thane[3] anesthesia. Note the similar slopes of the dose response curves. Similarly, curves A and D show the reduced doses of *d*Tc required during enflurane[2] as compared to halothane[4] anesthesia. However, the slopes of these curves are remarkably different, with the slope of enflurane (A) much steeper than the slope for halothane (D).

Stanski also notes the nonparallelism of these dose response curves and suggests that this new time-dependent sensitivity effect explains the previous experimental findings. The problem with this explanation is that it is also possible that the nonparallelism observed in the previous studies might explain their time-dependent sensitivity.

Thus, I am left with three questions, the first being most important. Were steady state concentrations of *d*Tc actually achieved? If not, are we observing the pharmacokinetic effects of different approximations to the steady state in the two groups? Or, are we observing the effects of similar increases in *d*Tc concentrations with different pharmacodynamics of *d*Tc during enflurane anesthesia? Neither of these explanations necessitate any speculation about a time-dependent increase in sensitivity.

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In reply:—To be certain that steady state *d*-tubocurarine (*d*Tc) plasma concentrations were present in our study, an analysis similar to that performed on the steady state paralysis data was undertaken, but not reported in the original publication. Linear regression of time *vs.* the *d*Tc plasma concentrations after achieving steady state was performed, and the 95 per cent confidence band of the slope of the regression

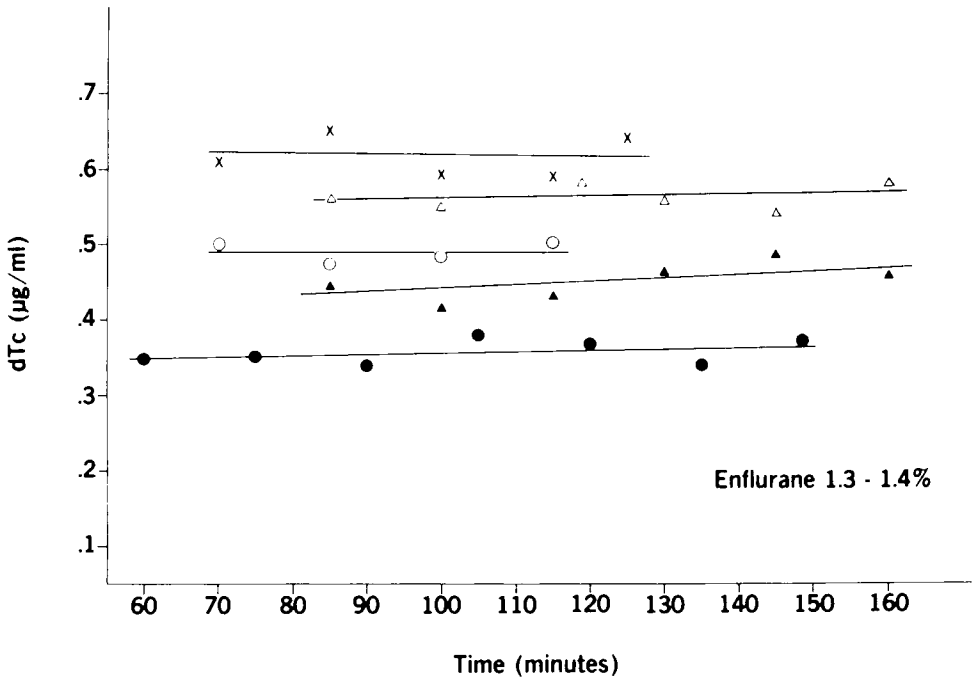

FIG. 1. The steady state *d*Tc plasma concentrations achieved is plotted against the time from the beginning of the first rapid infusion which was followed by a slower maintenance infusion. The solid line represents the linear regression line for the individual patients in the enflurane group.

line examined. For all of the 9 patients shown in figure 2 of the original publication, the slope of the steady state *d*Tc plasma concentration *vs.* time was close to zero, and the 95 per cent confidence band of the slope included zero. This indicates that the *d*Tc plasma concentrations were not changing significantly with time at steady state. Figure 1 presented here, demonstrates the data for the 5 patients receiving enflurane. The fact that all the *d*Tc plasma concentrations were not identical at steady state reflects the greater variability that occurs in measuring *d*Tc plasma concentrations *vs.* the degree of paralysis. The over-prediction of *d*Tc concentrations at 50 and 160 min, and underestimation thereafter in figure 1 of the original publication occurred because the nonlinear regression computer program attempted to choose model parameters that would result in minimal differences between the original and predicted drug concentrations, thus representing characterization of random error, not model bias. Statistically we are able to demonstrate that *d*Tc plasma concentrations were constant in our study at steady state and that the significant increase in paralysis over time with enflurane, but not halothane, must reflect a changing sensitivity to *d*Tc. Additionally we have unpublished data, using the cumulative dose-response technique, demonstrating that the sensitivity to *d*Tc increases with an increasing duration of enflurane anesthesia.

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