

20% and 30% burn compared with controls, as was the total body weight. In contrast, the mice with 50% TBSA burn had an increase in effective dose for d-tubocurarine associated with decreases in body weight and increases in oxygen consumption. All our studies, therefore, point to the importance of burn size and the need for the continued presence of a catabolic state (weight loss) in inducing changes at the neuromuscular junction. The importance of a catabolic process induced by inflammatory mediators in producing pharmacological alterations has been reconfirmed in another pathological state: sepsis. It was observed that weight loss induced by sepsis occurred concomitantly with a rightward shift of d-tubocurarine dose-response curve while malnutrition induced weight loss was without any neuromuscular changes.<sup>5</sup> Additionally, burn injury in humans results in an acute phase reactant (inflammatory) response including the release of  $\alpha_1$  acid glycoprotein which increases the binding of muscle relaxants.<sup>6,7</sup> A rodent is also capable of an acute phase reactant response.<sup>8</sup> In the rodent model studied by Marathe *et al.*, the presence of a weight loss or a catabolic process in their animals is not evident from their reports.<sup>1,9</sup> The absence of a catabolic or inflammatory process in these animals is, however, suggested by the absence of alterations in protein binding to atracurium in the rodent<sup>9</sup> and contrasts, therefore, with their clinical report.<sup>7</sup> All these point to the inadequacy of a 30% TBSA burn in a rodent to completely replicate the clinically observed neuromuscular changes.

We also wish to take exception to the statement many times in the text that a 30% BSA burn in the rat "exhibits the distinctive time course of resistance similar to that found in burned patients: normal response to NDMR for approximately 10 days, peak resistance at 40 days, and a decline in resistance at 60 days." The clinical report<sup>10</sup> by this group contradicts this statement. We quote from their clinical report "of those patients studied after 6 days post injury and who had burns less than 33% TBSA, only one showed less than 100% twitch depression. Their (*i.e.*, patients with burns < 33% BSA) time to onset and recovery to 50% twitch were not significantly different from control (table 1)."<sup>10</sup> The data of table 1<sup>10</sup> indicate no statistical difference in atracurium-induced maximal depression within 6–60 days postburn in humans who had suffered up to 33% TBSA burn. The data in table 1 are in opposition to aforementioned statement that patients with 30% TBSA burn have peak resistance at 40 days. The importance of critical burn size (usually exceeding 30% TBSA burn) in inducing neuromuscular changes has been observed in numerous studies.<sup>11</sup> With that clinical observation, one therefore wonders why a model with only a 30% TBSA burn was studied since a 30% TBSA clinically does not show resistance to NDMR.

Multiple factors may play a role in the altered sensitivity of NDMR, and may include changes in AChR number, acetylcholinesterase activity, pharmacokinetics, protein binding, and affinity of the NDMR to the AChR. In the rat model with 30% BSA burn, as suggested by Marathe *et al.*, the modest resistance to NDMR observed may well be due to the latter. There is in fact indirect evidence that there is an altered affinity between d-tubocurarine and AChR following burns evidenced by the significantly flatter and smaller slope of the dose-response curves in burned animals compared with controls.<sup>3</sup> The re-

sistance observed with larger burns may involve all of the different etiological factors enumerated above including AChR number.

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*In Reply:*—We would like to thank Drs. Martyn and Tomera for their comments regarding our paper.<sup>1</sup> Our findings of no increase in the density of AChR following thermal injury do contradict their findings and, as we suggested in the paper, the different findings may be related to the differences in the animal model.

The principal point of issue is the 30% TBSA rat burn model used in our study. We chose a 30% body surface area burn because it provides us a "clean burn" not complicated with factors such as sepsis, weight loss, and inactivity. Thus we have studied the role of thermal injury itself in the resistance developed to NDMR in the thermally injured

patients. Neuromuscular disorders such as denervation injury, and upper motor neuron injury which lead to muscle wasting and inactivity, are well known to produce an increase in the AChR density.<sup>2</sup> As pointed out by Drs. Martyn and Tomera, weight loss induced by sepsis also resulted in a rightward shift of dose-response curve of d-tubocurarine. In the rat burn model studied by Kim *et al.*,<sup>3</sup> the effect of burn injury on the neuromuscular junction is complicated by several other variables such as weight loss and sepsis, and therefore the increase in the AChR density cannot be attributed to the thermal injury per se. Drs. Martyn and Tomera allude to the likelihood that the changes in AChR density they have observed are actually due to sepsis rather than thermal injury.

We believe that our animal model adequately replicates the response to NDMRs observed in thermally injured patients. The thermally injured rat with a 30% body surface burn does become resistant to atracurium unlike the study of Tomera *et al.*<sup>4</sup> where mice with 30–40% TBSA burn showed no resistance to d-tubocurarine.

The time course of resistance to atracurium in our thermally injured rats is similar to that observed in patients who develop resistance. We see no reason why Drs. Martyn and Tomera take exception to this statement. In both rats and humans that develop resistance to NDMR following injury, a similar (and unusual) time course is followed. Also, the mechanism in both patients and rats is pharmacodynamic as shown by an increase in the Cp50 of atracurium (plasma concentration required to cause 50% twitch depression at steady state).<sup>5,6</sup>

Since we have replicated the characteristics of thermally injured patients in rats with this 30% TBSA burn, uncomplicated by sepsis, we regard it as an appropriate model of the uncomplicated injury. In our studies of postsynaptic factors that might contribute to resistance, we studied tissue from rats with verified resistance. We saw no correlation in the AChR density in the gastrocnemius muscle and the resistance to atracurium as given by the maximal twitch depression after a single iv dose of atracurium. In our rat burn model, therefore, resistance to atracurium is not explained by an increase in the density of AChR. We are not certain why Drs. Martyn and Tomera think that the resistance in our rats was "modest." In our opinion the resistance shown by our rats was adequate for investigation of its mechanism.

We agree that our rat burn model does not replicate all the clinically observed pathophysiological changes. More importantly, it allows us to isolate the effect of thermal injury alone. There are some differences between the rat model and patients (*e.g.*, protein binding results). We have shown that both humans and rats develop resistance through a pharmacodynamic mechanism, and have examined the rat in an effort to elucidate aspects of the mechanism.

Our rat burn model, is similar to thermally injured patients with regards to NDMR resistance. As suggested by Drs. Martyn and Tomera, multiple factors may play a role in the altered sensitivity to NDMR. However, an increase in the AChR density is not one of them in uncomplicated thermal injury. Along with the AChR density, we have also ruled out the possibility of a decrease in the activity of acetylcholinesterase and an increase in the density of voltage-sensitive sodium

channels as possible mechanisms at a 30% burn. We do not rule out the possibility of an increase in the AChR density at a larger body burn, where muscle inactivity, weight loss, and sepsis can all complicate the response to NDMR. Presynaptic mechanisms also have not been addressed.

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