gadopentetate. We are writing to correct some misunderstandings about gadopentetate and to suggest an alternative explanation for this observation. The authors state that the whole-body retention of gadopentetate is 10% at 24 hr, and that because of this there must be significant translocation of gadolinium from DTPA into other body stores. The first statement does not strictly reflect the data, and the second is not correct.

With respect to the potential whole-body retention of gadopentetate, it should be noted that gadopentetate has a volume of distribution of 266 ± 66 ml/kg (mean ± s.d.), which is equal to that of extracellular water, and has a mean elimination half-life of 1.6 ± 0.13 hr in man. Twenty-four hours after intravenous injection, it is not detectable in plasma, and 91% ± 13% is recovered in the urine, with only 0.1% recovered in the feces (*2*). The urine value is not significantly different from 100% and suggests that the renal excretion of gadopentetate is essentially quantitative. [Mass balance studies are notoriously prone to collection losses, and a 90% total recovery is not uncommon. Less than 0.5% additional drug was recovered over an additional 2 days of collection, further suggesting that this was a quantitative recovery (Weinmann HJ, unpublished data).]

Concerning the possible translocation of gadolinium from DTPA into other body stores, animal studies have shown that the clearance of ^{153}Gd-DTPA is almost identical to that of ^{99m}Tc-DTPA (*3*). This demonstrates that no significant amount of gadolinium is released from the gadopentetate complex, although minute amounts may remain in the body (*4,5*). In summary, given the lack of release of gadolinium from the gadopentetate complex and the extremely efficient buffering of gadolinium by phosphate (*1*), it seems unlikely that free gadolinium can contribute to the reported interaction between ^{67}Ga and gadopentetate. Further, neither gadopentetate nor free gadolinium exhibit a measurable binding to transferrin under physiologic conditions (Weinmann HJ, unpublished data).

However, the commercial formulation of gadopentetate dimeglumine contains free DTPA, which can form very stable complexes with gallium. GaDTPA is known to deposit in the skeleton (*6*). Approximately 500 μg of free DTPA was administered to the patient described by Hattner and White, resulting in a plasma concentration of approximately 2 nmole/liter at the time of the administration of ^{67}Ga. Thus, it is likely that the interaction between ^{67}Ga and gadopentetate reported by Hattner and White was the result of complexation of gallium with free DTPA, and not to any inherent instability in the gadopentetate itself. All gadolinium-based MR contrast agents are formulated with additional free chelating ligand (*7–9*); the likelihood of interactions with such free chelates should be considered when organometallic complexes (such as gallium-citrate) are needed. From this theoretical interaction, it may be prudent to defer the administration of organometallic complexes until after the excess chelate contained in these MR contrast agents has cleared.

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REPLY: We appreciate very much the interest of Drs. Wiggins, Goldstein, and Weinmann in the ^{67}Ga stable GdDTPA antagonism which we believe that we have observed (*1*). We are happy that our publication produced exactly what we had hoped—a better explanation of the phenomenon.

As we stated, the physicochemical evidence supporting our theory of a carrier effect of gadolinium on gallium was weak, and Wiggins' et al. contention of an effect of free DTPA from the GdDTPA with subsequent GaDTPA skeletal localization is preferable.

Wiggins et al. strongly reject the concept that GdDTPA is anything other than an ECF/GFR agent, using evidence that however suggests the opposite. They state the volume of distribution of GdDTPA is 266 ml/kg and equal to extracellular water. ECF determined by inulin, thiosulfate, and thiocyanate is 156, 163, and 229 ml/kg, respectively—all lesser than GdDTPA, suggesting translocation of gadolinium to another compartment (*2*).

GdDTPA's elimination half-life of 1.6 hr is substantially longer than the 1.2 hr attributable to a GFR of 140 ml/min. This also suggests another compartment. To say that the 91% recovered is not significantly different from 100% belies the fact that 91% was observed, and recovery losses in supervised urine collections of 10% must be rare. "... no significant amount of gadolinium is released from the gadopentetate complex ...," is simply not supported by this data.

Finally, Wiggins et al. belief that gadolinium is not bound to transferrin under physiologic conditions is at odds with the gadolinium-transferrin stability constant of 8.90 logs observed by Zak and Aisen in physiologic bicarbonate concentrations (*3*).

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Nonuniformity in Myocardial Accumulation of Fluorine-18-Fluorodeoxyglucose in Normal Fasted Humans

TO THE EDITOR: A recent paper by Gropler et al. (*1*), reporting the heterogeneity of fluorodeoxyglucose (FDG) myocardial uptake in fasted humans, raises a number of issues concerning the physiologic pattern of regional glucose myocardial consumption and the methodology for evaluation of this variable by use of FDG and PET. The study of Dr. Gropler also prompted an editorial by Schwaiger and Hicks (*2*), who pointed out the need to perform FDG studies of myocardial metabolism under strictly defined and monitored conditions and suggested that more work is needed in this area before drawing conclusions.

We want to comment on the clinical implications of the heterogeneity of FDG uptake under "fasting" conditions and on Dr. Gropler's statement "It therefore appears essential to recognize that results of PET cardiac studies with FDG are likely to be definitive under those conditions in which the metabolic question of interest can be optimally answered with the patient studied in the postprandial state."

It seems to us that issues related to myocardial metabolism and their implications in the evaluation of this function with imaging techniques cannot be addressed unless the following requirements are met:

1. A definition of fasting or fed state based upon biochemical criteria (plasma concentration of glucose, free-fatty acid (FFA) and insulin) rather than on chronologic criteria (hours of fasting), unless chronologic criteria ensure that the subject is either in the fed state, i.e., following glucose load, or postabsorptive state, i.e., overnight fasting. Indeed the measurement of some plasma variables does not ensure that the tissue examined is in a steady-state. It has been shown that the relative proportion of oxygen uptake for carbohydrate oxydation versus FFA oxydation in the human heart decreases quite slowly from the postprandial to the fasting state, and that glucose oxidation in the heart is still high after fasting only few hours, i.e., an intermediate condition between the postprandial one and the overnight fasting (*3*). In addition, it has been shown that the insulin level appears to be a more important predictor of glucose metabolism than FFA in the glucose-loaded state (*4*) and that insulin action persists, beyond the disappearance of insulin from the plasma, in various organs (*5*) and in cultured cells (*6*), possibly due to intracellular multiphasic feed-back control mechanisms of enzymatic activities (*7*, *8*).
   In Dr. Gropler's study, all subjects were fasted for 5–8 hr only and insulin levels were not measured. Thus, the study was carried out under conditions that might not be representative of a fasting state, since the patient's status was not documented by biochemical records other than glucose and FFA-plasma concentrations. It seems unlikely that from these data conclusions can be drawn about the assessment of myocardial metabolism with FDG after overnight fasting.
   We have examined the uptake of FDG in four normal subjects twice within 24 hr, by administering FDG after 5 hr and after 16 hr of overnight fasting, respectively. Although no FDG uptake was observed after overnight fasting in any of the four subjects, a diffuse FDG uptake was observed in two subjects when the heart scan was performed 5 hr after the administration of FDG (unpublished data).
2. A complete cardiologic evaluation of the subject under examination, in order to rule out any possible heterogeneity in the FDG uptake due to previously undetected myocardial disease. It is known that in skeletal muscle oxygen consumption and heat production are directly related to the duration and degree of muscle tension (*9*); the free wall of the left ventricle has the greatest radius of curvature and, accordingly, the highest calculated wall tension. Any condition apt to cause an increase in the tension of the inferoposterior wall, such as mitral valve prolapse and intense physical training, could well determine the observed avidity of FDG after 5–8 hr fasting.
   In their paper, Gropler et al. do not state which procedure was followed to rule out the presence of myocardial diseases in his subjects, although he provides the clinical criteria on which the diagnosis of normality was based. Under these circumstances, the FDG uptake has been uniquely considered as an indication of a physiologic heterogeneity in glucose metabolic rate. Although this explanation is certainly plausible, other causes such as the presence of minimal myocardial pathology cannot be excluded.
   We have used PET and FDG to study 11 subjects without record of cardiovascular disease after overnight fasting for at least 16 hr before FDG administration, and found FDG uptake localized to the free wall in three subjects (unpublished data). A complete Doppler-echocardiographic study was performed and a mild mitral regurgitation with slight prolapse of the posterior leaflet was observed in the subjects with FDG uptake in the free wall.
3. Maintainance of rest conditions during the study in order to avoid artifacts due to changes in the workload. Dr. Gropler states that four of the subjects examined were removed from the scanner after the injection of the tracer. Since the heart responds quickly to a higher workload by incrementing glucose use, there is the possibility that, at least in these four subjects, an increase in cardiac work induced by physical activity during the 30 min off the tomograph induced some myocardial uptake of FDG. It appears from Table 3 of Dr. Gropler's paper that the rate pressure product was consistently higher following the glucose load study; however, Table 2 shows an important reduction in the measured myocardial blood flow following glucose loading, without concurrent changes in acetate kinetics. Could this be due to a lack of a steady-state during the studies?

Our results, obtained after 5 hr of fasting, are in keeping with the findings of inconsistent myocardial FDG uptake after 5–8 hr