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(Accepted for publication December 29, 1989.)

Anesthesiology
72:768–769, 1990

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.[1–5] 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; 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 the withdrawal response and are abolished when consciousness is lost.[7] Finally, the effects of fentanyl on cerebral blood flow (CBF) and oxygen consumption ($CMRO_2$) 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 $CMRO_2$ 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 $CMRO_2$ significantly fell.[7] In this way fentanyl may act like other anesthetic agents, such as the barbiturates, which decrease CBF and $CMRO_2$ 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.[9,10] Indeed, it is precisely because patients may be awake during high-dose fentanyl anesthetics 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 insupportable, 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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(Accepted for publication December 29, 1989.)

Anesthesiology
72:769, 1990

Correction

To the Editor:—We failed to state in our article[1] that Ovassapian *et al.*[2] proposed that glycine may produce visual disturbance. It was our oversight, and there was no intention to not give credit where credit is due.

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(Accepted for publication January 16, 1990.)

Anesthesiology
72:769–771, 1990

Cardiovascular Responses to Noxious Stimuli in Experimental Animals: "Pressor or Depressor"?

To the Editor:—We read with interest the recent reports by Gibbs *et al.* of cardiovascular reflex responses to noxious stimuli in rats.[1,2] In their study, noxious stimuli to the rat's tail were applied during halothane anesthesia by clamping with a rubber-shod clamp, a commonly used and "standard" method of evaluating anesthetic potency for animal experiments.[3] In rats, increasing depth of halothane anesthesia reversed the cardiovascular responses to the noxious stimulation from the pressor (hypertensive) to the depressor (hypotensive) responses.