REPLY: We are pleased to see so much recent interest in the use of F-DOPA in positron tomography as a tracer for DOPA decarboxylase activity and wish to thank Drs. Cumming, Gjedde and Reith for their interest, however critical, in our work and to apologize for instances in which our citations may have appeared to be either selective or biased. In response, we would like to address the issue which we feel is at the heart of this controversy: the fact that the presence of OMFD in the circulation and in the brain complicates the analysis of F-DOPA studies. One approach to dealing with this nuisance is to propose "physiologically reasonable assumptions" based on some elegant studies that these authors performed in the rat. Another is to actually measure independently the time course of OMFD in the primate brain and the circulation, as has now been attempted by several laboratories (*1–3*). If the results of these experiments differ with the assumptions mentioned above, then the experiments should certainly be scrutinized for "pitfalls in the PET measurements," but assumptions must also be very critically re-examined.

A third, perhaps more fruitful, approach is the use of fluoro-*m*-tyrosine as an alternative tracer which is not subject to *O*-methylation. We have found the results of preliminary studies in humans to be promising (*4*), as have Barrio et al. (*5*) in nonhuman primates. What is important to us is the evaluation of striatal dopaminergic function in health and disease in humans. We are encouraged, in fact, to note the general agreement of the results from several very different methods of analysis, as highlighted by Dhawan et al. (*3*). It is our hope that through the collegial collaboration of the various research groups interested in this problem, assays of dopaminergic function which are both clinically useful and biologically informative will emerge.

REFERENCES

1. Doudet DJ, McLellan CA, Carson R, et al. Distribution and kinetics of 3-*O*-methyl-6-[^{18}F]fluoro-L-DOPA in the rhesus monkey brain. *J Cereb Blood Flow Metab* 1991;11:726–734.
2. Wahl L, Chirakal C, Firnau G, Garnett ES, Nahmias C. The distribution and kinetics of [^{18}F]6-fluoro-3-*O*-methyl-L-dopa in the human brain. *J Cereb Blood Flow Metab* 1994;14:664–670.
3. Dhawan V, Ishikawa T, Patlak C, et al. Combined FDOPA and 3OMFD PET studies in Parkinson's disease. *J Nucl Med* 1996;37:209–216.
4. Nahmias C, Wahl L, Chirakal R, Firnau G, Garnett ES. A probe for intracerebral aromatic amino-acid decarboxylase activity: distribution and kinetics of [^{18}F]6-fluoro-L-*m*-tyrosine in the human brain. *Mov Disord* 1995;10:298–304.
5. Barrio JR, Huang SC, Yu DC, et al. Radiofluorinated L-*m*-tyrosines: new in-vivo probes for central dopamine biochemistry. *J Cereb Blood Flow Metab* 1996;16:667–678.

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REPLY: We read with interest the comments of Cummings and colleagues concerning our work on the kinetic modeling of [^{18}F]Fluorodopa (FDOPA) and the related work of Wahl and Nahmias (*1*). We will respond to the issues raised by these readers by addressing their three primary concerns in order.

Choice of Assay

In our articles, we suggested that PET determinations of striatal k_3^D (representing DOPA decarboxylase activity) currently lack sufficient precision for use in the study of Parkinson's disease. We did not imply that attempts to measure k_3^D in Parkinson's disease (PD) are *misguided* as the authors state. Rather, we believe that major improvements in the accuracy and precision of k_3^D (or other specific parameters of interest) are needed if they are to prove useful. Indeed, we found that simpler parameters such as K_i^{FD} and SOR can provide critical objective information for differential diagnosis and disease severity assessment. The authors of the above letter seem convinced that there is no information of biological interest inherent in K_i^{FD} or striatal occipital ratio (SOR). Nonetheless, they have not demonstrated the existence of novel information concerning the parkinsonian disease process that can be extracted using their parameters that is not already available with the simpler PET measurements. One wonders what advantage can be obtained by the application of such complex measures when simpler ones can be used to approach the important clinical problems of preclinical detection and longitudinal assessment of presynaptic nigrostriatal dysfunction. It is incumbent upon the authors to demonstrate the unique biological attributes of k_3^D which might justify its continued use in clinical investigation.

In this vein, the authors raise an artificial distinction between clinical diagnosticians and neuroscientists, implying that these two species of investigators can never overlap. Regardless of orientation, all researchers in this field share an interest in delineating the mechanisms of disease and search for pathological or neurochemical features that separate patients from normals. This is especially important in parkinsonism where an early and potentially brief preclinical period may be characterized by very subtle dopaminergic defects. One clearly wishes to identify PET parameters that can be sensitive to such small pathological abnormalities. Also, it is extremely important to validate these parameters in affected patients in order to demonstrate that they in fact reflect the disease process and do not merely exist in the compartmental model of the neuroscientist. This simple validation can be accomplished by assessing whether the estimated parameters correlate with independent objective measurements of a patient's clinical state. This step is particularly critical if the PET parameter is to be used to follow the native course of disease and to assess the utility of potential neuroprotective and surgical therapeutic strategies. Our studies revealed that once again simple PET measurements provided useful indices of disease severity which were not in any way inferior to k_3^D estimates obtained as they are with a requisite set of assumptions. It is surprising that these readers fail to mention our recent demonstration of a significant correlation between SOR and UPDRS motor ratings evident with a high sensitivity PET tomograph (*2*). While we do not wish to discount the utility of parameter estimation, it is incumbent upon the investigator to provide biological validation through correlations with specific aspects of the disease process. The search for such associations may be fruitful pursuit for all investigators in this field.

Choice of Model

While uncertainties exist concerning the pathogenesis of PD in humans, the essential histological and biochemical abnormalities underlying this disease are well appreciated. In addition, unlike animal models of parkinsonism (which may not strictly parallel the disease in humans), disease severity can be accurately assessed in living patients. Clinical signs of tremor, rigidity and akinesia with a clear positive response to levodopa define a likely diagnosis of this disorder. Additionally, UPDRS motor ratings provide a useful and reproducible measure of the extent of disease. The authors state that in a meeting in Belgrade in 1987, it was concluded that the information gained from MTGA (multiple-time graphical approach or Patlak Plot) is "useless" because DOPA normally derives not from circulation but from tissue where it is derived in situ. Firstly, neither we nor the authors have designed tracers that can specifically quantify the in situ production of DOPA in the human brain. In spite of this limitation, we found that far from being useless, FDOPA/PET studies analyzed with MTGA have routinely provided important information concerning the parkinsonian disease process in humans. Secondly, one can only wonder why these readers are so concerned by our statement that the "nomenclature was retained for comparison purposes." We do not have any problem with their nomenclature. The choice of q for the transport ratio is quite arbitrary and we could just as easily have selected another symbol. However, we chose to keep the same notation in order to make the comparison easier to appreciate. Thirdly, the

authors say that in order to reduce the number of parameters, the Montreal group selected Ve and q as constants based upon physiologically reasonable criteria. This approach is used by most modelers (including us) because of the limitations inherent in the estimation of multiple parameters with acceptable precision given the current state of the PET art. But once these assumptions and simplifications are made, one must also question how realistic these models are in comprehensively representing underlying physiochemical processes which can be extremely complex. Hav ing agreed to make such assumptions, the least we can do is not to fixate upon a single estimated parameter such as k_3^D.

Transport Ratio

The authors suggest that the blood brain transfer ratio can be determined accurately only in the absence of significant tracer metabolism as is the case with 3OMFD. Nonetheless, our results show that if the metabolic process is incorporated in the model, then there is no reason why the blood brain transfer ratio cannot be determined even with a longer study duration. The question is then which estimate of q is correct. The authors have claimed that "no estimate of q, other than the original one of 2.3, determined as an abscissa intercept, actually meets these requirements." However, it is interesting that in a recent article, these authors reanalyzed their rat kinetic data and estimated the parameters K_1^M and K_1^D to be 0.08 and 0.07, respectively, and go on to state "the value of q in humans may also be close to 1" (*3*). Why did the authors not mention their own article in this letter?

The authors also neglected to refer our work on FDOPA kinetics in the presence of entacapone, a peripheral COMT inhibitor. This material was presented at Brain PET 95 and appeared in the proceedings of that meeting (*4*) and subsequently was published in the *Journal of Cerebral Blood Flow and Metabolism* (*5*). In this study, we found that the use of a erroneously high q value (greater than 1.0) resulted in an incorrect finding regarding the pharmacological effect of entacapone, i.e., the spurious result that this agent reduces striatal DDC activity. It is known that entacapone primarily prolongs the peripheral circulation time of levodopa without any central effect on catechol O-methyl transferase (COMT) or DDC activity. Therefore, the claim by the authors that a use of q value from 0.5 to 3 had minimal effect on k_3 is not applicable to human studies when COMT inhibitors are administered. Moreover, our results are in complete agreement with those of other investigators which also suggest a q value of 1 (*1,6,7*).

How are these different estimates of q to be reconciled? We would like to speculate into a possible source of error in the estimation of the q value of 2.3 in the rat study (*8*). The value of q was obtained from the slope/intercept ratio of a plot of the function: $K_1^*/f^D = K_1^M R + K_1^D$ (Fig. 6, ref. 8). The linear regression is heavily weighted by the last two data points which were acquired toward the end of the experiment. At that time, the error in the HPLC metabolite data is expected to be maximal due to the small fraction of FDOPA present in the plasma. The slope of the line decreases significantly when these last two points are eliminated, yielding an estimate of q value closer to 1.

Partition Volume Ve

Our estimated mean value of Ve^D is lower in frontal cortex as compared to the striatum. The authors have provided several explanations as to why Ve can sometimes exceed 0.8 (binding of 3OMFD to DDC without being metabolized etc.). In our study we did not detect any penalty in the estimates of k_3^D by fitting K_1 and k_2 as independent parameters. This suggests that striatal Ve need not be fixed to other regional values such as that estimated for the frontal cortex. The authors suggest that our estimation of Ve may be artifactually elevated due to diffusion of LNAA from plasma into erythrocytes. However, in our study arterial blood samples were immediately placed in ice and centrifuged within a few minutes of the collection making this possibility unlikely. Moreover, such a diffusion artifact should equally affect both striatum and frontal cortex and does not explain the basic observation that Ve is larger for striatum than for frontal cortex.

Choice of Citations

Our articles focus on the technical issues of the determination and application of striatal DDC activity measurements obtained with FDOPA/PET. These manuscripts were not intended as review articles to document the historical origins of the Patlak plot or as summaries of all the earlier rodent studies. The work of Cummings and his colleagues has been acknowledged in reference 29 of our paper. In that reference the authors cite most of their previous animal studies. The readers of the *Journal of Nuclear Medicine* may refer to these publications should their interest dictate.

REFERENCES

1. Wahl L, Nahmias C. Modeling of fluorine-18-6-fluoro-L-DOPA in humans. *J Nucl Med* 1996;37:432–436.
2. Kazumata K, Dhawan V, Chaly T, et al. Comparative nigrostriatal dopaminergic imaging with [^{123}I]βCIT-FP/SPECT and [18F]FDOPA/PET [Abstract]. *J Nucl Med* 1996;37(Suppl):133P.
3. Cumming P, Kuwabara H, Gjedde A. A kinetic analysis of 6-[^{18}F]Fluoro-L-Dihydroxyphenylalanine metabolism in the rat. *J Neurochem* 1994;63:1675–1682.
4. Ishikawa T, Dhawan V, Patlak C, Chaly T, Eidelberg D. Fluorodopa positron emission tomography with an inhibitor of catechol-O-methyltransferase: effect of the plasma 3-O-methyldopa fraction on data analysis. In: Myers R, Cunningham V, Bailey D, Jones T, eds. *Quantification of brain function using PET*. San Diego, CA: Academic Press; 1996:232–236.
5. Ishikawa T, Dhawan V, Chaly T, et al. Fluorodopa positron emission tomography with an inhibitor of catechol-O-methyltransferase: effect of the plasma 3-O-methyldopa fraction on data analysis. *J Cereb Blood Flow Metab* 1996;16:854–863.
6. Doudet DJ, McLellan CA, Carson RE, et al. Distribution and kinetics of 3-O-Methyl-6-[^{18}F]Fluoro-L-DOPA (OMFD) in the rhesus monkey brain. *J Cereb Blood Flow Metabol* 1991;11:726–734.
7. Carson RE, Doudet DJ, McLellan CA, Adams HR, Aigner TG, Cohen RM. Combined modeling analysis of 6-[F-18]Fluoro-L-DOPA (FDOPA) and 3-O-Methyl-6-[F-18]Fluoro-L-DOPA (OMFD) in non-human primates. *J Nucl Med [Suppl]* 1992;33(5):945.
8. Reith J, Dyve S, Kuwabara H, Guttman M, et al. Blood-brain transfer and metabolism of 6-[^{18}F]fluoro-L-dopa in rat. *J Cereb Blood Flow Metabol* 1989;10:707–719.

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Nigrostriatal Dopaminergic Imaging with Iodine-123-βCIT-FP/SPECT and Fluorine-18-FDOPA/PET

TO THE EDITOR: We read with great interest the study by Ishikawa et al. on SPECT and PET imaging of the dopamine transporter (*1*). They examined 12 patients with Parkinson's disease (PD) and 15 healthy control subjects using both [^{123}I]βCIT-FP/SPECT and [^{18}F]FDOPA/PET. A highly significant correlation was found between the striatal-occipital ratios (SORs) obtained for both ligands. They also reported a significant correlation between the SORs obtained with either SPECT or PET and the severity of motor signs [i.e., the UPDRS score (Pearson correlation coefficients: 0.69 and 0.60, respectively)]. Based on these findings, the authors state that βCIT-FP/SPECT is a useful and simple noninvasive method in the quantification of dopaminergic defects.

Recently, we reported on the use of [^{123}I]FP-CIT ([^{123}I]βCIT-FP) SPECT in various stages of PD (*2*), but we failed to find a significant correlation between UPDRS ratings and SPECT measures. Therefore, we also examined 21 early and nonmedicated patients with PD using the same ligand (data not published). Since age and disease duration may confound the correlation between disease severity and SPECT measures, as has been suggested by others (*3*), we controlled for these variables in the later study.