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Response

To the Editor: We appreciate the interest of Dr. Cunnane and Dr. Likhodii in our recent paper (1). Their letter, which raises a number of excellent points, allows us to make some additional comments about the ketogenic diet and correct one error in our paper.

The first concern by Dr. Cunnane and Dr. Likhodii is that the paper is seriously flawed because of the high fat to protein + carbohydrate ratio of 8.6:1 used in our study. While it is true that this ratio is higher than that typically used in children, we have encountered situations where over-zealous parents have approached this ratio. Moreover, our goal was not to provide an identical diet given to children but rather study the effects of ketosis on cognitive abilities in growing rats. While Dr. Cunnane and Dr. Likhodii would have preferred another diet, our use of this particular diet was not flawed. The diet has been previously used by other investigators (2–5) and, as noted in our paper, the animals tolerated the diet well and gained weight, albeit at a significantly lower rate than that seen in the control animals.

Nevertheless, as we discussed in the paper, we do share the concerns of Dr. Cunnane and Dr. Likhodii about weight gain in relationship to cognitive function. In recent work (6), we have found that caloric restriction during the 1st weeks of life leads to mild cognitive impairment. Interestingly, caloric restriction has been shown to reduce seizure susceptibility (3,5,7). We agree that future studies evaluating the ketogenic diet should use a lower ratio of fat to carbohydrate + protein and avoid the growth failure seen in our animals. The suggestions regarding future study design by Dr. Cunnane and Dr. Likhodii are excellent.

As noted by Dr. Cunnane and Dr. Likhodii, the phenomenon whereby the brain is protected during food deprivation was observed in this study. Nevertheless, brain size did differ among groups. It is not clear why they feel our comments in the text and abstract in regards to brain size are misleading.

Dr. Cunnane and Dr. Likhodii note that the cognitive impairment seen in rats and humans used lower fat concentrations than in our study. We agree and it was for this reason that we have concerns about the cognitive effects of even higher fat concentrations. Dr. Cunnane and Dr. Likhodii will get little argument from us that in some metabolic disorders therapy with the ketogenic diet can be quite beneficial.

As we discussed in the paper, individuals with epilepsy treated successfully with the ketogenic diet with a marked reduction in seizure frequency or intensity often demonstrate dramatic improvements in cognitive function. In our study we found that significantly fewer rats on the ketogenic diet experienced spontaneous seizures than rats on the control diet (Chi-square test = 3.91, $p < 0.05$). We incorrectly stated in the paper that the results were not statistically significant and apologize for this error. The reduction in seizure susceptibility supports prior work from our laboratory that shows a dissociation between the effects of the ketogenic diet on cognition and seizure susceptibility (2).

Finally, we agree that determining the cognitive effects of the ketogenic diet requires a rigorous evidence-based approach. Regrettably, this should have been done in children years ago.

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To the Editor: We read with great interest the recent article by Timmons *et al.* (1) on stress/inflammatory responses to exercise in boys and men. While we applaud their efforts to directly compare subjects from these two age groups to research maturational mechanisms of immune responses, one aspect of their data caused us some concern. The authors report that the exercise bout had no effect on circulating interleukin-6 (IL-6) in the boys. This was troubling because of the many cytokines previously reported to be altered acutely by exercise, IL-6 has proved to be the most reproducibly elevated (2). Moreover, we