it to the authors' particular problem (the determination of the reciprocal mean transit time) and experimental conditions. In addition to its simplicity, this method has the advantages of being independent of the particular recording system used and of being readily adaptable to computerized measuring systems.

Using the authors' symbols, let ρ_{i-1} and ρ_i represent the detection efficiencies for the areas of interest "a" (right atrium) and "v" (right ventricle). At time t_m (the time corresponding to the maximum of the activity curve based on "v"), the experimental counting rates $n_{i-1}(t)$ and $n_i(t)$ have the values H_{i-1} and H_i, respectively, such that:

$$H_{i-1} = n_{i-1}(t_m) = \rho_{i-1}C_{i-1}(t_m),$$

$$H_i = n_i(t_m) = \rho_i C_i(t_m),$$

where C_{i-1} and C_i are the right atrial and right ventricular concentrations. Since at this particular instant the tracer concentrations in the two chambers are equal, we have

$$\frac{H_{i-1}}{H_i} = \frac{\rho_{i-1}}{\rho_i}, \qquad (1)$$

a relation that facilitates normalization of the activity curves. In effect, we have

$$\frac{F}{V_i} = \frac{\rho_i C_i(t_m)}{\rho_i \int_0^{t_m} C_{i-1}(t)dt - \rho_i \int_0^{t_m} C_i(t)dt}$$

$$= \frac{H_i}{\rho_i \int_0^{t_m} C_{i-1}(t)dt - \int_0^{t_m} n_i(t)dt}.$$

Normalization consists in replacing ρ_i by ρ_{i-1} in the first integral of the denominator. Now, using Eq. 1, we obtain

$$\frac{F}{V_i} = \frac{H_i}{\frac{H_i}{H_{i-1}}\int_0^{t_m} n_{i-1}(t)dt - \int_0^{t_m} n_i(t)dt}.$$

We generally simplify this expression by equating the integrals to the areas S_{i-1} and S_i beneath the activity curves n_{i-1} and n_i for the interval $(0, t_m)$. Then, we have

$$\frac{F}{V_i} = \frac{H_i}{\left(\frac{H_i}{H_{i-1}}\right)S_{i-1} - S_i},$$

$$= \frac{1}{\left(\frac{S_{i-1}}{H_{i-1}}\right) - \left(\frac{S_i}{H_i}\right)}$$

which gives the following equation for the mean transit time of the right ventricle (chamber "i"):

$$T_r = \frac{S_{i-1}}{H_{i-1}} - \frac{S_i}{H_i}.$$

In practice, after having reviewed the recorded tape and defined the areas of interest ("a" and "v"), one has only to refer to the "odd" and "even" channels of the Dynacamera 2C data processor (these channels corresponding to the maximum of the ventricular activity curve) and to read both the contents of the channels (H_{i-1} and H_i) and the sum of the contents of the "odd" and "even" channels (S_{i-1} and S_i) between the channel corresponding to time zero and that defining the maximum.

Using more refined treatments, it is possible to investigate the maximum of the ventricular curve very precisely (parabolic adjustment) and, by analysis of the mathematical characteristics, to calculate the areas lying beneath the experimental curves.

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Reply

We agree with and have included a related method of normalization in our paper. We stated that "normalization is therefore easily accomplished by multiplying either curve by a constant to cause their intersection at the peak of the C_i curve." In the next sentence we explained our reasons for the more complex normalization scheme illustrated: "If the data processor does not have a multiplication capacity, this can be achieved by changing the size of the areas of interest chosen to generate the C_{i-1} and C_i curves."

We appreciate the suggested simplification to normalize time–activity dilution curves. While facilitating the dilution curve normalization, the suggested approach does not permit an easy solution for F/V over a variety of time intervals. Since the invariant solution of F/V over different time periods is a fundamental concept in the paper, we suggest the following expression, which incorporates the suggestions of Morin et al. and still permits solutions over varying time intervals:

$$F/V = \frac{n_i(t)}{\left(\frac{H_i}{H_{i-1}}\right)S_{i-1}(t) - S_i(t)},$$

where $n_i(t)$ is the value of the i-th curve at any time t, and $S_{i-1}(t)$ and $S_i(t)$ are the integrals of the respective curves over the interval (0, t).

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Effect of Tin-Induced Enzymes on Pertechnetate Distribution

The administration of Sn(II) salts or radiopharmaceutical agents containing Sn(II) can alter the in vivo distribution of ^{99m}Tc-pertechnetate administered subsequently, resulting in enhanced accumulation and retention of ^{99m}Tc in the choroid plexus (*1*) and red blood cells (*2,3*). Such effects persist for weeks after the initial administration of the tin-containing agents. Moreover, incubation of red blood cells in the presence of dilute tin-containing agents, fol-

lowed by incubation with pertechnetate, causes ^{99m}Tc to bind to the red blood cells even when no residual tin could be found in the red cells. In our own unpublished experiments, the efficiency of ^{99m}Tc binding to red cells increased with the time of exposure of the red cells to tin or ^{99m}Tc. We originally favored the hypothesis that Sn(II) entered the cells and awaited the entry of pertechnetate, which it subsequently reduced from its anionic (VII) state to the cationic (IV) state, in which form the technetium was then chelated by intracellular electronegative sites (*3*). However, a recent article in *Science* (*4*) has shown that tin is an unusually potent inducer of heme oxygenase in the kidney. Such induction was rapid and significant, and it occurred at levels of administered Sn(II) within an order of magnitude of the Sn(II) dose found in some radiopharmaceutical preparations and at substantially lower levels than that found in some diets. Thus, it seems reasonable to hypothesize that Sn(II) acts indirectly by altering redox mechanisms in the choroid plexus and red cells, resulting in a selective in situ capacity for reducing Tc(VII) to Tc(IV). Should this prove to be the case, it may be that the rate of Tc(VII) reduction (or reduction of similar metallic anions), as evidenced by regional fixation of selected radionuclides, may prove to be a sensitive measure of certain alterations in in situ redox systems. Practitioners of nuclear medicine should attempt to determine whether such Sn(II)-induced in situ redox changes, measured in vivo with radiopharmaceuticals, can offer new insights into pathophysiologic processes.

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Preparation of ^{99m}Tc-Labeled Red Blood Cells

The paper by Smith and Richards (*1*) deserves praise for its thoroughness in determining the conditions for ^{99m}Tc labeling of red blood cells (RBCs) with stannous citrate. We examined these parameters and found that 3–8 μg of stannous ion per 10 ml of whole blood is effective when stannous glucoheptonate is used to prepare ^{99m}Tc-labeled RBCs. Based on this observation, we have modified the stannous glucoheptonate method (*2*) to require 7% of the reported amount of stannous glucoheptonate (equivalent to 4 μg of stannous ion and 14 mg of sodium glucoheptonate), and we have eliminated the EDTA and one saline wash. In a further simplification of this method, we substituted a syringe apparatus (*3*) for the Unitag Bag serving as the tagging vessel. Labeling efficiencies in excess of 95% are obtained with canine and human RBCs. The time and number of centrifugations are comparable to the authors' method, and all the necessary components are commercially available in sterile pyrogen-free form.

We emphasize the lack of commercial availability of the authors' lyophilized stannous citrate kit, and the considerable effort, expertise, and equipment required to prepare these kits, compared to the readily available stannous glucoheptonate. These facts make it difficult to agree with the authors' statement that the stannous glucoheptonate method (either as published or as modified) is much more involved than the lyophilized stannous citrate method.

We note the remarkable splenic uptake of heat-damaged (HD) ^{99m}Tc-labeled RBCs reported in patients (90%). However, the specific method by which this figure was determined is not presented. Smith and Richards hypothesize that high splenic uptake is dependent on the injection of "small" volumes of HD radiolabeled RBCs, but the volumes injected are not reported. Working on the assumption that a 70-kg patient would receive 0.2 ml of HD ^{99m}Tc-RBCs, we determined the volume of packed RBCs to be 0.0029 ml per kilogram. This calculation was based on the authors' reported specific activity of greater than 15 mCi/ml RBCs (*4*) and assuming an injected dose of 3 mCi of HD ^{99m}Tc-RBCs. In order to examine their hypothesis, we injected seven rats with homologous HD ^{99m}Tc-RBCs with the following volumes of packed RBCs: 0.002 ml/kg (two rats); 0.02 ml/kg (two rats); 0.2 ml/kg (two rats); 2.0 ml/kg (one rat). The animals were killed 1 hr after intravenous injection and spleen and carcass radioactivity were measured. No correlation was observed between splenic uptake and volume of packed RBCs. For the seven rats, the splenic uptake was 49.1 ± 4.4% (mean ± s.d.) of the injected dose, which is similar to our earlier published results (*2*).

The authors do not explain the reason for the apparent increase in splenic uptakes from 66% in their previously published report (*4*) to the 90% figure in their recent article (*1*).

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Reply

As we would with any radiopharmaceutical, we welcomed the improvements by Gutkowski et al. on their stannous glucoheptonate RBC-labeling method. We recognize that, while all the components required for their method are commercially available, the system is not available as a unit kit. We had not expected that individual investigators would