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Vive Pascal but Kilo Newton?

To the Editor:—Regarding de Jong's note¹ helping to enlighten readers about SI, the atmospheric pressure is not about 100 N/m², but about 100 kN/m² (101,325 N/m² is the standard atmosphere). Newton "kil"ed by a typo—even the teachers get confused! Perhaps de Jong was suggesting that Newton was worth 1,000 Pascals, an Anglic counterbalance to the Gallic assault on that little millimeter of mercury. Perhaps he was.

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Mechanism of Epidural Lidocaine Reversal of Tachyphylaxis to Epidural Morphine Analgesia

To the Editor:—Recently, McCoy and Miller reported in a single patient the efficacy of epidural lidocaine injections in reversing the analgesic tachyphylaxis associated with epidural morphine.¹ My response is to not discourage or object to this practice, since epidural local anesthetic injection can provide both temporary relief and prognostic information concerning the pain syndrome in question.² Rather, my primary interest in this report is twofold. First, I wish to report my inability to consistently reverse morphine tachyphylaxis with epidural local anesthetics. In this regard, a representative case is instructive. In February 1981, a 60-year-old man with squamous cell carcinoma of the lung and associated brachial plexus invasion was treated with thoracic epidural morphine injections after increasing doses of methadone (up to 40 mg/day) and hydromorphone HCl (up to 24 mg/day) failed to control his pain. Initially 6 mg of epidural morphine produced 12 h of nearly complete pain relief. Subsequently, a subcutaneous reservoir of the Ommaya® type was placed on the chest wall in series with a silastic thoracic epidural catheter to facilitate epidural narcotic delivery. During the next two weeks, progressive dosage increases were required, while the frequency of injection increased from once to twice daily. Injection of epidural local anesthetic (either 8 ml 1 1/2% lidocaine or 1/4% bupivacaine at T6) produced complete relief of pain, but this effect was sustained for only 2–3 h, and the tachyphylaxis to epidural morphine was not affected. More disconcertingly, attempts to control pain with parenteral morphine resulted in rapid tolerance to even massive doses (up to 175 mg/

h). He died after 1 month, at which time he was receiving 100 mg of morphine as an iv bolus every 2–3 h in addition to the continuous iv infusion. Seemingly, this patient was already significantly tolerant to opiates (prior to epidural morphine) at least at supraspinal opiate receptor sites. Aggressive opiate activation of spinal cord opiate receptors (spinal receptors were initially responsive, since epidural morphine analgesia initially was achieved) then occurred consequent to bolus epidural morphine thus, apparently leading to generalized opiate receptor indifference to even astronomic doses of parenteral morphine. In this regard, the case is similar to that described by Woods and Cohen.³ In selecting intraspinal narcotic therapy, one thus assumes that tolerance at the spinal cord opiate receptor is less pronounced than at supraspinal receptors, in spite of substantial conventional narcotic exposure. Thus the "multiplicative" antinociceptive interaction resulting from both spinal and supraspinal opiate receptor activation (see Yeung and Rudy⁴) may be lost more completely than if only one opiate receptor site has been activated substantially and continuously. This may explain a related phenomenon; namely, spinal opiate tolerance appears to occur more rapidly during continuous intrathecal morphine use as opposed to chronic epidural administration. Alternately, since different opiate receptors may predominate at the spinal cord level (for example the delta opiate receptor subtype as proposed by Pasternak), agonists with lesser affinity at this receptor may become more effective with direct intraspinal application.

Secondly, I am interested as to the mechanism re-

sponsible for reversal of epidural narcotic tachyphylaxis in the case reported by McCoy and Miller and, more importantly, my failure to obtain this outcome following epidural local anesthetic in the majority of cases in whom I have attempted it. Rather, it has been my experience that either a protracted series of epidural local anesthetic blocks or continuous epidural infusion often is required. The resultant duration of analgesia is usually consistent with the duration of local anesthetic blockade. The efficacy of epidural local anesthetic injections for relief of cancer pain is well appreciated.² The resulting analgesia may be short-lived or in some cases quite sustained for as long as several weeks or more. The latter response may occur because of an underlying reflex sympathetic dystrophy.² Given the likely biochemical basis for opiate tolerance^{5,6} and the time frame required to reverse this effect in animal models (1–2 weeks), it would be naive to simply assume that responsiveness to epidural narcotics had returned following epidural injection of a local anesthetic. Rather, the response in such patients is likely singularly due to the effects of the epidural local anesthetic, *i.e.*, sympathectomy. This issue is of major importance, because spinal narcotic tolerance seems to be the limiting factor in successful application of chronic epidural narcotic therapy. This also accounts for the interest in other forms of epidural therapy, given the multiple receptors, modulators, and substrates involved in spinal nociceptive pathways.⁷ Perhaps a trial of epidural local anesthetic therapy should precede attempts to use

epidural narcotics, because some patients may have protracted pain relief following epidural local anesthetic therapy alone.

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Anesthesia-induced Hepatotoxicity

To the Editor:—The letter by Strunin and colleagues¹ proposing abandonment of the rat model of anesthesia-induced hepatotoxicity invites further comments. The rat model has certain problems that Strunin *et al.*¹ have emphasized. However, one should not expect from a model more than the model can give. Obviously, the rat model cannot solve all problems related to the whole spectrum of liver injuries. I think that there are at least three different types of postoperative liver dysfunction in humans. One of these is fulminant halothane-induced hepatitis; there are some old² and some very important recent^{3,4} data strongly suggesting that this form of hepatitis is mediated immunologically. Another form of postoperative hepatitis is viral hepatitis, which coincides with the perioperative period.^{5–7} Finally, liver damage can develop in response to intermediates of reductive metab-

olism of halothane and/or a substantial decrease in oxygen availability to the liver *per se* due to respiratory and/or circulatory (systemic or regional splanchnic) depression.⁸

The rat model has not been very helpful in elucidating the first two forms of liver injury; however, it seems to be suitable for the last one. The article by Plummer *et al.*,⁹ which evoked the letter to the editor,¹ is a good example of the fruitfulness of the rat model in elucidating a metabolic etiology of anesthetic hepatic toxicity. Many recent publications have shown the usefulness of the model in evaluation of oxygen availability to the liver.^{8,10,11}

I think the rat model is still in its infancy; the model actually was born only 4 years ago, when liver injury could be reproduced regularly.^{12,13} Since then, many factors have been shown to influence liver damage in the