perimental attempt was made to measure k_{organ}, the underlying process cannot be evaluated in their model. The estimate that the unknown elimination process accounts for 60% of the total *plasma* clearance of atracurium *in vivo*[1] remains valid, since it can be derived independently of the model (as demonstrated in 4)). However, this information has been available from earlier reports. We have indicated previously[2] that the faster degradation of atracurium *in vivo* than *in vitro* points to an additional inactivation process *in vivo*. From the data of Ward *et al.*[3] ($t_{1/2\ in\ vivo}$ = approx. 20 min; $k_{in\ vivo}$ = approx. 0.0347 min^{-1}) and of Merrett *et al.*[4] ($t_{1/2\ in\ vitro}$ = approx. 45 min; $k_{in\ vitro}$ = approx. 0.0154 min^{-1}), it can be estimated that the unknown mechanism accounts for 56% of the *in vivo* rate constant. Thus, the results of Fisher *et al.*[1] support the old data, but do not offer any new insights. Specifically, the pharmacokinetic model, though plausible, needs appropriate experimental verification.

VLADIMIR NIGROVIC, M.D.
Departments of Anesthesiology and Pharmacology
Medical College of Ohio
Toledo, Ohio 43699

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In reply:—Dr. Nigrovic agrees with our finding[1] that approximately 60% (63%, according to his calculations) of atracurium's elimination cannot be explained by degradation occurring *in vitro*. In addition, he contends that our results "support the old data but do not offer any new insights." In contrast, I believe that the "old data" bears little relevance to our study. For example, the study by Nigrovic *et al.*[2] demonstrated that inactivating enzymatic (*i.e.*, ester) hydrolysis markedly prolonged the duration of action of atracurium-induced neuromuscular blockade. However, these authors did not determine the relative contribution of Hofmann elimination and organ-based elimination to the rate of recovery. In addition, the study was conducted in rats, and Nigrovic *et al.* noted that "the rat is generally not considered to be the most suitable animal for the study of muscle relaxants."

I agree with Dr. Nigrovic that Ward *et al.*[3] reported an *in vivo* elimination half-life of approximately 20 min. However, I question the applicability of the data obtained by Merrett *et al.*[4] Although the latter investigators determined a "half-life" *in vitro*, they evaluated the neuromuscular effects of atracurium which had been incubated in plasma or buffer for varying periods of time (using a bioassay), rather than the rate of decline of plasma concentration of atracurium (using a biochemical assay, as in our study). I accept the findings of Merrett *et al.* regarding the comparisons of patients with normal or absent pseudocholinesterase activity. However, I question the advisability of comparing the data obtained by Merrett *et al.* to the data obtained in studies using biochemical assays.

Finally, Nigrovic advocates a single-compartment pharmacokinetic model for atracurium, claiming that our figure 4 suggests a monoexponential decline of atracurium plasma concentrations *in vivo*. However, because the data in figure 4 were obtained during and after an infusion, the ability to demonstrate a distribution phase is minimized. Fahey *et al.*,[5] in figure 3 of their paper, demonstrated that following administration by bolus, a two-compartment model is necessary to describe the pharmacokinetics of atracurium.

In summary, I believe that our study is the first demonstration in humans that Hofmann elimination and ester hydrolysis are not the sole major elimination pathways for atracurium.

DENNIS M. FISHER, M.D.
Assistant Professor of Anesthesia and Pediatrics
Department of Anesthesia
University of California
San Francisco, California 94143-0648

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