TABLE 2. RESIDENCE TIME IN SOURCE ORGANS* (hr)

	Liver	Spleen	Red marrow	Heart	RBC	Residual
			Fe-52, Mn-52m			
MIRD†	0.22	0.037	8.7	0.18	0	2.8
FORSIM	0.31	0.12	7.1	0.32	1.4	2.8
FOR-EXC	0.30	0.12	7.0	0.31	1.3	2.7
FOR-APR	0.31	0.12	7.1	0.32	1.4	2.8
			Fe-55			
MIRD†	3400	2300	3300	2200	22,000	1400
FORSIM	3900	2500	4500	2000	20,000	1800
FOR-EXC	3200	2000	3700	1700	16,000	1500
FOR-APR	3400	2300	3300	2300	20,000	1400
			Fe-59			
MIRD†	87	78	150	110	1100	23
FORSIM	87	78	140	110	1100	20
FOR-EXC	85	76	140	110	1100	20
FOR-APR	87	78	150	110	1100	21

* See Ref. *1* for a description of the organs.

† Normal values from Table 4 of Ref. *1*.

Ref. (*1*). In order to see whether the SAAM-25 (*1*) or the FORSIM implementation of the model was at fault, the ratio of activity in several compartments after equilibrium is reached with a chronic input was calculated and compared with the ratio of residence times taken from Table 1. The reason for doing this is that the activity in a compartment from chronic intake at equilibrium is numerically equal to the integrated activity following a single intake (*5*).

Ratios considered are Compartments 5 to 6 for Fe-52 (equal to 2.9) and Compartments 1 to 2 for Fe-59 (equal to 0.66), as these will not be affected by the approximations. These values were calculated using the rate constants given in Table 3 of Ref. (*1*). A comparison of these values with those calculated with the SAAM-25 program (MIRD) and the FORSIM program from Table 1 indicates that it is the SAAM-25 program that is at fault.

The effect of the above-mentioned assumptions, and of the differences between the results calculated by SAAM-25 and FORSIM on dose, can be estimated by comparing the residence times in organs, as is done in Table 2. It can be seen that the differences in organ residence times, and hence organ doses, are significant only for Fe-52 and Fe-55. The largest difference for Fe-52 is for the residence time in the spleen, which in turn arises from the difference in the residence time for the RBC compartment (Table 1). The maximum difference for Fe-55 is less than 40%, which is probably less than the uncertainty resulting from individual variability in metabolism and organ size.

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Reply

In response to Johnson's and Dunford's letter regarding a comparison of their calculation of residence times in the iron model with those of the MIRD Committee, I would like to begin by welcoming this independent approach. A long-existing weakness of the use of the SAAM method of analysis has been the unavailability of competitive methods. The overall agreement obtained is, of course, also gratifying.

Some of the discrepancies noted are readily explained, others involve the philosophy of modeling.

In the first category is the absorbed dose to the RBC compartment from Fe-52 and Mn-52m. As was mentioned in the MIRD report (*1*) the delay time for iron in the marrow is 3 to 5 days. Because of this and the 8.2-hr half-life of Fe-52, no appreciable amount of Fe-52 reaches the circulating RBCs. Therefore, for Fe-52 the marrow should not be considered to be a well-mixed compartment, but should have a delay time, as is done for the RBCs. This delay however, did not seem to be important for Fe-55 and Fe-59. Although a simplification was implied but not explicitly stated in the MIRD report, rather than complicating the model we adopted the simple expedient of using a transfer rate of zero for the red marrow to RBC compartments when Fe-52 was con-

sidered. We note that the results shown in Johnson's and Dunford's Table 1 agree exactly with the MIRD value if the marrow and red blood cell (RBC) values are added, except for the slight difference when excretion is assumed. Putting activity into the RBC compartment also introduces changes in the residence times in organs, particularly in the spleen.

Some of the other points depend upon whether modeling is to be used to achieve an estimate of radiation dose or to simulate the physiological aspects of iron metabolism. For radiation-dose calculations, continuous infusion and single injections give the same results, but the amounts present at a given time in a particular compartment or organ are different. The use of the 120-day life for RBCs is a reasonable assumption for radiation dose calculations, but in reality there is an appreciable range from 100 to 135 days, as noted in the MIRD report. Even in an individual the spread in RBC lifetimes results in a progressive smearing out of the spectrum of the times at which iron is released from the RBCs and is reutilized. The difference between the assumptions made for the dose calculations and reality after 400 days could be significant. We realized that by continuing the 120-day recycling after 400 days, an answer would be obtained different from that obtained by assuming exponential decay thereafter, but we question whether such a refinement gives a more reliable estimate of the real absorbed dose. As Johnson and Dunford point out, by this time the effect of excretion will have become significant for Fe-55, and this is probably more important than the other suggested refinements of the calculation.

We feel that, by possibly erring on the high side in the dose estimates for the bone marrow, we are being conservative and that if these estimates are used for restricting the amount of activity administered to patients, the risk to the patients is minimized. Absolute accuracy is a desirable goal, but it is unrealistic in the presence of wide individual variations in the kinetics of iron metabolism. The model has been kept sufficiently simple to be used in the relatively small computers available in nuclear medicine laboratories while preserving at least the main features of iron metabolism that are significant in calculations of the absorbed dose.

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REFERENCE

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Re: Receptor Binding of F-18 Haloperidol and Spiroperidol

In a recent editorial Dr. Timothy Tewson (*1*) gave three possibilities for the inconsistencies in the distribution of H-3 haloperidol and F-18 haloperidol as described by Zanzonico et al. (*2*). These can be outlined briefly as: (a) artifacts from using a labile tritium-labeled compound; (b) the difference in distribution between ligands of high and low specific activity; and (c) flow-limited distribution. This analysis raises a number of important points.

Zanzonico et al. have used their F-18 distribution data (Table 1 of Ref. *2*) and the dose dependency indicating receptor binding (Fig. 2 of Ref. *2*) to suggest that F-18 haloperidol is superior to spiroperidol because the absolute concentrations are higher whereas the striatum-to-cerebellum ratio is similar (Table 1 of Ref. *2*). Creese et al. (*3*) however, have shown that for a great number of drugs there is a correlation between the pharmacologic effect of a drug and the receptor affinity determined in in vitro experiments using isolated tissue. This recent *Science* article showed that spiroperidol has a higher pharmacologic effect and a higher in vitro affinity constant relative to haloperidol. The use of an extreme example (domeridone) by Zanzonico et al. does not nullify the correlation of Creese et al. Since Zanzonico et al. have shown that H-3 haloperidol resists detritiation in in vitro assay systems, the determination by Creese et al. should be accurate. But the F-18 haloperidol distribution data (Table 1 of Ref. *2*) do not agree with the pharmacologic data. The key word in the Creese correlation is "pharmacologic." The average clinical dose for spiroperidol is 58 nmol/kg, and for haloperidol 152 nmol/kg (*3*). Zanzonico et al. used doses from 0.01 to 100 μg/kg (or 0.02 to 250 nmol/kg), the latter clearly in the range of the pharmacologic dose. Therefore, there should be a correlation between the pharmacologic effect and the affinity constant, and a correlation between the affinity constant and receptor occupancy (radioligand distribution) by the laws of mass action. Since receptor occupancy is related to pharmacologic action, then either Creese's correlation is incorrect or the F-18 haloperidol distribution data of Zanzonico et al. are incorrect. The fact that H-3 haoloperidol is rapidly metabolized is an important observation, but it may not be relevant to the argument that F-18 haloperidol as prepared by Zanzonico et al. gives the actual haloperidol distribution. Even if haloperidol did not release tritium, it may still not show receptor binding in vivo.

Nevertheless, proof of receptor binding based on the operational definition of biological or pharmacologic specificity is difficult, because of the effect that specific activity can have on the distribution. Krohn et al. (*4*) did indicate that ligands of high specific activity may not distinguish between different receptor concentrations, as Tewson stated. But Krohn's argument is based on the fact that at "low-receptor-occupancy . . . pharmacologically active ligands . . . will not distinguish receptor population from rate-constant effects. Receptor mapping will be accomplished only if the binding rate constant is pathologically invariant, a situation that should not be assumed without thorough testing in vivo (*4*)." This argument is not relevant to the present case, and cannot be used to explain the higher receptor binding of haloperidol relative to spiroperidol, as reported by Zanzonico. These results are also unrelated to the paper by Klotz, who is dealing with the analysis of multicomponent curves (*5,6*). Klotz discussed the difficulty in the proposed methods of analyzing in vitro binding data to provide (a) the number of components, (b) the respective affinities of each component for the radioligand, and (c) the biological relevancy of each component. He likewise was not commenting on the determination of the receptor concentration using radioligands of different specific activity. The more relevant discussion of the effect of specific activity has been put forth by us to explain attempts at in vivo determinations of receptor density (*4,8*). No in vivo data have been put forward as a determination of receptor density; rather receptor density has been determined by in vitro tests using isolated tissue. (Recently Mintun et al. have presented a model to calculate receptor concentration in the dopamine system (*9*).) We, in fact, have argued that these in vivo experiments attempting to prove agreement between in vitro and in vivo data actually achieved only apparent agreement because of the specific activity used. The coincidental "self-fulfilling prophecy" has been disproven for H-3 QNB. At various specific activities, various striatum-to-cerebellum ratios are obtained. Even the maximum value underestimates the relative muscarinic-receptor densities found in those two structures.

The final argument also attributed to Krohn et al. (*4*) does not seem to apply in the case of these agents in the brain. If they are measuring blood flow, the uptake values would be the same. Again