

## Correspondence

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### Blood-CSF Barrier to *d*-Tubocurarine

*To the Editor:*—Using radioimmunoassay, Matteo *et al.*<sup>1</sup> found *d*-tubocurarine (*d*Tc) in the cerebrospinal fluid (CSF) of man after its intravenous injection. We wish to draw attention to our publication on this subject in 1973,<sup>2</sup> where the presence of *d*Tc in the CSF of patients receiving clinical doses was described. We observed that 15 min after intravenous injection of *d*Tc, 30 mg, CSF concentrations ranged from 0.05 to 0.33  $\mu$ g/ml, and that *d*Tc was still present in CSF 60 min later. We have also shown that gallamine, 2–3.8 mg/kg, given intravenously to man passes into CSF.<sup>3</sup> The above observations in man have also been confirmed in dogs given continuous intravenous infusions of the muscle relaxants. Samples of perfusate from the cerebral ventricles contained muscle relaxants. Finally, the central effects of small doses of *d*Tc injected into cerebral ventricles have been described by Haranath and Shyamalakumari.<sup>4</sup> We observed sleep as the predominant effect when *d*Tc, 500 ng, was injected into the lateral cerebral ventricles of dogs. We have suggested that this sleep-inducing property of *d*Tc is probably located in hippocampal region.<sup>5</sup> We observed sleep after injection of a small dose of *d*Tc, 20 ng, into the inferior horn of the lateral cerebral ventricle in the unanesthetized dog. All of the papers cited review the

state of the blood-CSF barrier to *d*Tc and indicate that the small amounts of *d*Tc that pass from blood into CSF after clinical administration do have pharmacologic actions on the central nervous system.

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*In reply:*—We agree with Dr. Haranath in his main premise that small quantities of *d*-tubocurarine do indeed penetrate the blood-CSF barrier. There are two areas of difference between us. One area is in the quantities of *d*Tc found in the CSF of man after intravenous injection of the drug. In our study, 15 min after a single intravenous injection of *d*Tc, 0.3 mg/kg, the CSF contained 3.5 ng/ml, and at one hour it had reached an average value of 15 ng/ml. Dr. Haranath reported values of .05–.33  $\mu$ g/ml of *d*Tc in the CSF of man 15 min after an intravenous injection of a comparable dose of *d*Tc. This is 15 to 100 times the amount we found. One possible explanation for this difference is the method of analysis. Dr. Haranath used a biological assay employing the frog rectus muscle for measurement of *d*Tc, while we measured *d*Tc directly by means of radioimmunoassay. The second area of difference is one of interpretation. Finding a relatively large amount of *d*Tc in the CSF of man and comparing it with levels of CSF *d*Tc that caused symptoms in dogs, Dr. Haranath suggests that sufficient quantities of *d*Tc may pass into the CNS of man to cause symptoms. Because of our finding of

less *d*Tc in the CSF of man and comparing it with CSF levels of *d*Tc necessary to cause CNS symptoms in cats, we suggested that the quantities of *d*Tc that pass into the CSF of man after an intravenous injection are insufficient to cause CNS symptoms. The crucial experiment of injecting *d*Tc into the CSF of man cannot, of course, be performed. In view of the millions of doses of *d*Tc that have been administered to man without any report of CNS sequelae, we still hold to our conclusion that “the quantities of *d*-tubocurarine we found in the cerebrospinal fluid are unlikely to produce any pharmacologic or adverse effects in man.”

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