in vitro (heat, oxidative stress, and nitrogen species as triggers) or *in vivo* (using ^{31}P MRI)[6] need to be developed."

Regarding item 2: Again, the statement about possible indicators for individuals at risk for nonanesthetic MH was taken from the original context. It is very clear from the whole paragraph and the statements made immediately preceding the statement in question that we are stating our opinion—in accordance with the purpose of an editorial—and drawing our own conclusions from the cases reported by Groom *et al.*[2] "Alternatively only one RyR1 mutation (*i.e.*, in only 16% of the tetrameric RyR1 complexes, all four RyR1 subunits are impaired) might be sufficient if combined with a second mutation that is associated with a congenital myopathy. Therefore MH susceptible individuals presenting with ophthalmoplegia and muscle hypotonia, hypertrophy, or spasms will be at risk for nonanesthetic MH." Therefore, it is evident that we are not citing a large-scale human study but rather identifying ophthalmoplegia, muscle hypotonia, hypertrophy, and spasms as possible indicators of an undetected, underlying myopathy.

Regarding item 3: Nowhere in the text do we assign any blame to the parents. We state, "As children have less developed compensation mechanisms for increased body heat and a higher incidence of MH events than adults (1:15,000 *vs.* 1:100,000),[7] their parents should be particularly careful." Obviously, the parents must be more careful with any temperature elevation in children at risk than are parents of unaffected children. *A personal or family history of heat intolerance* should cause avoidance of hot environments, exhausting physical exertion, high fever, and all drugs that increase heat production and reduce heat dissipation. During an episode, cooling should be started immediately until dantrolene can be infused, as in a typical MH crisis. In the meantime, the recommendations given in our editorial have been supported by authorities in the field.[8,9] To avoid secondary organ damage, treatment in an intensive care unit is mandatory. The protection offered by various drugs against oxidative muscle damage should be tested as second-line therapy in MH animals, such as the naturally occurring MH-susceptible swine and transgenic mouse. The induction of MH by heat and the protection of MH by hypothermia have been described for these animals.[10,11]

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Perioperative Role of Methadone in Adolescent Patients

To the Editor:

We congratulate Sharma *et al.* for their study of pharmacokinetics of methadone and its effect on postoperative pain scores and opioid consumption.[1]

We had a few questions and comments regarding their study. This study is primarily designed to evaluate the pharmacokinetics of methadone, and not its opioid-sparing effects. Lack of standardization of the intraoperative management and postoperative pain management may lead to multiple recognized and unrecognized confounding factors being unadjusted between the treatment groups. These confounding factors may be responsible for a lack of difference in the amount of postoperative opioid consumption between the controls and the three-methadone groups.[2]

A randomized prospective pediatric study[3] and another study on posterior spinal fusion surgery patients[4] found a beneficial effect of methadone administration on postoperative opioid consumption and pain scores. This observational study may not have the power and design to look at the clinical effects of methadone in the postoperative period.

The small sample size could lead to a Type II error, *i.e.*, acceptance of the null hypothesis when there exists a differ-

ence because of a lack of power to detect it. The authors have not mentioned a power analysis in the statistical methods. Based on the numbers presented in the study, *i.e.*, a mean postoperative opioid use of 275 mg in the control group with a SD of 75 mg, we estimate that a sample size of 22 patients would be needed in each of the four groups to have a power of 80% (with a $\alpha = 0.05$) to show a decrease in opioid use of 75 mg between the groups with the largest and the smallest mean postoperative opioid consumption.

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In Reply:

We are glad to learn of the interest of Drs. Gurnaney, Kraemer, and Ganesh in the pediatric use of methadone,[1] a clinically effective and utilitarian perioperative opioid.[2] Gurnaney *et al.* write that they "had a few questions and comments." We find no questions in their letter, but can explicate their comments.

Gurnaney *et al.* comment that the study was "primarily designed to evaluate the pharmacokinetics of methadone and not its opioid sparing effects." They are correct. As was indeed stated in the manuscript, "The primary purpose was to determine the pharmacokinetics of intravenous methadone in children. A secondary purpose was to assess postoperative opioid consumption in pediatric surgical patients who receive methadone."[1] Gurnaney *et al.* also comment that "the study may not have the power and design to look at the clinical effects of methadone in the postoperative period." As Gurnaney *et al.* surely know, studies are not powered for secondary outcomes. Indeed, the manuscript explicitly stated "The investigation was not powered specifically to evaluate opioid consumption, which was a secondary outcome" and it was reiterated in the Discussion that the study was not designed primarily to assess opioid-sparing effects of methadone.[1]

Gurnaney *et al.* suggest that "lack of standardization of the intraoperative and postoperative pain management may lead to multiple recognized and unrecognized confounding factors being unadjusted between the treatment groups, (which) may be responsible for a lack of difference in the amount of postoperative opioid consumption between the controls and the three-methadone groups." Unfortunately, they did not identify these multiple recognized and unrecognized confounding factors. Certainly it was not the amount of opioid (either nonmethadone or total) administered intraoperatively, which was not statistically different between the methadone treatment groups.[1]

Gurnaney *et al.* comment that other studies have shown a postoperative opioid-sparing effect of methadone. Others have. We reviewed this previously,[2] and also discussed it quite extensively in the article.[1] Potential reasons for a difference between our and previous investigations were also well articulated in the article, including differences in surgical procedures, associated severity of pain, use of additional intraoperative opioids, the deliberately low methadone dose, and the dose of methadone relative to the total intraoperative opioid dose.[1] Gurnaney *et al.* suggest that the reason was "confounding factors" or sample sizes. Perhaps.

Gurnaney *et al.* state that one potential approach to achieving statistically significant differences in opioid consumption by scoliosis patients treated with 0.1–0.3 mg/kg methadone would be to increase sample sizes. Their sample size arithmetic is correct. However, as clearly stated in the manuscript, higher methadone doses are likely needed for scoliosis surgery, and other much more painful procedures. That seems a better approach to achieving statistical significance while delivering better care to our patients.

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