

the reported acetylation of Lys¹⁹⁹ by aspirin (5). Distances measured between various amino acids and bound ligands to HSA and bovine serum albumin obtained from spectroscopic data from a variety of fluorescence and resonance energy-transfer studies (6) support the AFP-type configuration. Finally, proteolytic cleavage of HSA would produce two halves of the molecule that could reassociate in solution, thereby restoring the binding properties of the intact albumin (7). Thus this quaternary arrangement is in more

general agreement with the chemistry and molecular biology of HSA.

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REFERENCES AND NOTES

1. D. C. Carter *et al.*, *Science* **244**, 1195 (1989).
2. Current MIR phases are produced from ten heavy-

atom derivatives through the combination of 19 individual data sets to give a mean figure of merit (FOM) of 0.64 (excluding anomalous signal) and 0.70 (inclusive of anomalous signal) for 8813 reflections greater than 5 σ to 4.0 Å. Several cycles of solvent flattening yielded an FOM of 0.85 and an *R*-factor of 0.29.

3. A. J. Luft and F. L. Lorscheider, *Biochemistry* **22**, 5978 (1983).
4. U. Kragh-Hansen, *Pharmacol. Rev.* **33**, 17 (1981).
5. J. E. Walker, *FEBS Lett.* **66**, 173 (1976).
6. N. Hagag, E. R. Birnbaum, D. W. Darnall, *Biochemistry* **22**, 2420 (1983); C. F. Chignell, *Mol. Pharmacol.* **6**, 1 (1970).
7. T. Peters, Jr., *Adv. Protein Chem.* **37**, 161 (1985).

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Deprenyl and the Progression of Parkinson's Disease

In the report by James W. Tetrud and J. William Langston on "The effect of deprenyl (Selegiline) on the natural history of Parkinson's disease" (1), the authors conclude that deprenyl treatment retards the progression of Parkinson's disease. They say they arrive at this conclusion because they found that a group of placebo-treated patients required L-dopa treatment sooner than a group of deprenyl-treated subjects; however these investigators assessed the apparent severity of the illness while the patients in the deprenyl group were receiving deprenyl. Thus one group was receiving treatment with a monoamine oxidase inhibitor, which increases dopamine levels in the brain, while the other group was receiving no active treatment at the time of the assessment.

It seems quite probable that the deprenyl group would appear to have progressed less compared to the placebo group simply because they were receiving deprenyl and thus displaying fewer symptoms. The authors attempt to deal with this possible confounding factor by showing that at the time the deprenyl group required L-dopa for symptom control, they did not get worse when the deprenyl was discontinued. This, however, is not an adequate demonstration that deprenyl was not producing therapeutic benefits at earlier assessment points when the Parkinson's was less severe (that is, when the deprenyl group appeared to have an advantage over the placebo group).

In order for Tetrud and Langston to have correctly arrived at their conclusions, the subjects should have been withdrawn from deprenyl at each assessment point and the assessment carried out after deprenyl wash-out, so that Parkinson's status could have been assessed in an untreated state. Alternatively the placebo group could have been treated with deprenyl before each assessment so that the same level of monoamine oxidase inhibition could be achieved in each group.

In the absence of a comparable assessment of the two groups it is not justifiable to conclude that deprenyl retards the progression of Parkinson's disease, however attractive this possibility is from a theoretical standpoint.

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REFERENCES

1. J. W. Tetrud and J. W. Langston, *Science* **245**, 519 (1989).

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I read with interest the report of Tetrud and Langston (1) on the effect of deprenyl on the natural history of Parkinson's disease. The data clearly demonstrate an effect on the clinical status of treated patients. I take issue, however, with the authors' conclusion that deprenyl slows the progression of Parkinson's disease. The authors suggest several mechanisms for the observed effect, all of which imply a greater preservation of nigral neurons. This preservation needs to be more clearly demonstrated.

The end point of the study was the patients' requirement for L-dopa therapy. Deprenyl may forestall the need for L-dopa by means of its synaptic effect, without protecting nigral neurons. Deprenyl is a monoamine oxidase-B inhibitor, used in Europe for more than a decade as an adjunct in the treatment of Parkinson's disease. Patients taking deprenyl commonly require a downward adjustment of their L-dopa dose by 20 to 30%. It may be that deprenyl has a modest effect as *primary therapy* in early Parkinson's disease. Perhaps it acts to increase the synaptic persistence of endogenously released dopamine. If so, it might delay the requirement for supplemental L-

dopa by some months. (This is an issue that will also need to be addressed by the DATATOP study cited by the authors.)

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REFERENCES

1. J. W. Tetrud and J. W. Langston, *Science* **245**, 519 (1989).

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Response: Both Sudarsky and Friedhoff raise the important issue of whether or not a symptomatic effect of deprenyl, rather than a slowing of the disease process, could account for the results of our study. As pointed out by Sudarsky, since deprenyl is an inhibitor of monoamine oxidase, it might increase the synaptic persistence of endogenously released dopamine, thereby leading to some degree of symptomatic improvement. To assess this possibility, two steps were taken in our study. First, patients were carefully reevaluated 1 month after the study drug was started to see if they had improved compared to their baseline evaluation (this would have indicated a symptomatic effect). At this 1-month "wash-in" evaluation, no symptomatic improvement was observed. Even more important, when patients reached end point (that is, the need for L-dopa therapy), the study drug was stopped for an entire month ("wash-out"), after which they were carefully reevaluated. Had deprenyl been providing a symptomatic effect later in the course of treatment, one would have expected deterioration, and none was observed. While it could be argued that the wash-out period might have been too short, we are unaware of any antiparkinsonian drugs that provide an unremitting symptomatic effect for as long as 1 month after they are discontinued.

Friedhoff raises the interesting point that

deprenyl could have provided a symptomatic effect during the trial that was lost by the time patients reached end point. If this had been the case, symptomatic effects would not have been detected by the wash-out examination. The critical observation here is that these patients had gone almost a year longer than their placebo-treated counterparts before reaching a similar stage of parkinsonism on the basis of wash-out evaluation. Thus, regardless of whether or not deprenyl provided a symptomatic effect at some point during the study, these patients actually gained an extra year of functional time when they were assessed off medication. We believe this observation is most compatible with the suggestion that the

disease itself may have been slowed.

We would also like to note that the results of our study support the findings of Birkmayer and his colleagues (1), who observed that patients treated with deprenyl and levodopa showed a prolonged life expectancy when they were compared to patients treated with L-dopa alone. The results of our study are also similar to those of an interim report from a multi-institutional study of deprenyl and tocopherol (2).

In spite of the foregoing, we agree with both authors that, as stated in our report, while our results "support the hypothesis that deprenyl slows the progression of Parkinson's disease," they by no means constitute proof. Unfortunately, until we have

better techniques for biologically monitoring the actual process of nigral cell base degeneration in living humans, this question will be difficult to definitively answer.

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REFERENCES

1. W. Birkmayer et al., *J. Neural Transm.* **64**, 113 (1985).
2. Parkinson Study Group, *N. Engl. J. Med.* **321**, 1364 (1989).

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"Dr. Jenkins has a mind like a steel trap. Unfortunately, it's never caught anything."