mimicking a pharmacodynamic change in drug sensitivity.

Could this equilibration delay explain Gronert's data? Is perfusion of the neuromuscular junction different in immobilized, atrophied muscle than in normal muscle? The author suggests that muscle blood flow was unchanged by immobilization, but bases that conclusion on earlier work under different anesthetic conditions. Rather than debate this issue from available data, further investigation would seem warranted. The cumulative dose-response technique used by Gronert is not optimal for this sort of study. In fact, when 0.1 mg/kg pancuronium is administered over 90 minutes, the cumulative dose is probably no longer the accurate approximation of a single dose that Donlon *et al.*[4] described when examining the cumulative dose response technique over a 15 minute interval. An infusion of drug to steady state, perhaps accelerated by a loading dose, would be a more satisfactory method of estimating neuromuscular junction sensitivity. At steady state, temporal dysequilibrium between plasma concentration and effect is no longer an issue, since both are constant. A difference in response between two hind limbs of the same animal would then represent a real difference in receptor number or sensitivity—a pharmacodynamic difference.

The clinical reports cited by the author,[5,6] involving patients with upper motor neuron lesions, are suggestive of altered pharmacodynamics. These patients may well have increased receptor number or sensitivity, as manifested by their hyperkalemic response to succinylcholine. The issue of muscle relaxant resistance deserves further investigation, under steady state conditions, in human subjects.

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In reply:—Dr. Holley states that changes in the rate constant for equilibration (k_{eo}) can produce a shift in the dose-response curve and misleadingly suggest relaxant resistance due to pharmacodynamic factors (drug concentration *vs.* biologic effect) rather than pharmacokinetic factors (drug concentration *vs.* time). He refers the reader to figure 7 from the Sheiner *et al.* study[1] which states that k_{eo} equals the ratio of blood flow to tissue partition coefficient, if drug effect is not rate-limited by either diffusion from the blood or a delay after receptor combination.

From the cited figure 7, assuming a constant partition coefficient, blood flow would have to decrease about 50 per cent to account for the relaxant resistance noted in disuse atrophy of the canine gastrocnemius[2] (background anesthetic pentobarbital nitrous oxide). Prior data indicate that blood flow to the canine gastrocnemius is unchanged by total paralysis with gallamine in normal[3,4] and denervated muscle,[4] although the trend is to decrease (background anesthetic halothane). Also, disuse atrophy tends to increase muscle blood flow in this same preparation[5] (background anesthetic halothane; no data regarding nondepolarizing relaxants). As Holley suggests, conditions in these studies are different enough that the data cannot be used to directly answer his criticism. He is of course correct that a study during steady state drug levels should settle the issue in both canine disuse atrophy and humans with relaxant resistance.

One should remember that resistance to nondepolarizing relaxants is estimated by the response of receptor sites activated by nerve terminals. A pharmacokinetic explanation would suggest decreased perfusion or increased tissue partition coefficient in my dog model because the responses of the normal muscle and the contralateral atrophied muscle were measured simultaneously in the intact dog.[2] Immobilization disuse atrophy results in enlargement of the muscle end-plate area and a modest increase in muscle membrane sensitivity to acetylcholine.[6] Thus, the more numerous receptor sites would bind more molecules of relaxant, necessitating a greater total

dose of relaxant to the muscle—presumably this might be an example of an increased "overall" tissue partition coefficient (a pharmacokinetic basis that is itself due to a change in pharmacodynamics). However, if increased blood levels during a steady state are needed for paralysis (pharmacodynamic basis), then the end-plate receptors must somehow be different as well as more numerous. This difference may be related in part to the interaction among the nerve terminals, the increased total number of innervated receptor sites and the relaxant molecules.

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Positive End-Expiratory Pressure (PEEP) and Renal Function

To the Editor:—We would like to comment on the recent review, "Respiratory Support and Renal Function," by Dr. Berry.[1] As indicated in the review, we previously had thought that the redistribution of flow from the cortical to the juxtamedullary nephrons might be an important contributory factor in initiating antidiuresis and antinatriuresis during ventilation with PEEP.[2] However, in a recent study[3] using the radioactive microsphere technique for the evaluation of intrarenal blood flow distribution,[4] we were unable to demonstrate any redistribution of renal blood flow during the ventilation with PEEP. The difficulties in reproducing and comparing results obtained by the inert gas washout method[5] with those obtained by the microsphere technique[4] have been summarized previously in detail.[6,7] The microsphere technique assesses glomerular perfusion, whereas the inert gas washout method assesses peritubular, postglomerular hemodynamic status which does not always reflect the intrarenal distribution of filtration. It is, therefore, unlikely that redistribution of renal blood flow plays an important role in the pathogenesis of the observed alterations in renal function during ventilation with PEEP.

In contrast to previous work,[8] we could also show that the fall in cardiac output ($\dot{Q}$) during PEEP was associated with a rise rather than a fall in transmural cardiac filling pressures. This confirms similar results of recent studies.[9,10] It is of interest to note that the blood transfusion of 25 ml/kg body weight during PEEP completely restored renal function despite the fact that $\dot{Q}$ had returned to only 70 per cent of its control value. This finding may be explained by the further increases in cardiac filling pressures following the transfusion which in turn caused the reflex suppression of low pressure volume receptors in the cardiac atria, baroreceptors in the aorta and carotid sinus, and the renal sympathetic nerves. These findings suggest that an adequate intravascular volume may be at least as important for maintaining normal renal function during ventilation with PEEP as a normal $\dot{Q}$ or perfusion pressure.

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