Dr. Wasnick believes that my proposal is not radical enough to fully transform our training programs. To clarify, my suggestion that each resident choose either a critical care or pain medicine track in the core residency program is an acknowledgment that very few anesthesiologists practice both pain medicine and critical care medicine. An emphasis on education in one perioperative specialty in the core residency, *versus* superficial training in both, might be a better way to develop the aspects of our practice that are likely to assume a greater prominence in the healthcare system of the future.

Dr. Wasnick then suggests that we might accomplish core clinical training in a 3-yr continuum and then mandate a second stage of training of 2-yr duration, which could include subspecialty training, research experience, or other combined training. Board certification would be possible only at the end of a 5-yr training period. This suggestion is another example of a possible new curriculum, and it is likely that many more could be developed. However, any such proposal would require serious consideration of its implications by departments, institutions, and various accrediting and certifying bodies.

In Dr. Wasnick's proposal, the status of the clinical base year is not specified or described. Given the increasing acuity of our patients and the complexity of their surgical and anesthesia procedures, it seems unlikely that 2 yr of clinical training in anesthesiology would suffice for achievement of competency for the independent practice of intraoperative care.

In addition, Dr. Wasnick's proposal is essentially an across-the-board mandate to extend the duration of training from 4 to 5 yr—and a source of support for the extra year is not specified. This factor would be of extreme importance given Dr. Wasnick's laudable idea that the residents' time in postgraduate years 4 and 5 would be "protected" from service demands.

Certainly, as we think toward the future, a number of proposals, like Dr. Wasnick's and my own, will be generated and require evaluation. At present, our specialty is in the early stages of innovative curriculum development. As Dr. Cox *et al.* suggest, it is imperative that a thoughtful and evidence-based approach be applied to ensure that our innovations create the type of physicians we need for the future.

I agree with my colleagues' assertions that our specialty has a great opportunity through educational innovation and technology to make these determinations and to recruit the top students to our discipline. I suspect that the Accreditation Council for Graduate Medical Education and the American Board of Anesthesiology, among others, will expect such evidence as they consider fundamental changes to our residency and fellowship program requirements.

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Anesthetics and Circadian Regulation: "Hands" or "Gears" of the Clock?

To the Editor:

We have read with great interest the manuscript entitled "Propofol anesthesia significantly alters plasma blood levels of melatonin in rats,"[1] and we would like to comment on this interesting and provocative study. Previous studies have suggested that circadian variation in drug metabolism may be linked to anesthetic drug efficacy. It remains unclear, however, whether anesthetics themselves can directly influence the regulation of the circadian clock.

In the present study, the authors injected rats intraperitoneally with either propofol or intralipid (control) and measured subsequent melatonin secretion. The authors observed an acute suppressive effect of propofol on plasma melatonin concentration, which normalized within 24 h. On the basis of these findings, the authors concluded that these results established "disturbing effects of propofol anesthesia on the circadian rhythm of plasma melatonin" and that these results "parallel the desynchronization of the circadian rhythms of locomotor activity observed after propofol."

Although we would like to commend the authors for performing this interesting and important investigation, we remain concerned that the conclusions drawn are premature and not fully supported by the data.

First, the study design does not allow the authors to determine definitively whether the effects of intraperitoneal injection of propofol are linked, in full or in part, with propofol-induced anesthesia. Depth of anesthesia was not measured by the authors, making it is unclear to what extent the consciousness of the individual rats was impaired. It is also interesting to consider the established ability of propofol to induce a pleasant affective state in rats at subanesthetic doses (as well as during recovery from an anesthetic dose).[2] Perhaps, then, the effects of propofol injections parallel those of opioids, which themselves have been shown to affect melatonin secretion indirectly.[3]

Second, contrary to the suggestion in the section "What This Article Tells Us That Is New," neither a visually nor a statistically significant phase advance of melatonin secretion was shown by the present study. In fact, the authors report only a "trend" towards this putative phase advance, and we wonder if this could be just as reasonably explained by the cocinar methodology, which is sensitive to artifacts such as changes in the waveform used in the analysis (in this case, driven by the acute suppression of melatonin at the first two Zeitgeber times after injection). Furthermore, the magnitude

of the putative phase advance is slight. Given then the small magnitude and the transient nature of the "circadian" response, it does not seem prudent to link postsurgical fatigue, drowsiness, sleep disorders, and mood alterations to anesthetic-induced changes in the circadian clock. In fact, the definitive studies to provide the necessary data to support this conclusion have not yet, to our knowledge, been performed.

Third, the authors conclude that the effects of propofol on melatonin injection "parallel the desynchronization of the circadian rhythms of locomotor activity previously observed after propofol." However, the cited study[4] was not performed in constant darkness, which is necessary to establish a direct linkage between anesthetic administration and circadian clock disruption. Interestingly, previous work in humans has shown that even 3 h of anesthetic exposure in humans does not affect the circadian phase of the body temperature rhythm.[5] In summary, it must be stressed that the ability to distinguish between effects occurring directly on the circadian pacemaker and those occurring "downstream" from the pacemaker on other physiologic control systems requires extremely rigorous experimental conditions. These conditions have yet to be met, and so for now, it is more prudent to interpret the effects of propofol on the melatonin rhythm as "masking." In other words, the data more strongly support the concept that the "hands " of the clock, rather than the "gears " of the clock, have been influenced by the propofol stimulus.

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In Reply:

We thank Drs. Eikermann and Chamberlin for their comments about our article.[1] We agree entirely that the key issue is whether anesthetics themselves can directly influence the functioning of the brain circadian clock. They contend that it is unacceptable for us to conclude that propofol anesthesia acts directly on the circadian rhythm of circadian melatonin as well as the circadian rhythm of rest-activity and temperature in rodents.[2]

First, they make the point that the effects of intraperitoneal injection of propofol cannot be linked with propofol-induced anesthesia, arguing that the study design was not appropriate. We concur with them that we did not assess the depth of anesthesia; this was not the aim of our study. Because it is unclear in the first place from any clinical data available in the literature whether propofol injection could modify per se the plasma melatonin within the following 24 h, our study was designed to clarify this point. To the best of our knowledge, the loss of righting reflex in rats is an agreed upon method for assessing clinical anesthesia in rats in these circumstances.

Likewise, they use unusual logic to conclude that propofol has an opioid effect on melatonin secretion: (1) propofol has a pleasant effect that might be linked to an opioid effect; and (2) opiates indirectly affect melatonin secretion. As we know, the pleasant effect could be due to other factors, such as a dopaminergic effect.[3] Such tautology does not permit us to concur with them on this point.

Second, we understand that the suggestion in the single sentence in the "what this article tells us that is new" may appear provocative. It is always challenging to summarize the innovative aspects of data in one brief sentence. However, as an in-depth reading of the results and discussion sections clearly show, there is an evident visual phase advance of melatonin secretion with significant differences between propofol injection and control at early (decrease) and late (increase) periods of melatonin collection. Cosinor analysis of the raw data supports this observation with a statistical trend ($P = 0.06$). Moreover, we have very clearly pointed out the limitations of our study and have stated that "from our data obtained in rats, we cannot demonstrate that the fatigue, drowsiness, and sleep disorders observed in patients are related to a disturbed circadian pattern of human melatonin." We also suggest that our data provide an opportunity to open new lines of research to better understand these symptoms. Indeed, there is no clear explanation yet for these undesirable symptoms that could occur even after a short duration of anesthesia for small medical procedures.

Third, using a similar approach, Drs. Eikermann and Chamberlin do not accept our statements of a previously described desynchronization of the rest-activity rhythm induced by propofol because, as they claim, the data were not obtained in constant darkness. To support their statements, they cite one of our previous articles where experiments were performed in dark/light conditions.[2] However, we are fully aware that it is necessary to have data in constant darkness to establish a direct linkage between anesthetic administration and circadian clock disruption. To that end, we published a study[4] in *Neuropsychopharmacology* in 2007 (cited in the article) in which the same experiments were performed in constant darkness. This