

the realm of respiratory physiology. He instead mounts an *ad hominem* attack on Davy for his youth and recklessness. If youth truly deserves our censure in connection with scientific discovery, then Haridas must broaden his denouncement. With respect to self-experimentation, undertaken, as Haridas observes, at considerable peril, Davy would doubtless hold himself guilty as charged; to Davy, science was exploration, and incidental threats to his personal safety were of little consequence. In this regard, we may perhaps compare Davy's experiments to those of August Bier and August Hildebrandt in spinal anesthesia,<sup>2</sup> or of William Halstead in local anesthesia.<sup>3</sup> Halstead, as a consequence of his studies, struggled with and ultimately overcame cocaine addiction,<sup>4</sup> and Haridas, in turn, invites us to speculate whether Davy may have been addicted to nitrous oxide. Although Davy's pattern of daily nitrous oxide use during his time at the Bristol Pneumatic Institute suggests, at a minimum, a maladaptive pattern of behavior, there is no indication either from Davy's exhaustive notes, or from the many accounts of friends and colleagues, that Davy would have met modern criteria for substance dependence. There is, furthermore, no record of Davy having consumed nitrous oxide following his tenure in Bristol. Inexplicably, Haridas equates Davy's work with nitrous oxide to Charles Thomas Jackson's claims of priority with ether anesthesia, before abruptly conceding that Jackson never published experimental results pertaining to the anesthetic properties of ether.<sup>5</sup>

Haridas' critique ultimately appears to crystallize into one of pragmatism: Davy, he asserts, was a failure because he did not put nitrous oxide into practical use as an anesthetic. Haridas asks us to believe that Davy's body of work at the Pneumatic Institute has no intrinsic value: No matter that Davy conducted and published an unprecedented series of experiments on nitrous oxide and other inhaled gases, he did not "follow up." Haridas will have us stop there, but many, ourselves included, will continue to wonder why not only Davy, but also the innumerable readers of his work, did not follow up, or why not even Horace Wells' failed attempt to demonstrate nitrous oxide anesthesia did not provoke greater interest in the technique. Science does not exist in a vacuum, nor do its results always succeed, in the near term, on their merits; rather it is, and always has been, vulnerable to cultural context and a socially determined sense of possibility. Haridas chooses to evaluate Davy's work on strictly utilitarian grounds and concludes that it was a failure on this basis, in that it did not lead directly to the development of nitrous oxide anesthesia. We instead see in Davy's experiments the first systematic approach to the evaluation of several gases of immense practical significance to anesthesiology; it is this approach which, to our minds, defines the first practice of anesthesiology as a science, whereby we call Davy the first anesthesiologist.

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## Importance of Body Temperature and Clinical Data in Behavioral and Anesthesia Studies

*To the Editor:*

We have read with great interest the recent article "Anesthetic Ketamine Impairs Rats' Recall of Previous Information: The Nitric Oxide Synthase *N*-nitro-L-arginine Methyl ester Antagonizes this Ketamine-induced Recognition Memory Deficit,"<sup>1</sup> and we would like to address some comments. This study stresses that nitric oxide metabolism may modify the anesthetic effects of ketamine. Although this relation has been described previously, the approach using the *N*-nitro-L-arginine methyl ester (a nonselective nitric oxide synthase inhibitor) to influence the cognitive deficits induced by the posttraining administration of ketamine was interesting. Moreover, these effects were observed only when associated with a change in room temperature, suggesting that this change is a key factor in this study.

This article referred to the hypothermic properties of ketamine; however, hypothermia is usually induced in laboratory animals by anesthetics in general. Bouladakis and Pitsikas suggested that the effects of ketamine in cognition were dependent on the room temperature. Importantly, body temperature values for the tested animals were not shown in this study; instead, the authors forward the readers to a previous article, in which initial and 120-min postadministration temperatures in similar conditions were reported.<sup>2</sup> Although we agree that the body temperature values for animals tested in this study are probably within the same interval as those reported previously, we strongly disagree that these measures may be sufficient. Mild hypothermia values were observed at 120 min after anesthesia in the ketamine group kept at 21°C when animals were already recovered. However, it is highly probable that these values may have been lower during the anesthesia period. Therefore, body temperature curves throughout time should have been registered. The report of the body temperature curve would also dissipate the doubts about a potential hypothermic period in the

animals anesthetized in a room at 25°C. Moreover, it would be helpful to have the body temperature of the animals that received only *N*-nitro-*L*-arginine methylester, because this substance may have an effect on thermoregulation.<sup>3</sup> Ulugol and colleagues showed that high doses of ketamine and *N*-nitro-*L*-arginine methylester may cause hypothermia, indicating an involvement of the *N*-methyl-*D*-aspartate receptor and nitric oxide in the thermoregulation pathway.<sup>3</sup> The authors suggested that ketamine hypothermic properties at a room temperature of 21°C may exert neuroprotection; however, it would be interesting to consider the room temperature increase from 21°C to 25°C as a potential stressful event that increases brain vulnerability and may potentiate ketamine-induced deficit.<sup>4</sup>

It is important to notice that in laboratory animal practice, anesthesia must always be performed under controlled temperature by using a homeothermic blanket connected to a rectal probe. However, the measurement of rectal temperature in awake animals could cause stress and consequently may influence body temperature.<sup>5</sup> To avoid the stress of a rectal probe, the temperature data of an awake rat could be obtained using subcutaneous probes or digital scanners.<sup>6</sup>

Clinical observations, such as respiratory rate, heart rate, and blood pressure, should have been reported because *N*-nitro-*L*-arginine methylester may induce hypertension; moreover, these hemodynamic parameters may influence the outcome of the study because of potential differences between groups.

Finally, we would like to highlight some differences between humans and animals. This article stresses the hypothermic properties of ketamine and its negative impact on the information previously learned by rats, whereas in humans, ketamine revealed no impairment in retrieval<sup>7</sup> and is known to reduce the possibility of hypothermia.<sup>8</sup>

In summary, our main concerns are related with the lack of data regarding body temperature and clinical information. Possible differences between temperature evolution within groups during the 120-min period may have influenced the results of the study.

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## In Reply:

We thank Dr. Valentim *et al.* for their comments about our article.<sup>1</sup> In that work, we did not seek to determine the effects produced by hypothermic ketamine on memory. We sought to investigate the effects of posttraining administration of anesthetic ketamine on rats' recognition memory and to evaluate whether the nitric oxide synthase inhibitor *N*-nitro-*L*-arginine methylester (*L*-NAME) was able to reverse the expected behavioral effects produced by anesthetic ketamine. In designing and performing this study, we had two main targets: (1) a clinically relevant amnesic animal model and (2) producing a behavioral outcome not confounded by other not cognitive parameters (hypothermia, sensory motor factors, *etc.*). Therefore, anesthetic ketamine's effects on rats' memory abilities were evaluated using the novel object recognition task, a behavioral procedure that reflects episodic memory in rodents,<sup>2</sup> a type of memory impaired by ketamine in humans.<sup>3</sup> Moreover, because ketamine induces hypothermia in rodents, but not in humans,<sup>4</sup> it was mandatory for us to assess the effects of anesthetic ketamine on rats' recognition memory using a condition in which the drug did not display a hypothermic profile. This issue has been investigated in a previous study in which it was revealed that maintaining the animals for 2 h after drug administration at 25°C, but not at 21°C, caused recognition memory deficits without inducing hypothermia.<sup>5</sup> Because the condition of 25°C seems to produce results similar to those obtained in humans,<sup>3,4</sup> it was chosen for the current experiment.<sup>1</sup> Data presented here are in line with studies carried out in humans<sup>3</sup> and in rats.<sup>5</sup>

We do not agree with the authors' assertion that "this study stresses that nitric oxide metabolism may modify the anesthetic effects of ketamine. Although this relation has been described previously ...." Valentim *et al.*, did not provide any source of information about their statement (where has this relation been described?). In contrast to this assertion, the findings reported in our article are innovative because it is the first time to our knowledge that the effects of anesthetic ketamine on posttraining memory components