Sophistry in Medicine: Lessons From the Epidural Space

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Having spent my academic career in the anesthesia department built by Dr Bonica, I have been the beneficiary of his wisdom, his vision, and his indefatigable efforts on behalf of academic anesthesiology. If I have contributed anything to our profession, it is because physicians like Dr Bonica have paved the way. Thus, it is a great pleasure to be able to honor Dr Bonica by giving this year's John J. Bonica Lecture at the Fall Pain Meeting of the American Society for Regional Anesthesia and Pain Medicine.

When I was invited to give this lecture, the request was that I "present a 35-40 minute original lecture, with an emphasis on pain medicine as it relates to your area of expertise." To the extent that I have any expertise, it is the physiology governing the behavior of drugs, particularly opioids, in the epidural and intrathecal spaces. So, I will talk about that, but I want to do so in a broader context.

I would like to begin by taking a brief look at a few examples of some quaint medical practices from our profession's past. These practices were based on reasoning and the belief that reasoning alone could divine medical truths and thereby identify the best therapies for patients. At the time, these practices were considered state-of-the-art and the beliefs on which they were based were considered immutable (sadly, some "practitioners" still consider them so today). In retrospect, we may find these practices amusing, ridiculous, or even barbarous. However, we should be circumspect in our criticism, because, as I hope to convince you, we also divine medical and physiological truths by application of reasoning alone. And, we sometimes stubbornly hold onto these "beliefs" in the face of data showing them to be false.

I think it is reasonable to lay blame for the tendency to substitute reason for evidence squarely at the feet of the Sophists (since they are not here to object, it is also safe). The Sophists first came to prominence in Greece during the 5th century BCE. Their guiding "philosophy" was that the truth of any matter, from mathematics, to art, to politics, could be arrived at by mere application of logic and strength of argument. In effect, they held that as long as the reasoning was sound, the conclusion that followed must be correct. Although this practice was first "codified" by the Sophists, it has been practiced by many cultures and is thought by some to be a natural outgrowth of the human desire to make sense of the world.

Certainly, examples of sophistry can be found in many disciplines, but medicine provides some particularly striking illustrations. Consider the Doctrine of Signatures, which was introduced by a German shoemaker named Jakob Bohme. In his book *De Signatura Rerum* (The Signature of All Things), Bohme claimed that he had experienced visions in which he was told that God marked everything in creation with a sign (signature) indicating the purpose for which it was intended. Although Bohme made no claims that the doctrine applied to medicine, entrepreneurial physicians adopted his work as evidence that they could divine the medicinal use of a plant by observation alone. For example, William Cole, a follower of Paracelsus, writing in the 17th century about the Lily of the Valley flower claimed, "It cureth apoplexy by Signature; for as that disease is caused by the dropping of humours into the principal ventricles of the brain: so the flowers of this Lily hanging on the plants as if they were drops, are of wonderful use herein."

In fact, application of the Doctrine of Signatures to medicine was such a powerful and widespread practice that it is responsible for the common names (and in some cases the scientific names) that we still use for many plants. For example, (1) liverwort (*Anemone hepatica*) relieves liver trouble, (2) lungwort (*Sticta pulmonaria*) cures lung disease, (3) maidenhair fern (*Adiantum pedatum*) relieves baldness, (4) wormwood (*Artemisia absinthium*) expels intestinal parasites, and (5) pilewort (*Ranunculaceae ficaria*) cures hemorrhoids (still available for this

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indication at http://www.head2toes.co.uk/info/pilewort-ointment.html).

Bloodletting is another example of sophistic logic applied to medicine. Although bloodletting has been used by many cultures (and is still practiced in some parts of the world), it is Galen (131-201 CE) who is credited with popularizing this therapy in Western medicine. Galen, who lived in Greece during the second flowering of the schools of sophistry, reasoned that disease was caused by an imbalance in the 4 primary humors: blood, phlegm, yellow bile, and black bile. Galen reasoned further that, because disease was caused by an imbalance among the four humors, it was clear that disease could be cured by restoring the balance. Because blood was the primary humor, blood removal became a mainstay of medical therapy. This belief was taken to the extreme by Dr Benjamin Rush (a representative of the colony of Pennsylvania and a signatory to the Declaration of Independence) whose influence played a role in George Washington being bled 4 quarts of blood for what many believe was a case of epiglottitis—an act that certainly contributed to, even if it did not directly cause, his death.

Bloodletting persisted well into the 19th century and was still being recommended for some illnesses in the 1923 edition of Sir William Osler's authoritative textbook *Principles and Practice of Medicine*. Like the Doctrine of Signatures, the practice of bloodletting has cultural resonance today as the ubiquitous "barber pole." The barber pole was placed outside the "office" of barber surgeons where the red stripes were meant to represent the blood seeping through bandages after a professional bloodletting.

These are but 2 of many possible examples of ridiculous medical practices that achieved widespread popular application based solely on reasoning and logic. At the outset, I intimated that one of my goals was to convince you that there are still many beliefs in medicine that are derived solely from deduction, some of which are rigidly held even in the face of contrary scientific evidence. To illustrate this point, let us consider some commonly held beliefs in just one very small area of medicine—the anatomy and physiology of spinal drug delivery.

For approximately 100 years, physicians have been putting a variety of drugs in the epidural space with the intent that the drugs will reach the underlying CSF, spinal nerves, and spinal cord to produce an intended effect (e.g., neural blockade). The fact that drugs placed in the epidural space do reach the CSF and spinal cord is clear. What is less clear is how drugs move from the epidural space to reach the targeted neural tissues.

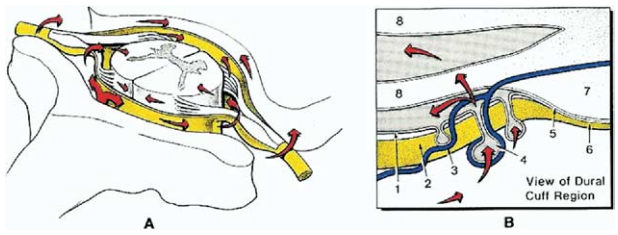

Fig 1. (A) Epidurally deposited drug (arrows) spreading laterally from the midline. (B) An expanded view of the spinal nerve root cuff that shows drug entering the subarachnoid space by traversing the arachnoid granulations (villi). There are no data to support this mechanism, although there are direct experimental data refuting it (see text). 1, arachnoid mater; 2, dura mater; 3, epidural vein; 4, arachnoid granulation; 5, epineurium/arachnoid mater; 6, epineurium/dura mater; 7, dorsal root ganglion; 8, spinal nerve roots. (Reprinted with permission from Cousins, MJ, Bridenbaugh, PO (eds.) *Neural Blockade in Clinical Anesthesia and Management of Pain*. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 1998.)

If one looks in current textbooks, you will find several proposed mechanisms to explain how drugs redistribute out of the epidural space and into the CSF. Figure 1 is taken from a widely read textbook of regional anesthesia,[1] and it depicts drugs spreading laterally in the epidural space and preferentially diffusing through the spinal nerve root cuff to reach the CSF. This concept has been logically deduced from several facts. Firstly, it is known that arachnoid granulations (villi) are present at the spinal nerve root cuff of most human spinal nerves.[2] These arachnid villi are identical to those present in the brain, and they function as egress points for CSF to leave the subarachnoid space. Secondly, it has been known since the work of Key and Retzius in the late 1800s that, if you put particulate matter in the spinal CSF of animals, it will later be found in the epidural space.[3] Thirdly, subsequent work showed that red blood cells were removed from the CSF by passage through the arachnid villi.[4] These 3 facts were logically woven together to suggest that drugs, which are much smaller than red blood cells, could also move through the arachnoid villi to get from the epidural space to the CSF. Although this argument is seductive (a hallmark of Sophistry), it is wrong. Neurophysiologists have shown experimentally that movement of materials through the arachnoid villi occurs by micropinocytosis and that the direction of movement is only out of the CSF[5-8] (if this were not the case, then any molecule in venous blood, into which most arachnoid villi protrude, would gain ready access to the CSF and thereby circumvent the blood-brain barrier).

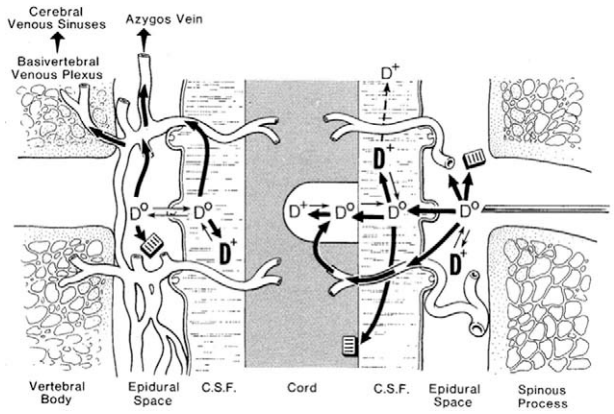

Fig 2. Diagram showing drug (D) being deposited in the epidural space. The more lipid-soluble, unionized fraction of the drug (D^0) is seen to preferentially diffuse across the spinal meninges and to enter the radicular artery by which it is carried to the spinal cord. There are no data to support this mechanism, although there are direct experimental data refuting it (see text). (Reprinted with permission from Cousins, MJ, Bridenbaugh, PO (eds.) *Neural Blockade in Clinical Anesthesia and Management of Pain*. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 1998.)

Although knowledge of normal arachnoid villi physiology would seem to preclude the idea that drugs could be transported via them from the epidural space to the intrathecal space, we performed a study designed to test this hypothesis directly. We measured the permeability of morphine, fentanyl, and lidocaine through the spinal meninges of both dogs and monkeys. We compared the drugs' permeability through a section of tissue that included a nerve root cuff, with that through an immediately adjacent area of meningeal tissue lacking a nerve root cuff. We reasoned that, if drugs moved preferentially through the arachnoid villi of the spinal nerve root cuff, then drug permeability would be greater in the tissue that included a root cuff. However, we found that the permeability of all 3 drugs was identical in tissues with and without a root cuff in both species.[9] Thus, the available experimental evidence indicates that the arachnoid villi associated with the spinal nerve root cuff are not a preferred route for drugs to move between the epidural space and the spinal cord. Yet, you will still find this idea featured prominently in current texts.

Another idea that has been suggested to explain drug distribution between the epidural space and spinal cord is that drugs, particularly lipid soluble drugs, can diffuse through the wall of the radicular arteries as they traverse the epidural space and then be carried by the radicular blood flow to the spinal cord. Figure 2, which is taken from a current textbook of regional anesthesia,[10] depicts this process. Again, the reasoning is somewhat seductive and the idea has achieved widespread circulation, although there are no data to support it. Therefore, we conducted a study aimed at determining whether radicular blood flow contributes to drug movement between the epidural space and spinal cord.[11]

A microdialysis probe was placed in the spinal cord of anesthetized pigs to permit continuous sampling of the spinal extracellular fluid space. Fentanyl was then injected into the lumbar epidural space and the lumbar spinal cord sampled via the microdialysis probe to determine the rate at which fentanyl reached the spinal cord. This was done twice in each animal: once with intact radicular blood flow and once with the aorta cross-clamped at the diaphragm to eliminate distal radicular blood flow. We reasoned that, if radicular blood flow contributed to movement of epidural fentanyl to the spinal cord, then fentanyl should reach the spinal cord much more slowly when the aorta was cross-clamped. However, that is not what we found.[11] During aortic cross-clamp, fentanyl reached the spinal cord at exactly the same rate that it did in the

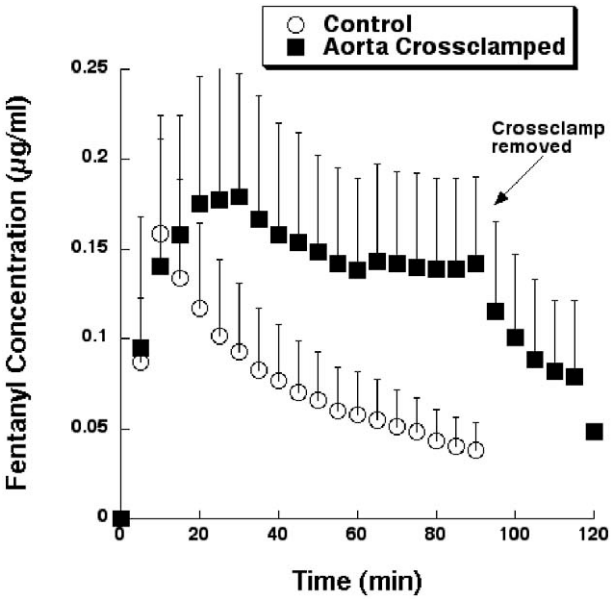

Fig 3. Plot showing fentanyl concentration in pig spinal cord after epidural injection with intact radicular blood flow (control: open circles) and with radicular blood flow eliminated by abdominal aortic cross-clamp (aorta cross-clamped: filled squares). Fentanyl reaches the spinal cord at the same rate whether radicular blood flow is present or not. However, fentanyl is removed much more slowly from the spinal cord while radicular blood flow is eliminated. These data indicate that the spinal radicular blood flow plays an important role in fentanyl removal from the spinal cord but not in fentanyl distribution from the epidural space to the spinal cord. (Data from Bernards et al.[11])

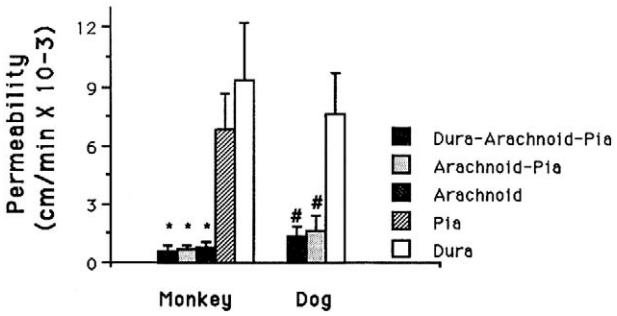

Fig 4. Plot showing morphine permeability through the intact spinal meninges and through the individual meninges of both the dog and the monkey. Contrary to conventional wisdom, the dura mater is the most permeable meninx not the least permeable. The arachnoid mater is responsible for approximately 90% of the resistance to drug diffusion through the meninges. (Reprinted with permission.[12])

absence of the cross-clamp. What was dramatically different was that the fentanyl concentration was higher and persisted longer in the spinal cord while the aorta was cross-clamped. When the cross-clamp was removed, fentanyl rapidly washed out of the cord at almost exactly the same rate that it did in the absence of the cross clamp (Fig 3). Thus, contrary to what had been "reasoned" to occur, radicular blood flow did not move fentanyl into the spinal cord. Quite the opposite; radicular blood flow was actually important for washing fentanyl out of the spinal cord. Why the mechanism proposed in Figure 2 continues to be published, despite the absence of any direct evidence supporting it and in the presence of experimental data refuting it, is unclear.

To date, the only mechanism that has been shown experimentally to explain drug movement between the epidural space and the CSF/spinal cord is simple diffusion through the spinal meninges.[12,13] Because it is so much thicker than the other meninges, the dura mater has long been assumed to be the most important barrier to drug diffusion between the epidural space and the underlying neural tissues. For example, consider the following comments sampled from several anesthesia textbooks.

1. There is good evidence that local anesthetics injected into the epidural space not only reach the spinal nerves but also pass through the dura mater into the subarachnoid space . . .[14]
2. The major site of action of local anesthetic solutions placed in the epidural space appears to be the spinal nerve roots where the dura mater is relatively thin.[15]
3. However, disposition after extradural administration is more complex, since the drug disperses . . . through the dura and into nerves traversing the epidural space . . . the dura acts as a simple diffusion barrier . . .[16]
4. First, a portion of the drug crosses the dura mater to enter the CSF.[17]

Further evidence of the widespread belief that the dura mater is the primary meningeal permeability barrier comes from multiple in vitro studies in which investigators characterizing the permeability of human dura mater to a variety of drugs.[18-21]

However, these statements and studies aside, the dura mater is not the principal meningeal permeability barrier. We measured the permeability coefficients of morphine and alfentanil through each of the spinal meninges in both dogs and monkeys and found that the dura mater is actually the most permeable of the spinal meninges (Fig 4).[12] In fact, it is the very thin arachnoid mater that accounts for greater than 90% of the resistance to drug diffusion through the spinal meninges. The reason that this is the case is that, although the dura mater is much thicker than the arachnoid mater, it is composed primarily of collagen fibers[22] and the molecular distances between the individual fibers is large enough that it presents very little resistance to drug movement (Fig 5). The arachnoid mater, on the other hand, is composed of overlapping tiers of flattened epithelial-like cells that are connected to one another by frequent tight junctions and occluding junctions (Fig 5). It is this cellular architecture that accounts for the high resistance to drug movement

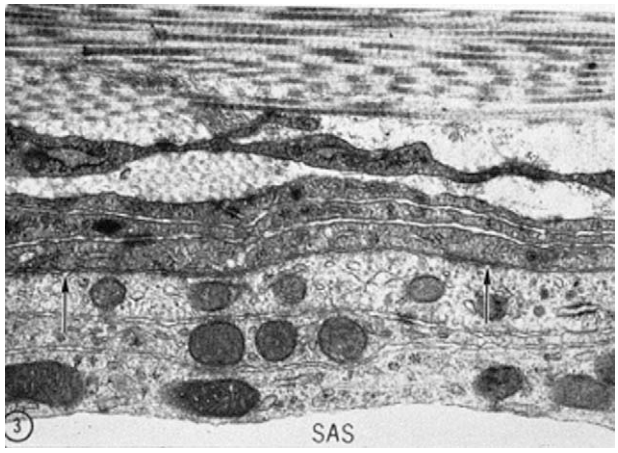

Fig 5. Transmission electron micrograph of the acellular dura mater (collagen bundles in the top one third of the micrograph) and the cellular arachnoid mater (bottom two thirds of the micrograph). Arrows indicate tight junctions, "SAS" indicates subarachnoid space, and circled "3" identifies a mitochondrion. Note that the collagen bundles of the dura mater course in multiple planes (parallel, perpendicular, and oblique to the plane of section), whereas the arachnoid cells lie in a single plane oriented cephalocaudad.

through the arachnoid mater. In fact, it is the low permeability of the arachnoid mater that explains the fact that CSF is contained in the subarachnoid space and not the subdural space.

Incorrectly assigning the dura mater the role of principal permeability barrier has also led to a misrepresentation of its role in the genesis of "postdural puncture headache." If we accept the probably correct notion that spinal headache results from persistent leakage of CSF through a hole in the spinal meninges, then it is essential that we correctly identify which meninx is responsible for the persistent leak. Given that CSF is contained within the subarachnoid space, it must be assumed, until proved otherwise, that the ongoing CSF leak is the result of a persistent hole in the arachnoid mater, not the dura mater. Unfortunately, we have simply reasoned, and not proven, that the nature of the hole in the dura mater is responsible for "spinal headache." This assumption is evidenced by numerous studies examining the size and shape of the hole in the dura and/or the rate at which fluid leaks through it after puncture with needles of differing size and tip design.[23-27] However, unless and until it is proved that it is the hole in the dura mater that causes spinal headache, these studies are of little or no value as mechanistic explanations for postmeningeal puncture headache.

That is not to suggest that the clinical observations that smaller diameter needles, pencil-point needles, and parallel insertion of beveled needles reduces spinal headache are incorrect. On the contrary, these observations are clearly correct, but the sophistry used to explain the mechanisms responsible for the clinical observations are just as clearly incorrect or at least unproved.

For example, consider the mechanistic explanation invoked to explain the clinical observation that inserting a bevel-tipped needle parallel to the spinal axis results in a lower incidence of spinal headache. In one of the earliest clinical studies of the effect of bevel orientation on postspinal headache, Mihic showed that parallel insertion of a needle's bevel decreases the incidence of postspinal headache. Unfortunately, despite the fact that his study did not examine the mechanism responsible for the difference in headache incidence, Mihic claimed to have confirmed Greene's 1926 hypothesis that, "if the bevel of the spinal needle were inserted parallel with the longitudinal dural fibers, the fibers would be separated and not cut."[28]

This idea has now become dogma and multiple current textbooks include Mihic's diagram as evidence supporting this mechanism.[29-32] They ignore the fact that Mihic's study did not examine a single dural fiber and his diagram was based only on Greene's 1926 hypothesis.

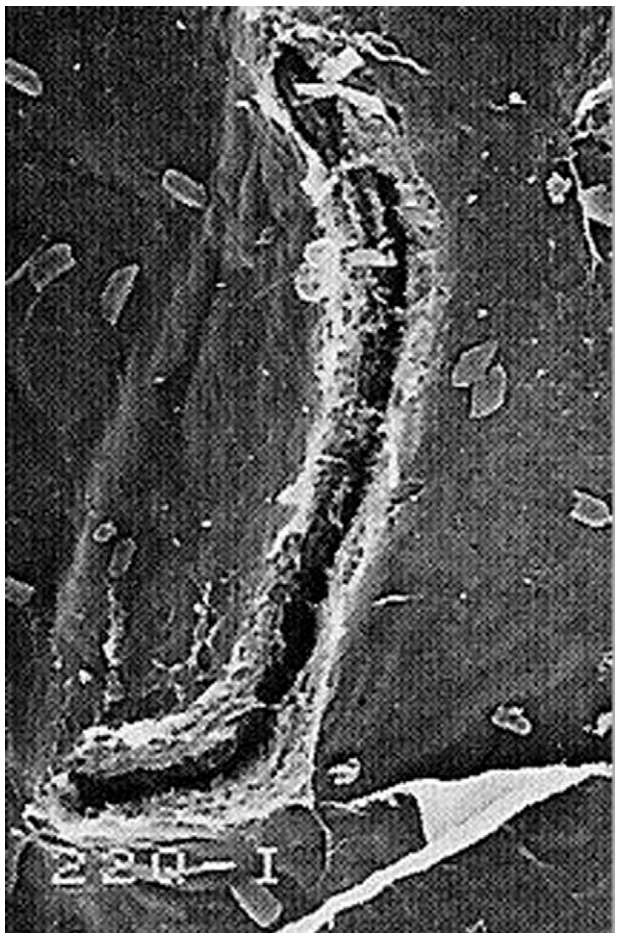

Fig 6. Scanning electron micrograph of the dura mater punctured by a beveled spinal needle. (Reprinted with permission from Raj PP (ed.) *Textbook of Regional Anesthesia*. New York: Churchill Livingstone; 2001.)

One major problem with this dogma is that it completely ignores the fact that Fink and Walker[22] (and others) showed that dura mater collagen fibers are not oriented only in a cephalocaudad direction as suggested (Fig 5). In fact, they do not have a predominate direction of orientation. Consequently, just as many dural fibers are likely to be cut by parallel orientation of a beveled needle as by perpendicular orientation.

Interestingly, although the collagen fibers comprising the dura mater are not oriented parallel to the long axis of the spinal cord, the cells of the arachnoid mater are (Fig 5). In addition, puncture of the arachnoid mater with a beveled spinal needle results in a narrow slit-like hole (Fig 6). Consequently, it is to be expected that parallel insertion of a beveled needle will disrupt/kill many fewer arachnoid cells than will perpendicular insertion. I

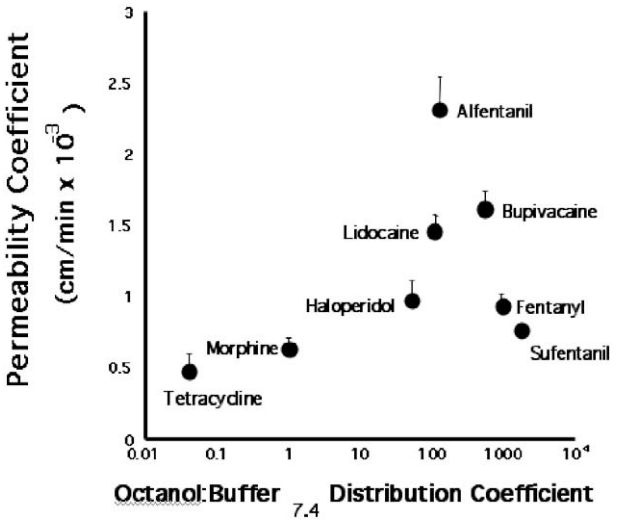

Fig 7. Plot of meningeal permeability versus octanol: buffer distribution coefficient (lipid solubility). Note that meningeal permeability is maximal for drugs of intermediate lipid solubility and that there is no difference in meningeal permeability among morphine, fentanyl, and sufentanil despite large differences in meningeal permeability. (Data from Bernards et al.[34])

am not trying to inject my own sophistry into this discussion by claiming that it is differential damage to arachnoid cells that explains the difference in headache rate between parallel and perpendicular insertion of beveled spinal needles. Instead, I am trying to use "sophistry" to generate a hypothesis that then must be tested and not simply accepted. This is the appropriate role for sophistry in science and medicine.

In short, we really do not know as much about the cause of spinal headache as we think we do. Until we actually identify whether it is the hole in the dura mater or the arachnoid mater that is responsible for the persistent CSF leak, we are unlikely to make much progress in preventing or treating this complication. Until we do clarify the etiology, we should at least refrain from using the term "postdural puncture headache" and perhaps adopt a more mechanistically neutral term like "spinal headache" or "postmeningeal puncture headache."

Identifying the arachnoid mater as the principal meningeal permeability barrier helps to explain the seemingly odd relationship between a drug's meningeal permeability and its lipid solubility. Conventional "wisdom" has maintained that drugs of greater lipid solubility will penetrate the spinal meninges (and other tissues) more readily. This reasoning led, in turn, to the widespread belief that lipid soluble opioids like fentanyl and sufentanil are better choices for epidural use than are less lipid soluble drugs like morphine because they should produce a more rapid onset of spinally selective analgesia. For example, consider the following statement from Shnider and Levinson's *Anesthesia for Obstetrics,* "The application of significant amounts of lipid soluble opioid should produce a rapid onset of analgesia."[33] However, the experimental data show that the meningeal permeability of morphine is not significantly different than that of fentanyl and sufentanil (Fig 7).[34] In fact, drugs of intermediate lipid solubility (e.g., lidocaine, alfentanil, bupivacaine) are more permeable than are drugs of high (fentanyl, sufentanil) or low (morphine) lipid solubility.

The reason for this is thought to stem from the fact that to diffuse from the epidural space to the subarachnoid space drugs must cross through the cells of the arachnoid mater because intercellular tight junctions prevent passage between these cells. To cross through the arachnoidal cell, the drug must first partition into the lipid bilayer of the arachnoid cell membrane and then diffuse across the lipid bilayer and then partition from the lipid bilayer into the aqueous extra- or intracellular space. Given that the arachnoid mater is 6 to 8 cell layers thick, this process must take place 12 to 16 times before the drug molecule reaches the CSF. Because lipid soluble drugs are thermodynamically more stable in the lipid bilayer than the aqueous intra- or extracellular spaces, they readily partition into it. However, because they are stable within the lipid bilayer, it is "difficult" for them to partition

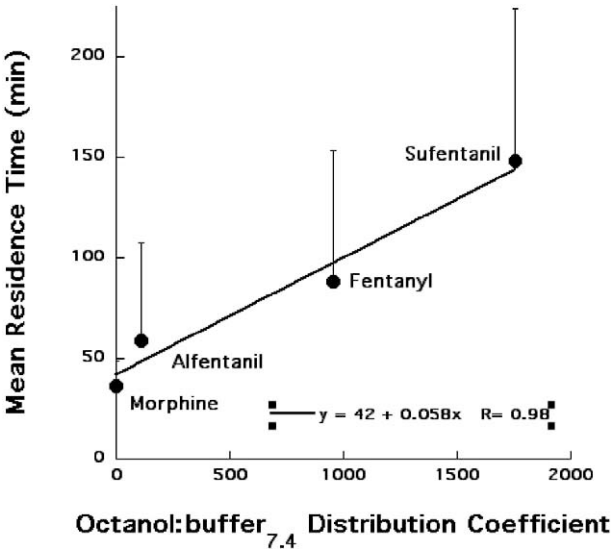

Fig 8. Plot showing the strong linear relationship between an opioid's octanol:buffer distribution coefficient (lipid solubility) and mean residence time in the epidural space. (Reprinted with permission.[39])

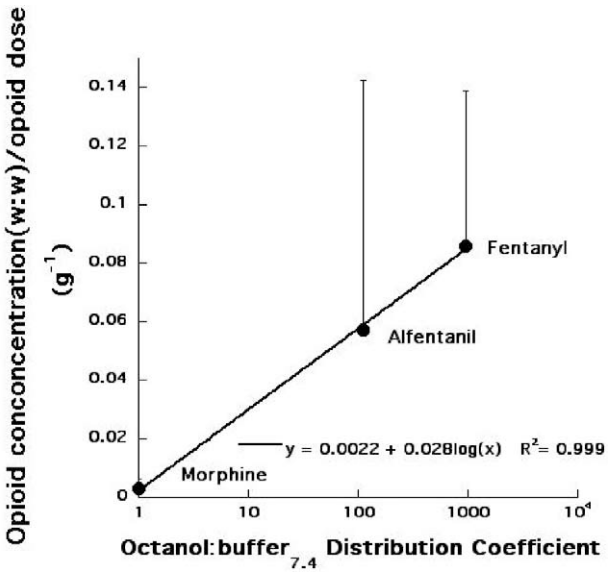

Fig 9. Plot showing the strong linear relationship between an opioid's octanol:buffer distribution coefficient (lipid solubility) and concentration in epidural fat. Importantly, drug "sequestered" in epidural fat has limited bioavailability in the spinal cord. (Reprinted with permission.[39])

from the cell membrane back into the aqueous intra- or extracellular space. This slows their diffusion through the arachnoid. Drugs that are poorly lipid soluble have the opposite problem. They are stable in the aqueous compartments but partition into the lipid bilayers with difficulty, and this slows their movement through the arachnoid mater. Because drugs of intermediate lipid solubility negotiate the aqueous-lipid interfaces with greater ease, they move through the arachnoid mater more readily.

Although this "biphasic" relationship between lipid solubility and arachnoid mater permeability may seem novel, it is not. The same relationship has been shown for skin penetration,[35] corneal penetration,[36,37] and even penetration of the blood-brain barrier.[38] Although the degree of lipid solubility that confers the greatest permeability differs among these different tissues, the general relationship between lipid solubility and permeability is comparable.

However, meningeal permeability is not the only aspect of epidural pharmacokinetics that is ruled by lipid solubility and perhaps not the most important. Another factor is the extent to which epidurally administered drugs are sequestered in epidural fat. This is an aspect of epidural drug delivery that has been largely ignored. However, we ignore it to our (and our patients') disadvantage. For example, we have recently shown that the residence time for opioids in the epidural space is linearly related to their lipid solubility (Fig 8) as is the amount of drug sequestered in epidural fat (Fig 9).[39] Because prolonged residence in the epidural space and the epidural fat reduces a drug's ability to reach the underlying spinal cord, this observation may explain the many studies showing that continuous epidural infusions of lipid soluble opioids (e.g., fentanyl and sufentanil) do not produce analgesia by actions within the spinal cord.[40-46] Rather, when administered by continuous infusion (as opposed to bolus administration), these drugs produce analgesia by uptake into the plasma and redistribution to the brainstem. (This may not be the case for bolus epidural administration of lipid soluble opioids. This is particularly true for fentanyl given that multiple studies have found that bolus fentanyl administration does produce analgesia, at least in part, by a spinal mechanism.[45,47])

Thus, despite decades of conventional wisdom asserting that lipid soluble drugs administered into the epidural space will have greater access to the underlying spinal cord, quite the opposite is true.

I would like to move from this brief look at misconceptions about the physiology and pharmacology of the epidural space and consider some misunderstood ideas about its anatomy.

Figures 10 and 11, which are taken from well-respected textbooks of regional anesthesia,[1,48] de-

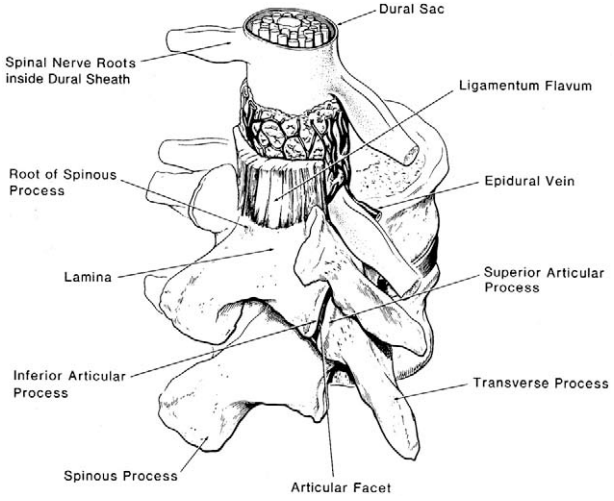

Fig 10. Diagram of the epidural space. Note the depiction of the epidural fat as a uniform sheet surrounding the spinal cord and the epidural venous plexus as a reticular network surrounding the spinal cord. These are common artist's renditions of the epidural space, but they are inaccurate. (Reprinted with permission from Cousins, MJ, Bridenbaugh, PO (eds.) *Neural Blockade in Clinical Anesthesia and Management of Pain*. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 1998.)

Fig 11. Another diagram of the epidural space. Note the depiction of the epidural fat as a uniform sheet surrounding the spinal cord and the epidural venous plexus as a reticular network surrounding the spinal cord. These are common artist's renditions of the epidural space, but they bear no relation to reality. (Reprinted from Covino B et al.[48])

pict a cutaway view of the epidural space. One can see clearly see that the epidural fat is depicted as a uniform sheet surrounding the dura mater and filling the entire epidural space. You can also see epidural veins forming a reticular network surrounding the entire spinal cord. This particular portrayal of the anatomy of the epidural fat and the epidural venous plexus (Batson's plexus) is not unique to these texts; in fact, it is found in almost every anesthesia textbook. The only problem with this version of anatomy is that it bears no relation to fact.

Figure 12 is taken from a 1981 paper by Meijenhorst,[49] who used computed tomography scanning to image the epidural veins. This figure shows very clearly that the epidural veins are restricted to the anterior epidural space. Similarly, Gershater et al,[50,51] who reviewed 1,200 cases of human venus epidurography, showed that the epidural veins lie in the anterior and lateral epidural space, which is why they were using epidural venography to diagnose vertebral disk herniation. More recently, Hogan[52] used cryomicrotome sections to examine the human epidural space and again showed the same anatomic distribution of epidural veins described by Gershater and Meijenhorst. Thus, textbook assertions aside, there is no anatomic evidence to support the depictions of epidural venous anatomy found in most anesthesia textbooks.

In addition to inaccurate representations of the epidural venous system, the epidural fat is also misrepresented in most textbooks. Almost all textbooks depict the epidural fat as a uniform cylinder surrounding the dura mater (Figs 10 and 11). However, there are no data to support this view. In fact, Hogan has shown quite clearly that the epidural fat is actually present as discrete pockets in the posterior and lateral epidural space (Fig 13).[52]

Given the overwhelming evidence that the epidural veins lie only in the anterior and lateral epidural space and that the epidural fat is distributed in the posterior and lateral epidural space, why do textbooks continue to portray this aspect of anatomy inaccurately? Too, given what has been learned from valid experiments about the physiology of the epidural space as it relates to drug delivery, why do so many incorrect ideas, with no experimental basis, persist in the anesthesiology literature?

Fig 12. Epidural venogram showing that the epidural venous plexus is largely restricted to the anterolateral epidural space. Some variation exists among individuals, but this is the predominate pattern. (Reprinted with permission.[49])

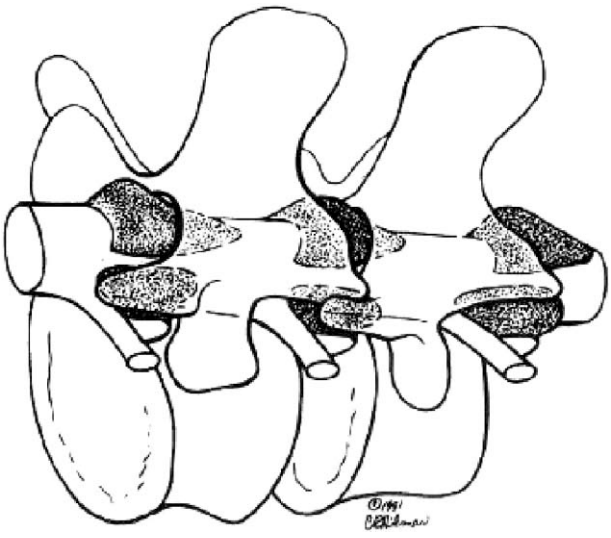

Fig 13. Diagram of the distribution of epidural fat (stippled areas) in the human epidural space. Contrary to what is normally depicted, the fat lies in discrete pockets and does not form a uniform epidural sheet. (Reprinted with permission.[52])

There are undoubtedly many reasons, but it is hard to conceive of any that are particularly valid. This may sound harsh, but given the ease with which information is obtained in our "modern" information age, it is hard to accept that the authors, reviewers, editors, and publishers who collect and disseminate the information we rely on for medical decisions cannot do a better job!

I would be disingenuous if I suggested that a great harm is being done to our patients because of the widespread acceptance of the inaccurate information I have presented. It is unlikely that this is the case. However, it is very likely that research time and money are being misspent and misdirected because experimental hypotheses are based on incorrect information (e.g., many tens of thousands of dollars have been spent in measuring fluid leakage through dura mater after a needle puncture in vitro, without a shred of evidence that it is the hole in the dura mater that contributes to spinal headache). Thus, adherence to old ideas, even in the face of countervailing data, necessarily delays development and discovery of new things.

Nor do I want to suggest that the substitution of sophistry for data is unique to the epidural space or even to anesthesiology. Clearly, it is not. For example, consider how many tens of thousands of people were sentenced to a bland diet because it made sense that spicy food must have something to do with peptic ulcer disease and gastritis or who underwent vagotomy because of the belief that acid secretion must be the proximate cause of gastric and duodenal ulceration. Fortunately, we now recognize that peptic ulcer disease is frequently caused by infection with *Helicobacter pylori,* not by spicy food or stomach acid. We owe this observation to the 2 Australian physicians (JR Warren and BJ Marshall) who persisted in opposing the medical establishment's conventional wisdom in the face of ridicule and derision of their data showing that bacteria were the cause of ulcerative disease in humans. Consider, too, the huge number of children who were sentenced to years of wearing a Milwaukee brace because it made sense to clinicians in the 1960s and 1970s that kyphoscoliosis could be cured by splinting the spine into correct anatomic position. Unfortunately, not only did the brace not cure the disease for which it was intended, it also caused significant orofacial and dental abnormalities[53-58] not to mention social hardship.

The point I do want to make, however, is that we cannot continue in this vein. Patients, governments, and third-party payers are rightfully demanding that we practice evidence-based medicine not sophistry-based medicine. To satisfy this demand, we must do a much better job of gathering data in a scientifically valid way and reporting it accurately to the physicians who will use the findings.

How can we accomplish this? Firstly, academicians (researchers, authors, reviewers, editors, and publishers) must be held to a higher standard. The examples I have presented of inaccuracies regarding spinal drug delivery found their way into the literature via the academic enterprise.

Holding academicians to a higher standard requires that clinicians read the literature with a more critical eye. Our parents were correct when they told us, "don't believe anything you hear and only half of what you read." The part that our parents never explained, however, is how to decide which half to believe. In science and medicine, it is the half that is supported by appropriate research. Statements in the literature that lack appropriate references should be viewed in much the same way that one would view statements from politicians—with caution and skepticism.

The flip side of holding academicians to a higher standard is that academic medicine needs greater support in this country. The pressure on academic medical centers to provide increasing amounts of clinical care and more resident teaching while at the same time competing for research funding is taking a toll. Evidence of this can be found in the marked decline in the number of studies from US authors being published in US anesthesiology journals.[59]

Finally, we must keep in mind that some current "beliefs," which are seemingly supported by appro-

priate data will, on occasion, turn out to be wrong. And, seemingly well-grounded practices in use today will be found "wanting" by the physicians who succeed us. But, the number of reversals of current practice will be minimized to the extent that we eschew sophistry and let appropriate data govern our practice of medicine.

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