

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

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REPLY: We read with interest the comments of Cummings and colleagues concerning our work on the kinetic modeling of [¹⁸F]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_1^{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_1^{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