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The True Epidural Space: Possible Consequences for Administered Material-based Drug Delivery Systems

To the Editor:—A recent paper by Hogan[1] showed that the epidural contents are found in repeating metameric segmentation in the longitudinal axis of the spinal canal. This finding could explain the distribution of a 10% n-butyl-p-aminobenzoate (BAB) suspension injected epidurally,[2] found at necropsy 36 days after its administration (fig. 1). The distribution of profound analgesia after epidural BAB administration corresponded well with the distribution of BAB along the segmental spinal nerve roots found at necropsy. The concept of epidural segmented subcompartments is important not only for understanding the mechanics and pharmacokinetics of solutions injected into the epidural space, but also for understanding how material-based drug delivery systems, such as a 10% BAB suspension, distributes into the epidural space. That the lateral epidural subcompartment is in close contact with the spinal nerve roots is of particular importance. Moreover, the various epidural subcompartments do not seem to communicate. This new anatomic insight may explain variability in responses seen after epidural injection of a 10% BAB suspension.[2]

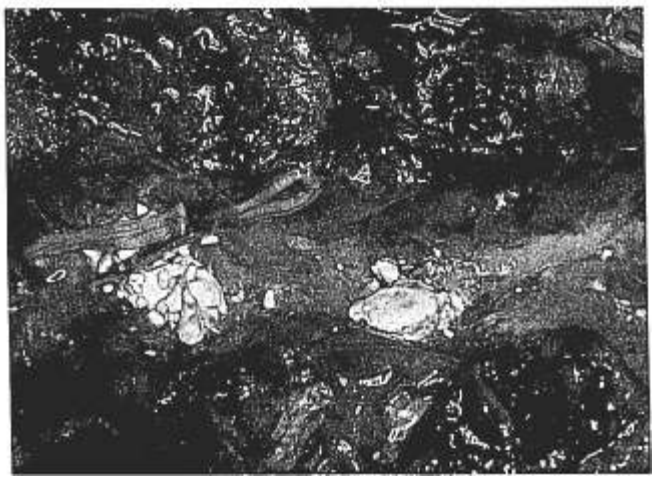

FIG. 1. Epidural dorsal subcompartment seen from the front, after removal of vertebral bodies, dural sac, and spinal roots. Thirty-six days after its epidural administration, BAB is found in repeating metamerical regions in the dorsolateral epidural subcompartments.

Advances in materials science and biotechnology are permitting the development of new material-based drug delivery systems,[3] already in use in medicine. Continued research may revolutionize the way drugs, including those intended for epidural administration, are delivered. Material-based drug delivery systems have many potential advantages, which include 1) maintenance of the drug in the desired therapeutic range by a single epidural administration; 2) less risk for general toxic reactions; 3) preservation of drugs that are rapidly destroyed by the body; 4) less need for follow-up care; 5) increased comfort; and 6) improved compliance.[3] In light of these pharmaceutical developments, the new knowledge of the anatomy of the epidural space is of particular importance.

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In Reply:—In considering the interesting observation by Korsten *et al.* of the segmental distribution of particulate matter in the epidural space, a distinction should be made between the location of natural epidural contents and the spread of injected material. The contents occur in segmented packets that are not in continuity with each other circumferentially or longitudinally. However, when observed by cryomicrotome section in cadavers or by computerized tomography *in vivo* (unreported results), injected solutions typically spread continuously in a sheetlike fashion, occupying without gaps the areas between the dura, canal wall, and epidural fat (fig. 1) because these tissues are mostly nonadherent to each other. The compartments must communicate (*i.e.*, allow passage between them) or solution would not spread and a catheter would not advance. Fortunately, nature has provided us with separable tissue planes.

Although epidurography[1–3] and radionuclide studies[4,5] proved that the distribution of injected solution is not discontinuous or interrupted, Nishimura (personal communication) showed that it is not longitudinally uniform, which may be due to the greater distensibility of the epidural

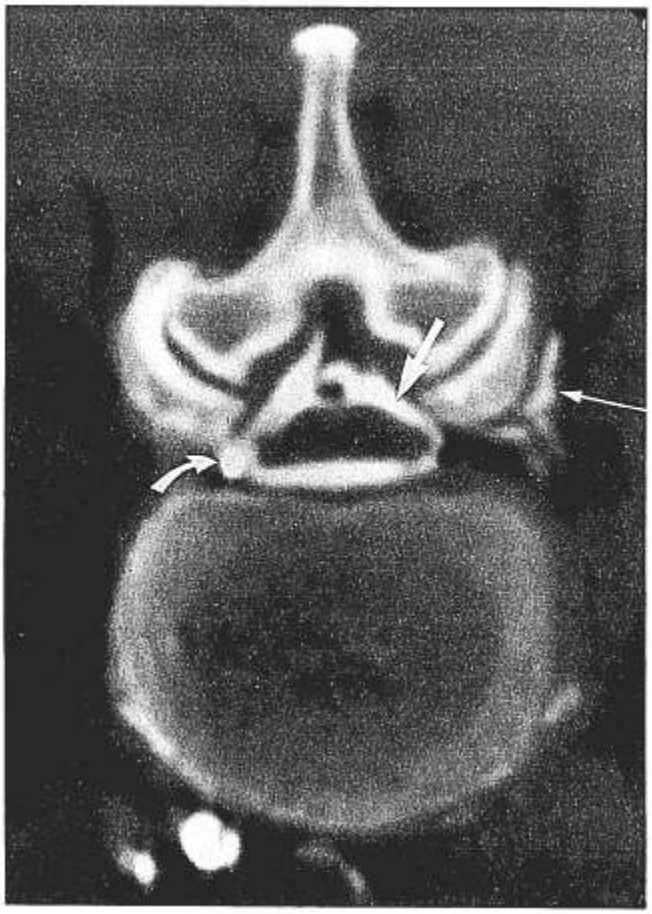

FIG. 1. Axial computerized tomography (CT) image at the third lumbar level showing contrast material (heavy straight arrow) encircling and compressing the dura and suspending the posterior epidural fat. An air bubble appears posterior to the dura, and lateral passage through the nerve root canal is evident (thin straight arrow), as is the epidural catheter (curved arrow). Adjacent CT images showed the contrast material to be continuous along the epidural space without gaps at the vertebral laminae.

space at the level of the posterior compartments than at the levels of the laminae. Uniquely, the n-butyl-*p*-aminobenzoate (BAB) suspension was found at autopsy by Korsten *et al.*[6] in completely discontinuous patches. Perhaps the posterior epidural compartments in which the BAB particles accumulated represent cul de sacs into which the material migrated after injection. The material appears clumped, as if it had solidified to some degree in the days after injection. If so, motion of the dural sac against the vertebral arch may have expelled the pieces from the regions under the laminae, where dura is directly in apposition to the bony canal. In any case, I believe further study will clarify the nature of the barriers and mechanical behavior of the epidural space, aiding the expanded use of new techniques such as that being developed by Korsten *et al.*[6]

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Does Surgical Site Correlate with Incidence of Side Effects, Complications, and Problems Induced by Epidural Morphine?

To the Editor:—The recent article by Ready *et al.*[1] addressed a question that concerns physicians and nurses when morphine is used epidurally for postoperative pain. Despite the importance of this work, I would like to address several issues raised in the paper.

First, table 1 reported data on morphine dose and pain according to surgical site. For example, thoracic surgery patients received twice as much morphine in 24 h as patients undergoing perineal surgery. Tables 2 and 3 described side effects, complications, and problems for all patients without specifying different surgical sites. Thus, because groups were not homogeneous for surgical site and dose of morphine, it would have been more informative to know whether the complications and side effects were different among patients undergoing thoracic, abdominal, lower extremity, or perineal surgery.

Second, respiratory depression in two patients is described. In the first case, the lowest respiratory rate was 14 breaths/min; Pa_{O_2} was 192 mmHg; Sa_{O_2} was 99%; and Pa_{CO_2} was 59 mmHg. The patient was also obese (131 kg), a condition associated with respiratory impairment.[2] In the second case, except for the low respiratory rate, there was no other way for the reader to evaluate respiratory depression; however, in the Discussion, the authors emphasized the usefulness of assessment of consciousness in establishing a diagnosis of respiratory depression.

Finally, I fail to understand why blood gas analysis is not included