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In Reply:—We thank Dr. Rampil for bringing up the matter of experiment design. Although in some circumstances system identification using a single fixed-size step change input may indeed suffer from the limitations described, our approach is very close to optimal. In our study,¹ we applied one or more steps in and out of end-tidal anesthetic concentration of variable duration depending on the observed dynamics of the bispectral index (BIS; see fig. 3).

When there is no information available on applicable model structures, a pseudorandom binary sequence can be a useful test signal, but the choice of length and switching interval need to be guided by step-response data.² However, when information on applicable model structures is available, it can be used to design more optimal test signals.^{2,3}

With the anesthetic literature in mind, it is reasonable to assume a nonlinear relation between effect-site concentration and electroencephalographic (EEG) effect parameter and that there is a lag between end-tidal concentration and effect that is mainly determined by the blood-brain tissue partition coefficient. The nonlinear relation can be identified from step-response data because the effect-site concentration does not change in a stepwise fashion.

For the proposed model and the estimated population parameters, and taking into account the experimental conditions, we constructed *a posteriori* an optimal binary sequence by maximizing the determinant of the information matrix.³ The information gained by using the optimal input signal (which deviated only minimally from step inputs) instead of the optimal single-step signal is negligible in the light of interindividual variability and the fact that step durations depended on the occurrence of near steady states in measured bispectral index (BIS) values. It is of interest to note that for a nonlinear model of the

ventilatory controller consisting of a slow and a fast compartment, Bellville *et al.*⁴ found that step changes provided the most information on the values of the model parameters.

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Chemical Skinning Artifact Appears to Increase Sensitivity of Masseter Muscle to Halothane and Succinylcholine

To the Editor:—The distinguished laboratory at Lille, France, has reported undue sensitivity to halothane¹ and caffeine² in fragments of human masseter muscle that have been chemically skinned and exposed to these agents at temperatures less than 37°C. Reyford *et al.*¹ conclude that this may help to explain causes of masseter spasm in humans who receive halothane and succinylcholine; however, Melton *et al.*^{3,4} have contradictory evidence regarding masseter responses. Biopsies of human masseter muscle were taken during complex facial and skull-base surgery, and the dissected bundles were exposed to halothane or caffeine at 37°C using the North American malignant hyperthermia testing protocol.^{3,4} These bun-

dles were not sensitive to either agent; only two bundles (40- and 50-mg tension) had a contracture after 3% halothane. Furthermore, the mean caffeine concentration producing a 0.2-g increase was 5.5 mM; one caffeine bundle increased tension at 2 mM, but only to 35 mg. Although calcium release in skinned masseter muscle is different from that of skinned vastus when exposed to these drugs, this difference may not directly apply to responses *in vivo*. We suggest that chemical skinning, perhaps related to use of fragments, may be responsible for this apparent discrepancy. Although the bundle weight in our study was less than that in the usual biopsy, twitch amplitude was excellent. Therefore, our *in vitro* results^{3,4} may

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more accurately reflect *in vivo* responsiveness; *i.e.*, the individual muscle fiber basis for masseter spasm is not yet explained.

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In Reply.—We greatly appreciate the interest of Drs. Melton, Gronert, and Antognini in our study. We do not believe that their findings of no response to halothane in cut masseter muscle bundles is necessarily inconsistent with our own observation of an increased sensitivity to caffeine and halothane in skinned muscle fibers.¹⁻³ Skinning muscle fibers may permit greater access of caffeine and halothane to the exposed contractile apparatus, which would account for the fact that the ranges of caffeine and halothane threshold concentrations in our study were lower than those found using different skinning and storage methods and different muscles.^{1,2} However, the results from skinned masseter muscle were obtained using the same standardized testing methodology, laboratory, technicians, and equipment used to study the vastus muscle. In addition, the loss of low-molecular-weight intracellular proteins from skinned fibers such as ions, nucleotides, lipid derivatives, or ryanodine receptor-protein interactions may lead to different results from those seen with cut bundles.⁴

If we compare the results of Dr. Melton's results with our own, it appears that masseter and vastus sensitivities to halothane and caffeine may depend on modulators of sarcoplasmic reticulum function that are destroyed in skinned fiber (*e.g.*, dihydropyridine receptors from the T tubules) but not in cut muscle bundle preparations. It would have been surprising that all cut masseter muscle bundles contract in response to halothane *in vitro* because volatile anesthetics *in vivo* do not systematically exert sustained increased in masseter muscle tone. Different experimental conditions may reflect different levels of control of electrocontraction coupling, and may account for variations in observed response of masseter muscle *in vitro*. Clearly, additional studies are needed to clarify the role of endogenous modulators and environmental factors in the triggering of a masseter spasm episode.

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