What Constitutes Adequate Anesthesia in Animals? In Neonates?

To the Editor.—The article in ANESTHESIOLOGY by Yaster et al.1 raises the important question of what comprises "adequate anesthesia" in animals, and, by extension, in newborn humans and others unable to communicate effectively. In their study, all of the newborn lambs that received very high-dose fentanyl (3000 μg/kg iv) without muscle relaxants were cataleptic and had profound respiratory depression. In addition, the authors describe only minimal hemodynamic changes to the noxious stimulus. Yet clamping of the tail with a hemostat (and "then moving it and the tail continuously") resulted in what the authors called "purposeful" movement.

It is possible that newborn lambs are different in their response to opioids from most preay animals (and humans). However, in the face of the other classical manifestations of high-dose opioids, the lambs must have had profound analgesia. Thus was the occurrence of "purposeful" movement really an indication of inadequate anesthesia? The response to noxious stimuli applied to the tail can be a spinal mediated reflex. In the apparent absence of hemodynamic response to stimuli, additional information would be necessary to determine whether the "purposeful" movement was due to peripheral reflexes as opposed to inadequate depression of consciousness.

The situation is complex: a high dose of opioids given to many classes of preay animals results in a constellation of behavioral signs indistinguishable from the "death-feign reflex."2 The animals become rigid, akinetice, analgesic, and hypothermic. Yet in response to auditory or tactile stimuli, they exhibit "explosive motor behavior," consisting of a startle response followed by festinating forward locomotion.3 The same constellation of signs can be elicited by extreme stress and appears to be mediated by endogenous opioid systems. This reflex is, therefore, believed to be protective in the event of sudden predator attack. Were the newborn lambs in Yaster's study simply expressing "explosive motor behavior" in response to tail stimulation? Is this a conscious (i.e., purposeful) act or simply a primitive reflex? This cannot be ascertained from the information provided by Yaster et al.

Lack of movement in response to surgical stimulation has been the traditional gold standard of depth of anesthesia but may have less meaning with the receptor-specific iv anesthetic agents, especially the opioids. Minimum alveolar concentration (MAC) was originally defined for inhalational agents as the "minimum concentration in the alveoli required to keep a dog from responding by gross purposeful movement to a painful stimulus"4 and was subsequently modified for application to humans as the alveolar anesthetic concentration at which one-half of the patients move in response to a surgical stimulus.5 Intravenous anesthetics produce effects that are both clinically and neuropsychopharmacologically different from the volatile agents. Until better measures of level of consciousness or brain function are developed, perhaps the criteria for anesthesia should be tailored to the agent in question as well as to the species under study.

Others have suggested that the proper assessment of anesthetic potency requires different endpoints of anesthetic effect corresponding to the different components of general anesthesia.6,7 The components of general anesthesia include a decreased level of consciousness, amnesia, lack of movement, analgesia, and blunted cardiovascular reflexes. Kissin et al.6,7 have demonstrated (in rats) that the ED50 values, slopes of the dose-response curves, and the relative potency ratios for different endpoints of anesthesia are, in fact, different for different anesthetics. For example, in one study,7 they found that much lower doses of fentanyl were required to block the movement response to a noxious tail stimulus (ED50 = 9 μg/kg) than to block the heart rate response (>1% increase above baseline) to the same noxious stim-

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In Reply—We could not disagree more with Drs. Weinger and Koob or with the implications of their letter. We absolutely disagree that clamping an animal's tail with a hemostat elicits only a "spinally mediated reflex" and is an inappropriate method of testing "anesthesia." Movement in response to tail clamping is the time-tested, gold standard method of assessing anesthesia and has been since the concept of "MAC" was introduced 20 yr ago.1,2 In fact, this technique has been used by many different investigators using various animal species, including rats, dogs, and sheep because it produces a supramaximal stimulus.3,4 When investigating the anesthetic effects of either iv or inhalational agents, a supramaximal stimulus is necessary in order to avoid misleading results and conclusions that may occur when a submaximal stimulus is used.1,2,4 In our studies of the newborn lamb's peripheral and cerebral hemodynamic responses to high-dose fentanyl administration, we assessed anesthesia using a 10-inch hemostat, clamped to the first ratchet for 30 s.6,7 It was clear in both studies that fentanyl could not reliably prevent purposeful movement to this stimulus.

Nevertheless, even if Drs. Weinger and Koob were correct about tail clamping, there is ample evidence to support our conclusion that fentanyl, when administered alone, does not produce anesthesia in newborn lambs. In our study, when fentanyl was administered alone, all of the lambs appeared awake only that is, their eyes were open and they turned their heads to sound.7 The addition of a subanesthetic dose of pentobarbital abolished these responses. Second, fentanyl administration was always accompanied by apnea which we treated with rapid endotracheal intubation and mechanical ventilation.6,7 All of the lambs physically resisted intubation by head withdrawal and closure of their vocal cords. They also developed tachycardia and hypertension during intubation. These behaviors and responses are commonly associated with inadequate anesthesia. Indeed, during the subsequent mechanical ventilation, the animals chewed on their endotracheal tubes. These physical behaviors and autonomic responses were similarly abolished with the addition of small, subanesthetic doses of pentobarbital.7 Third, systolic arterial blood pressure also increased following the tail clamp when fentanyl was administered alone. Adding a barbiturate abolished this autonomic reactivity. This confirmed our previous finding that increases in arterial blood pressure in response to a painful stimulus are directly related to the strength of withdrawal response and are abolished when consciousness is lost.7 Finally, the effects of fentanyl on cerebral blood flow (CBF) and oxygen consumption (CMRO2) also support our belief that the lambs were not anesthetized when fentanyl was administered alone. In our studies, when lambs responded to tail clamping and appeared awake, CBF and CMRO2 did not decrease.6,7 On the other hand, when the lambs appeared unconscious and did not respond to tail clamping, which occurred following the administration of both fentanyl and pentobarbital, CBF and CMRO2 significantly fell.7 In this way fentanyl may act like other anesthetic agents, such as the barbiturates, which decrease CBF and CMRO2 only when consciousness is lost.8

Based on our clinical and laboratory experience, we and many others believe that fentanyl, when administered alone, should not be considered an "anesthetic" nor should it even be expected to produce unconsciousness or amnesia in animals or humans.8,9 Indeed, it is precisely because patients may be awake during high-dose fentanyl anesthesic that most anesthesiologists add benzodiazepines, barbiturates, low-dose potent vapors, or nitrous oxide to their anesthetic regimens. In fact, this was the impetus behind our study.

Unfortunately, as our laboratory study and the clinical studies of Lunn et al. and Stanley et al.11,12 demonstrate, the addition of other agents may significantly affect the hemodynamic stability and safety of fentanyl "anesthesia." Thus, when used as a single agent, in the newborn, in critically ill patients, or in the laboratory for scientific investigation, fentanyl may not be a total anesthetic agent. However, the solution is not, as Drs. Weinger and Koob suggest, to add a muscle relaxant and think the problem is solved. Paralyzing an awake subject for surgery to prevent movement is an unconscionable approach that is unsupportable, either clinically or in the laboratory. Indeed, in this era of heightened concern for the welfare of animals, and by extension, for human newborns and others who are unable to communicate, we must increase our sensitivity to this issue and provide "anesthesia" when we say we are.

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