COMPARISONS OF ^{99m}Tc-POLYPHOSPHATE AND ^{18}F KINETICS

In the October issue of the *Journal of Nuclear Medicine*, Krishnamurthy, et al (*1*) compared the blood disappearance curves after intravenous injection of ^{18}F and an unspecified ^{99m}Tc-polyphosphate. On the basis of five blood samples per study taken at approximately hourly intervals, they resolved the blood activity curves into two exponential components. This sampling frequency is not sufficient to decide whether the data are best represented by one, two, or more exponentials. Our own data, to be published shortly, employing much more frequent sampling, indicate that the ^{18}F blood disappearance curve is best fitted by a three-component exponential up to 6 hr after injection.

Having extracted two exponentials from their data, Krishnamurthy, et al interpret them as representing bone and renal clearance. This analysis appears to be purely speculative and is almost certainly wrong; since ^{18}F is known to equilibrate rapidly with extraosseous ECF, it is much more likely that the fast exponential predominantly reflects this equilibration. Furthermore, no evidence has yet been presented indicating that the integrated bone uptake of ^{18}F reflects the true clearance. On the contrary, Costeas, et al (*2*) have provided evidence (confirmed in our laboratory) to suggest that there is a marked reflux of ^{18}F from bone.

Twenty years ago it was common practice to attribute individual components of multiexponential curves to single physiologic compartments or processes, but we would suggest that sufficient progress has been made in the mathematical analysis of tracer data to make such an approach appear somewhat naive in the absence of additional experimental data to support the assumptions made.

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We want to comment on the article by Krishnamurthy, et al (*1*).

Before studying kinetic data of a labeled compound a definition of the chemical state(s) of the administered radioisotope should be made. Polyphosphate like diphosphate (pyrophosphate) shows differences in organic uptake besides being hydrolyzed by phosphate enzymes in blood and bone (*3,4*). Furthermore, labeling efficiency of different polyphosphate kits with $^{99m}TcO_4^-$ in our experience has a variation of 75–95% from kit to kit. A varying part, therefore, of pertechnetate and reduced but not phosphate-bound technetium will be administered with the ^{99m}Tc-Sn-polyphosphate and in vivo the polyphosphates like the diphosphates will be hydrolyzed (*5*). We use, therefore, a diphosphonate for comparison of the kinetics of a technetium–tin–phosphate complex (*3*). The behavior of the fluoride ion is thought to be fairly consistent (*4*). Unfortunately, the chemistry of "carrier-free" ^{18}F is not well known; there might be less or more complexes with heavy metals (*6*). We use ^{18}F for kinetic studies together with a trace amount of 0.5 mg $Na^{19}F$ to reduce such complexes and to administer a constant amount of fluoride. We also use only preparations of ^{99m}Tc-EHDP which contain less than 2% of nonphosphonate-bound technetium.

The biexponential clearance from plasma in the first 4 hr was seen with these preparations too. Using a weighted least-squares computer fitting, we were able to calculate half-time clearances of both exponents. As we do not believe the first exponent represents bone uptake and the second renal clearance but that the first exponent represents mixture in the distribution volume and exchange with the "slowly exchangeable soft tissue pool" and the second represents both renal and bone clearance, we have studied the half-time clearances in various renal and bone diseases (Table 1).

Neither ^{18}F nor ^{99m}Tc-EHDP are accumulated outside bone or kidney region if there is no tumor, trauma, or infectious disease (*7*). Plasma clearance

TABLE 1. PLASMA CLEARANCE HALF-TIMES FOR EXPONENTS I AND II

Normal and abnormal kidney function	Na-^{18}F		^{99m}Tc-EHDP	
	$T_{I\ 1/2}$	$T_{II\ 1/2}$	$T_{I\ 1/2}$	$T_{II\ 1/2}$
Normal (n = 22)	8.7 ± 1.1	105 ± 14	9.7 ± 1.6	130 ± 21
Reduced kidney function (n = 5)	9.1 ± 2.3	128 ± 14	8.8 ± 2.2	158 ± 13
Without kidney function (n = 4)	8.9 ± 1.8	230 ± 22	8.0 ± 1.8	320 ± 45
Without kidney function with secondary hyperparathyroidism (n = 4)	9.2 ± 2.2	86 ± 25	9.3 ± 1.9	98 ± 35

$\bar{x} \pm s$

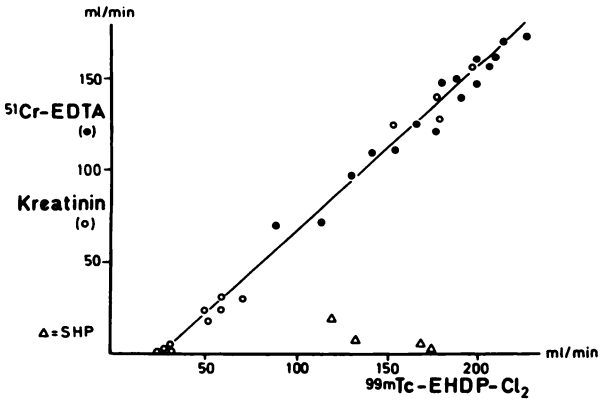

FIG. 1. Comparison of glomerular filtration rate and plasma clearance of ^{99m}Tc-EHDP. y = 0.98x − 30, r = 0.98.

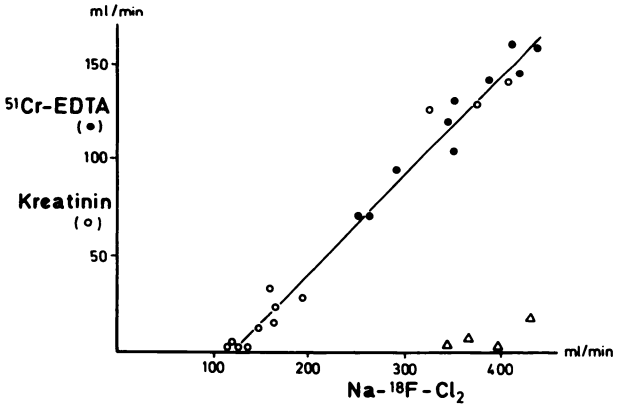

FIG. 2. Comparison of glomerular filtration rate and plasma clearance of ^{18}F. y = 0.47x − 110, r = 0.97.

represents both renal and extrarenal (for practical purposes equal to bone) clearance. This plasma clearance was calculated by the slope/intercept method. There is a significant correlation between glomerular filtration rate and both ^{18}F and ^{99m}Tc clearance (Figs. 1 and 2). In patients without any bone disease, the extrarenal clearance of ^{99m}Tc-EHDP is about 30 ml/min and up to 170 ml/min in patients with renal osteopathy. The corresponding values for ^{18}F are 110 ml/min and 430 ml/min, respectively.

In summary, kinetic studies with labeled compounds should not be done without prior examination of the chemical form(s) of the administered radioisotope. Our results indicate that the first exponent of the biexponential plasma clearance of bone-seeking radioisotopes represents not bone uptake or renal clearance but mixing in the distribution volume. This will be different for different radioisotopes; it is 54 liters/1.73 m^2 body surface using ^{18}F and twice as much as the ^{99m}Tc-EHDP volume ($y = 0.44x$, $p < 0.01$) (*3*).

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THE AUTHORS' REPLY

We appreciate the interest shown in our study by Wootton and Reeve, and Creutzig. It is an established fact that polyphosphate kits contain many molecules of different chain lengths and that the proportion of any one chain length may vary from batch to batch. We have used polyphosphate kits from two different sources (New England Nuclear and Diagnostic Isotopes) in three separate studies (*1,8,9*). We have carefully avoided introducing oxidizing agents in $^{99m}TcO_4$ solutions before and after adding $^{99m}TcO_4$ to the polyphosphate mixing vials. In three separate studies using different batches of polyphosphate, almost identical kinetic data were obtained indicating that there was no significant variation in the proportions of polyphosphate chain lengths from batch to batch. The salivary glands and stomach were not visualized and only rarely was the thyroid faintly visualized, suggesting that there was no significant in vivo breakdown of the radiopharmaceutical. Only in three instances was there any suggestion of either in vivo breakdown or poor in vitro labeling with diphosphonate (*8*).

In order to avoid the effect of equilibration or mixing on the shape of the blood disappearance curves, we obtained the first blood sample after 10 min. We do not feel that Exponent I is influenced by mixing of the radiopharmaceutical with the blood. In our recent study, we have excluded patients with bone lesions (*10*). In this study, it was found that the blood disappearance curve was, in fact, a composite of three exponentials as suggested by Wootton and Reeve. The clearance half-time of the first rapid component was calculated to be less than 5 min. It should be noted that this component had disappeared before the first 10-min blood sample was drawn in our original studies. Analyses based on the blood disappearance curve indicate that the first two exponents are representative of bone uptake primarily and, to a lesser degree, extraosseous tissue distribution. The third component is thought to represent renal excretion. This analysis is based on the assumption that, after uptake, there is no clearance of the radiopharmaceutical from the bone. This assump-