creatinine (*12*), a renal tubular urine compartment is required in order to provide backflow to blood. (Kidney ECF is included in the nonbone-ECF compartment).

Thus the smallest model that makes anatomic and physiologic sense appears to be a five-compartment model (Fig. 2), which we have previously simulated on the analog computer (*15*), and which forms the basis for these studies. The blood compartment can be subdivided further, if desired, into red-cell and plasma compartments in rapid equilibrium, for which partition ratios have been published. (*12*).

MODEL FOR FLUORIDE KINETICS

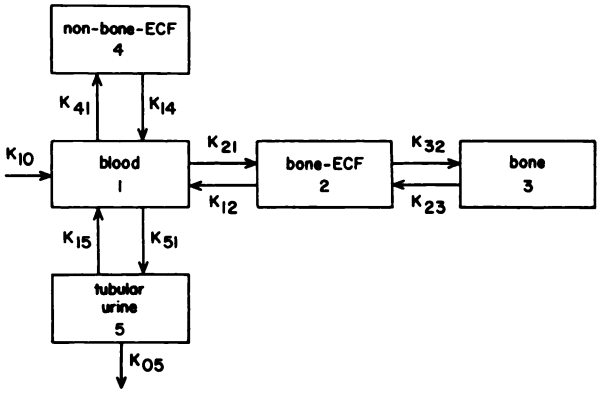

FIG. 2. Five-compartment model of fluoride kinetics in humans. Computer solutions for rate constants are given in Table 2.

RESULTS

Using the five-compartment model shown and providing the SAAM-25 program with *only* the blood and urine data, corrected for F-18 decay, the digital computer generated bidirectional rate constants between adjacent compartments (Table 2). These constants were then used to set the potentiometers of the analog computer, which displayed the continuous curves shown in Fig. 1.

In these studies, the rate constant representing fractional fluoride loss from blood to renal tubular urine (k_{51}) was taken to be the ratio of the glomerular filtration rate to blood volume, approximately 0.024/min in normal man. The rate constant for fluoride excretion, k_{05}, was then determined by the SAAM program by least-squares best fit from $k_{51}q_1(t)$ and the published values for urinary excretion (Table 1).

The whole-blood curve generated by the computer shows a good fit to the observed data points, passing within ± CL_{95} in most instances. (The computer iterations were continued until successive fits differed by no more than 0.01%). A sharp 'break' in the computer-generated blood curve is observed at about 2 min postinjection, followed by a slower, continuous decline in the fluoride levels. Bone activity is seen to rise rapidly, attaining a broad peak of about 60% of the administered dose at 70–100 min postinjection, with a 'half-uptake time' of about 13 min. Nonbone-ECF levels peak shortly after injection and thereafter fall almost in proportion to blood levels. The activity in bone-ECF is numerically small at all times, because of rapid bone extraction of the fluoride ion.

Evaluation of the rate constants concerned with

TABLE 2. COMPUTER-GENERATED RATE CONSTANTS FOR FIVE-COMPARTMENT MODEL OF FLUORIDE KINETICS (Fig. 2) IN MIN^{-1}

k_{12}	0.908 ± 0.42*
k_{21}	0.246 ± 0.011
k_{14}	0.567 ± 0.027
k_{41}	1.191 ± 0.059
k_{15}	0.388†
k_{51}	0.024†
k_{23}	0.020 ± 0.004
k_{32}	0.602 ± 0.030
k_{05}	0.612 ± 0.052
$\Sigma k_{21} + k_{41} + k_{51}$	1.462 ± 0.060
Blood volume (ml/Kg)	70
Cardiac output (ml/Kg-min)	102 ± 4
Fractional skeletal blood flow	0.168 ± 0.010
Skeletal blood flow (ml/100 g bone-min)	11.7 ± 0.7

* ± 1 standard deviation
† Assumes GFR 120 ml/min

fluoride egress from blood† in this group of normal and diseased persons indicates that the cardiac output was 1.42 ± .06 blood volumes per minute—i.e., approximately 7.0 ± 0.3 l/min. The fraction of the cardiac output distributed to the skeleton was (16.8 ± 1.0)%, or 11.7 ± 0.7 ml/100 g bone per minute.

Perturbing the model. Since the mathematical model does not include an explicit flow term, in order to simulate the effect of alterations in systemic blood flow on bone fluoride uptake the computer model was perturbed by increasing or decreasing the rate of tracer egress from plasma to both nonbone ECF (k_{41}) and bone ECF (k_{21}), keeping the ratio of egress to ingress constant in order to maintain constant ECF volume. The rationale for this approach is as follows. Consider a small volume of blood, ΔV, flowing past a capillary and containing F-18 at concentration C_A, at some time t. In the short time interval Δt, some fluoride, Δq, will have been lost from the blood to the surrounding ECF, giving a new concentration, C_V, in the volume ΔV. The amount lost, Δq, can be expressed as the product of the volume and the concentration difference, $\Delta q=(C_A-C_V)\Delta$ V, and also as a fraction, f of the original amount, $\Delta q = fC_A \cdot \Delta V$. During the brief interval Δt, the rate of loss is given by $\Delta q/\Delta t=fC_A\Delta V/\Delta t$, and as Δt becomes infinitesimally small, $dq/dt=fC_AdV/dt$. Now dV/dt is volume flow, F, so that $dq/dt=fC_AF$. In terms of the rate constant, k, this differential equation becomes $dq/dt=kC_AdtF$. Thus the rate of tracer loss, dq/dt, can be expressed either as a change in the volume rate of flow, keeping the rate constant the same, or as a change in the rate constant, keeping flow unchanged. In either case the numerical result is the same.

The rate constants to and from bone-ECF/bone were not altered, since a constant fractional extraction rate operating upon a greater (or lesser) concentration in bone ECF will result in a greater (or lesser) extraction by bone, without recourse to change in the extraction rate constant (*15*). The rate constants between blood and kidney were also unaltered in these perturbations.

The effect of perturbations simulating changes in systemic blood flow (cardiac output) over a fifty-fold range (from one-tenth to five times normal) and corrected for decay, are shown in Fig. 3. It can be seen that a simulated *decrease* in systemic blood flow markedly affects both the rate and the amount

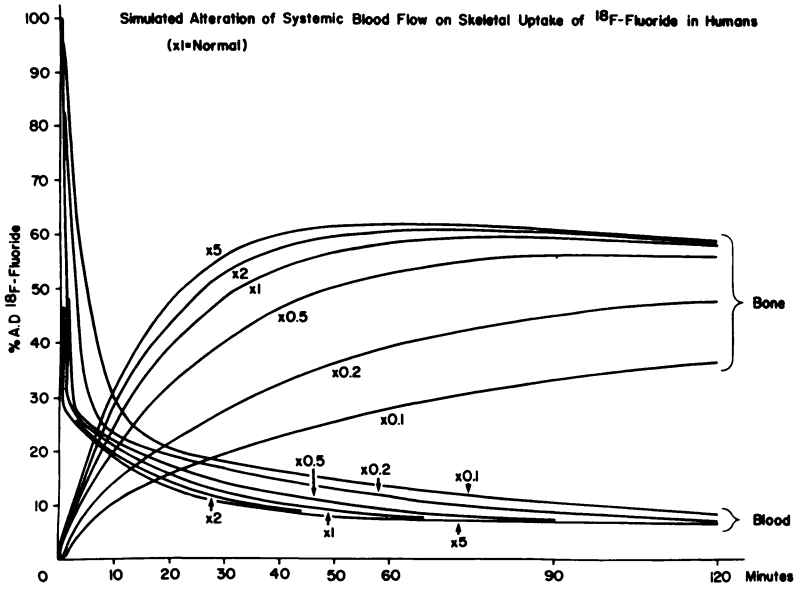

FIG. 3. Simulated perturbation of systemic blood flow and fluoride uptake by bone as a function of time. Normal blood flow = "x 1" (same curve as in Fig. 1). Note apparent saturation 1-2 hr postdose.

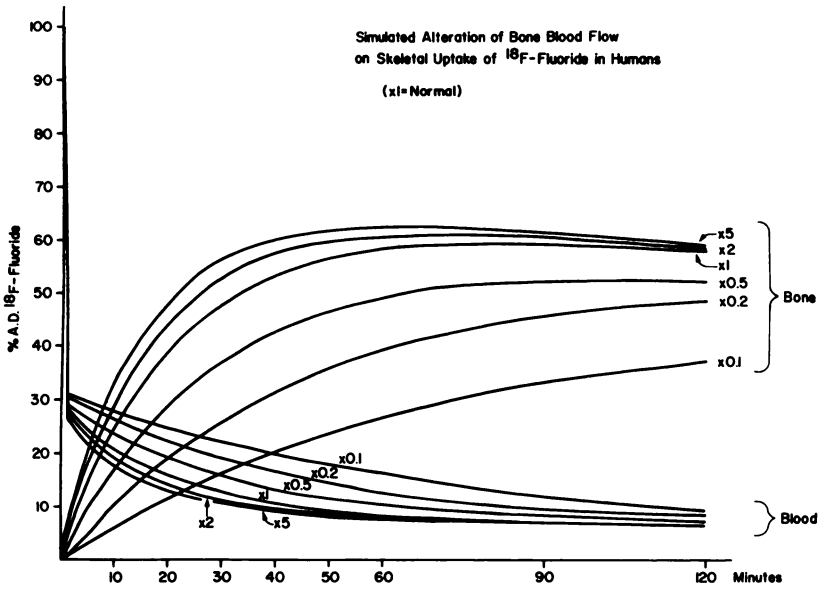

FIG. 4. Simulation of alteration in bone blood flow on bone uptake of fluoride. Note marked nonlinearity and apparent saturation, as in Fig. 3.

of tracer accumulated by bone up to 2 hr postinjection, but that even substantial *increases* in blood flow affect primarily the *rate* at which tracer accumulates in bone, and *not the final amount* at 1 or 2 hr postdose, a time when scans are usually made with this agent. When the computer-generated curves of Fig. 3 were replotted to relate skeletal fluoride uptake to relative blood flow, the relationship was seen to be markedly nonlinear.

A simulated change in skeletal blood flow (k_{21}) is shown in Fig. 4, with similar results. Again, the ratio $k_{21}:k_{12}$ was kept constant to maintain constant bone-ECF volume.

A simulated alteration in skeletal extraction rate (k_{32}) is shown in Fig. 5. Marked changes in bone fluoride uptake were found, unlike the simulated flow changes, although the system still behaves nonlinearly.

DISCUSSION

The computer-generated solution for the five-compartment model provides a good fit to the input data (blood and urine) and describes a bone-uptake curve that is qualitatively similar to that found for several animal species (*23,24*) and man (*7*). Quantitative comparison with animal data, however, reveals a much greater maximal skeletal fluoride accumulation in rats and rabbits than is predicted by the model for humans, in whom we found approximately 0.006% A.D./g (percentage administered

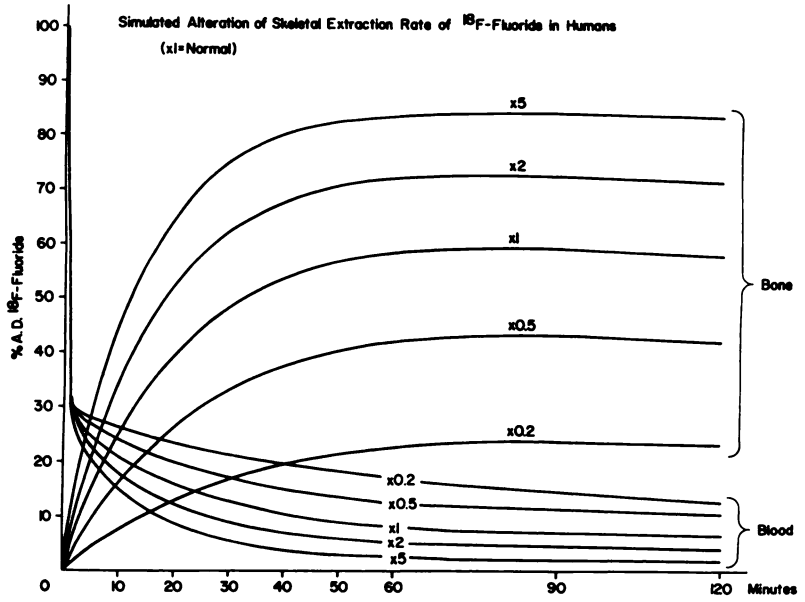

FIG. 5. Simulation of alteration in skeletal extraction rate (k_{32}) on bone fluoride uptake. Nonlinearity is not as marked as with changes in flow (Figs. 3 and 4).

dose per gram), assuming uniform distribution within the skeleton. Dworkin and LeFleur reported F-18 concentrations of .0017-.052% A.D./g in non-epiphyseal areas of normal bone in three humans who underwent bone biopsy 4½-7 hr postinjection (*25*)—a rather wide range, which encompasses the predicted value. Strontium-85 concentrations in normal human bones have been found to vary between .0015 and .0061% A.D./g at 4-5 days postdose (*26*), again similar to the computer-predicted value. [In normal rats, Sr-85 and F-18 bone concentrations are the same (*6*).] No actual ECF measurements have been reported for F-18 in humans, but the nonbone-ECF curve generated by the computer is similar to that reported by Costeas for F-18 concentration in muscle and skin of rabbits (*23*). Thus, the meager data available for evaluation of bone and ECF concentration of fluoride ion compare well with the model's predictions.

An important feature of the computer solution of the simultaneous differential equations that constitute the mathematical counterpart of the model is the generation of return rate constants from bone and kidney to the blood. Early studies with alkaline-earth cations, infused for 10 min or less into animals and designed to measure the 'extraction' of the tracers by bone, did not reveal a return flow, but when measurements were made over short intervals a progressive decline in the 'extraction fraction' was observed (*27*). Wootton (*28*) and Costeas (*29*) confirmed this observation for both calcium and fluoride ions, in studies extending up to 120 min, and Costeas pointed out its significance with respect to the return of tracer from bone to blood. The physiology of the 'reverse exchange' concept has been reviewed by Heaney (*13*), and it was therefore of interest to find that 'backflow' of fluoride ion is predicted by the solution of the model. Similarly, renal fluoride clearance has been found to be less than creatinine clearance in animals and man (*12*), implying tubular reabsorption, and this is also a feature of the solution. In both instances, therefore, the model has confirmed experimental findings.

Besides providing a reasonable fit to observed data, the model has the virtue of being based upon sound anatomic and physiologic principles, and it is here that it differs from some other models of skeletal tracer kinetics. Neither Van Dyke et al. (*7*), Wootton et al. (*30*), nor King et al. (*31*) identifies a discrete bone-ECF compartment, although it has been defined anatomically (*18,19*) and physiologically (*20-22*). In our initial computer studies we found it impossible both to fit the observed blood data and to describe an acceptable bone curve without providing a "buffer" space between blood and bone. Indeed, other computer models of skeletal tracer kinetics have included such a compartment (*32,33*), and in those that do not (*34,35*) the authors have concluded that "the uncertainty of the validity of the compartment models renders it difficult to attribute a precise anatomic or physiologic significance to the various compartments" (*35*). It is our opinion that the failure to include a bone-ECF space in a compartmental model of skeletal tracer dynamics seriously limits the confidence that can be placed in such a model and the conclusions drawn from perturbing it. Van Dyke et al., on the basis of their own studies, admit that "a labile fluoride pool in bone will probably be necessary in the future to fully interpret the human data" and that failure of their model to provide such a pool "is one of its drawbacks" (*7*).

In our model, the ECF space has been defined in a mammillary relationship to blood, which receives the bolus tracer injection (the 'forcing function', in mathematical terms). Rate constants to and from blood and ECF are then provided by the computer solution. Some other models either 'lump' the blood and ECF (*7,34,35*) or the bone-ECF and bone (*23,31*); in either case the system becomes less well defined anatomically and physiologically, so that the validity of the conclusions is not assured. When solutions had to be obtained by hand or by analog computer, 'lumping' was a virtue; but since the SAAM program can provide for up to 25 compartments in a matter of seconds at a nominal cost, there is now no reason *not* to identify those compartments that are thought to exist.

The models that most closely resemble our own (*32,33,36*) were designed to evaluate calcium and strontium kinetics, rather than fluoride, and include a long-term "nonexchangeable bone" compartment. This compartment includes significant nonbony calcium stores (*13*) of unknown fluoride content. Furthermore, since calcium accretion into this compartment is very slow compared with the rapid uptake by exchangeable bone from bone-ECF and is felt to be insignificant in the first few hours after injection (*13,29,33,35,36*), we neglected it in our model of short-term kinetics. As a result of the differences in the tracers used, the route of injection, and the objectives of the compartment analysis, our model cannot be compared quantitatively with these other models.

We specifically avoided the temptation to fit the blood data with a series of exponentials by "curve-stripping," even though apparently good fits can be obtained experimentally (*23,34*), because such an analysis lacks physiologic meaning. Unique, anatomically and physiologically defined compart-

ments cannot be deduced from such an approach. (*13,14,34,35*).

Furthermore, failure to obtain early blood levels can result in the missing of a rapid component that may constitute a significant fraction of the turnover and therefore result in erroneous rate constants when the curve-stripping method is used. This, we believe, occurred in Costeas' analysis (*23*), since he fitted a bi-exponential to the blood data when, in fact, three exponential terms would be required if early blood points are to be included. We found this to be true in analyzing the blood curve shown in Fig. 1, and it is also the experience of others. This erroneous bi-exponential was then used by King et al. as the driving function for their model (*31*), which in our opinion compromises their analysis.

The results of the perturbation analysis, simulating changes in systemic blood flow, proved unexpected. Although a decrease in flow diminished both the rate and amount of bone uptake of fluoride at 1-2 hr postdose, an increase in flow (up to five times normal) increased only the *rate* of bone uptake; the total *amount* was only minimally increased. Similar results were found when skeletal blood flow was altered (Fig. 4). With respect to blood flow, bone uptake of fluoride is markedly nonlinear. Bone therefore appears to behave *as if it were* saturable with fluoride, although true saturation is not present, since a second bolus injection of tracer will result in additional bone uptake. Rather, it is a result of equilibrium conditions and the *rate-limiting effect* of the much slower bone extraction ($k_{32} \cdot q_2 - k_{23} \cdot q_3$) in comparison with skeletal blood flow and net tracer flux into bone-ECF ($k_{21} \cdot q_1 - k_{12} \cdot q_2$).

Since a five-fold increase in systemic blood flow (cardiac output) is about the maximum that can be sustained by an untrained human, the implication for bone scanning at 1-2 hr post dose is that a marked, generalized increase in fluoride uptake by the skeleton is not the result of an increase in systemic or skeletal blood flow. Note, however, that evidence exists for the presence of a microcirculation in bone under neurogenic and chemical control (*37,38*), disturbance of which could open up vessels that are normally closed, thereby increasing the amount of bone surface available for exchange with fluoride and other ions ("recruitment"). The quantiative effect of this phenomenon is not known at present but is probably less than twofold—i.e., about half the microcirculation in bone is normally closed (Sagar et al., unpublished data). Increases in fluoride uptake greater than this are not the result of systemic 'recruitment' of normally closed vessels. A 'saturation effect' has been noted experimentally by several investigators in animal models over a range of flows (*39,40*) and also when the bone was injected directly (*41*). These findings support our perturbation analysis.

In contrast to the effect of blood-flow changes, the effect of an alteration in skeletal extraction rate on bone fluoride uptake is quite dramatic (Fig. 5). Although the system is still nonlinear, it is apparent that an increased avidity of the skeleton for fluoride (as might occur from an increase in surface area or hormonal influences) can significantly alter a fluoride bone scan 1-2 hr postdose. A comparison of a

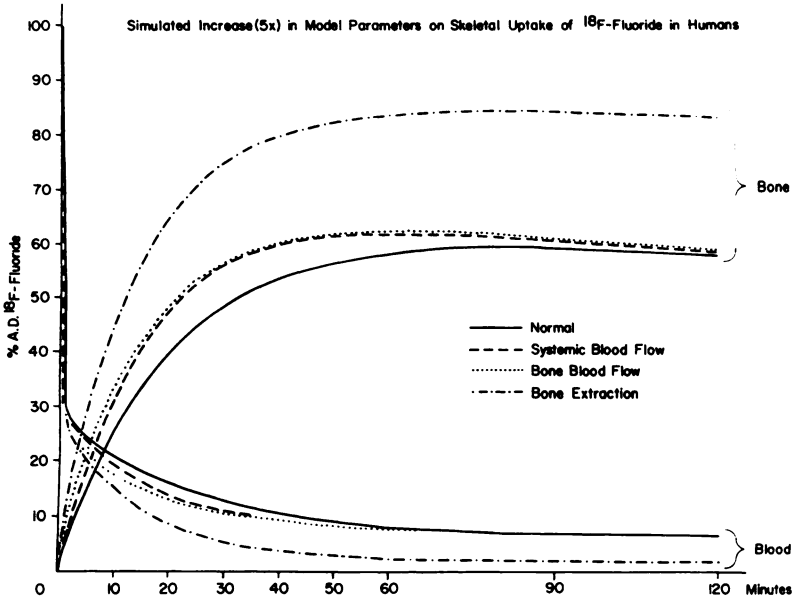

FIG. 6. Comparison of a five-fold increase in skeletal extraction rate, systemic blood flow, and skeletal blood flow on bone fluoride uptake. Note that at 1-2 hr postdose, when scans are usually made with [^{18}F] fluoride, only an increase in skeletal extraction rate would increase bone/blood contrast sufficiently to be visible as an abnormality.

simulated five-fold increase in systemic blood flow, skeletal blood flow, and skeletal extraction rate is shown in Fig. 6; *only the increase resulting from a change in skeletal extraction would be visible on a bone scan at 1-2 hr postdose.*

In patients with myelofibrosis, Van Dyke et al. have shown pronounced F-18 skeletal uptake 10-40 min after tracer administration; this they attribute to increased bone blood flow (*7*). This is quite consistent with the perturbation analysis of our model at this time postdose. Reference to Fig. 6, however, shows that the effect could occur equally well with a primary increment in the skeletal extraction rate. Differentiation appears possible by rescanning 1-2 hr postdose.

The results of our perturbation analysis are similar to those of King et al. (*31*), in that in both models the skeletal uptake of fluoride was found to be related nonlinearly to blood flow. Our analysis shows a more pronounced 'saturation effect,' similar to what has been found experimentally (*39,40*). We believe that the King model is less satisfactory than ours for quantitative analysis because the former employs an incomplete exponential input function, does not concern the system as a whole, does not provide a separate bone-ECF space, and fails to generate a significant return flux from bone/bone-ECF to blood.

Our estimate of skeletal blood flow—(16.8 ± 1.0)% of cardiac output, or 11.7 ± 0.7 ml/100 g bone per minute—is not significantly different from the value of 13.8 ml/100 g bone per minute obtained in unanesthetized dogs by Kane and Grim using Sapirstein's fractional distribution method with potassium-42 (*42*). This is not surprising, since both fluoride and potassium are freely diffusible ions (*43*). The skeletal blood-flow rate that we found is lower than that reported by Brookes for young rats (*44*), probably reflecting both species and age differences.

The value we determined for cardiac output—102 ± 4 ml/kg-min—is somewhat higher than that usually accepted for normal humans and is markedly dependent upon the 1-min input data for blood concentration. Since this was reported by only one investigative group (*4*), we do not attach great significance to the computed value for cardiac output. The rate constant for skeletal blood flow (k_{21}), on the other hand, is determined by events over the entire 2-hr period and is considered to be a reliable estimate.

The physiologic meaning of the 'saturation effect' is uncertain, but one may speculate that by preventing marked bone uptake of calcium during exercise it could constitute an important mechanism of calcium homeostasis. Bone would therefore function both as a mechanical scaffold and as a regulator of blood-calcium concentration by means of its ECF buffer. Such a role for bone has been proposed (*1*), and our findings support this concept.

The high rate of bone blood flow—16.8% of cardiac output—does not necessarily reflect a mineralization function. Since most of the flow to the skeleton is to the marrow rather than to the cortex (*45*), this probably largely reflects hematopoietic needs.

CONCLUSIONS

Our results suggest an important role for bone as a regulator of blood calcium concentration, with bone-ECF serving the function of a buffer. Experimental evidence in support of the model, however, is minimal at best. The model is readily susceptible to testing, and we have already undertaken such studies in animals. Should they confirm the model and its perturbations, current concepts concerning bone blood flow, scintigraphic interpretation, and the physiologic role of bone in calcium homeostasis may have to be revised.

FOOTNOTES

* IBM-370.

† It can be shown (*46*) that cardiac output = $(k_{21}+k_{41}+k_{51}) \times$ blood volume; fractional skeletal blood flow = $k_{21}/(k_{21}+k_{41}+k_{51})$; and absolute skeletal blood flow = $k_{21} \times$ blood volume.

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