Small trials, (*i.e.*, trials with relatively small numbers of subjects in each treatment group) cause difficulty in interpretation. Usually, this difficulty stems from a small trial's relatively weak power to detect differences between treatment groups. In this instance, the authors have detected a difference. Here, our concern is not with the trial's power, not that it may have missed an important true difference, but, rather, that it may have detected a difference where, in fact, no difference exists. This error, sometimes called a Type I or alpha error, would most likely be caused, in a small randomized trial, by initial inequality of the two groups. We see no convincing evidence to suggest such an error has occurred in this trial, but, with sample sizes of 25 and 28, our concerns remain.

If one assumes that the authors are correct and a real treatment difference exists, we, as readers, must take a further step. We must decide whether these results are generalizable to the patients we each see in our own practices.

Many who write about clinical trials draw a distinction between a trial designed to establish efficacy and one designed to establish effectiveness in clinical practice. These writers define a treatment's efficacy as the outcome observed in a specific population of patients who receive a narrowly defined treatment. Effectiveness is defined as the outcomes likely to be achieved when a treatment is introduced into wider clinical practice. If one narrowly defines the subjects admitted to the trial and the treatments applied, one sharpens the inference and increases the possibility that a real treatment effect will be uncovered. Yet, by limiting the patients involved and the treatments offered too narrowly, investigators impede generalizability. This tension between desirable homogeneity with resulting control and narrowness of inference is pitted against the desirability of heterogeneity of population and treatment yielding greater generalizability. In general, Yeager *et al.*'s design leans toward ease of generalization.

Nevertheless, generalizability remains a problem here. It is a problem each of us must consider as we decide how to use the authors' conclusions in our own work. Do the patients the authors describe sound like patients from our own practices? Does the general anesthesia given the standard treatment group in New Hampshire sound like the general anesthetic technique we use? Do the postoperative outcomes, the length of postoperative intubation and ventilation, and postoperative complications sound like those we observe in our own practice with high-risk surgical patients? These are difficult questions, and we must each answer them for ourselves. Would the institution of epidural anesthesia and analgesia as used by the authors be feasible in our practices? Could we actually deliver the treatment? Physicians will best determine appropriate anesthetic choice by considering, not only the authors' findings, but also the local experience of the anesthetist and surgeon and their facilities for caring for critically ill patients.

Some physicians will doubtless want to move ahead to adopt, in their own practices, the epidural anesthesia and analgesia regimen used by the present authors. Others will be more cautious and will wait until these conclusions have been confirmed in another trial; not because they distrust the authors' work, but simply because of the small size of the trial, they want a broader base for making such a major change in anesthetic practice.

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Neurotoxicology of Spinal Agents

DIRECT DELIVERY OF PHARMACOLOGIC agents into the central nervous system promises to achieve enhanced neuropharmacologic activity through avoidance of the blood–brain barrier. Worldwide recognition of this fact has led to clinical introduction of prolonged spinal delivery of a variety of analgesics, including narcotics, alpha 2 agonists, and peptides.[1–4] In fact, chronic intraventricular and spinal drug infusion has rapidly burgeoned to now include non-cancer pain patients,[5] neurologic patients with spasticity,[6] amyotrophic lateral sclerosis,[7] and Alzheimer's

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dementia.[8] Interestingly, introduction of spinal agents has occurred despite limited evidence that chronic delivery is nontoxic to meninges, nerve roots, or to the spinal cord itself. The prospective preclinical toxicologic study of chronic intrathecal bupivacaine in the dog, presented in this Journal by Kroin *et al.*,[9] is an important scientific step in rectifying this deficit.

In contrast with the established laboratory investigations of known noxious elements, such as lead or mercury, studying the chronic spinal effects of narcotics and local anesthetics involves asking the most basic questions. Which animal is best for the study of intrathecal or epidural agents? What are the key lesions to look for in the spinal cord? Are microscopically visible changes in myelin, neuronal body, or axons adequate indicators? Should we be assaying antecedent changes that affect neurotransmitter levels or receptors?

Spinal toxicity may involve multiple components of the axial nervous system. Vascular injury, vasoconstriction, and injury to supporting leptomeningeal structures with resulting repair are all as potentially devastating as direct damage to axons or their coverings. Recent studies document the capacity of some local anesthetics to alter spinal cord blood flow (SBF).[10] Yaksh has emphasized, in an earlier editorial, the crucial impact of putative intrathecal drugs on SBF, citing the lack of acute effect on SBF from intrathecal morphine.[11] Clearly, no current study of the chronic spinal cord model adequately addresses these questions.

It is remarkable that Kroin *et al.* found little impact on the leptomeninges or myelin of nerve roots following chronic bupivacaine administration *via* an indwelling catheter. In previous studies, multiple investigators have noted that chronic spinal cannulation and drug delivery induces extensive changes in the epidural and subarachnoid spaces of various animal models.*[12] The changes have included massive fibrosis with indentation of adjacent cord and roots, as well as epidural granulation tissue. During infusion of one synthetic opioid spinal parenchymal infarct, syrinx, and abscess were noted. Since some of these lesions were seen in control animals infused only with saline, the separation of drug-induced *versus* chronic catheter-induced changes is exceedingly difficult. Prior laboratory and clinical experience with lumboperitoneal catheters describe systems dedicated to passive drainage of CSF rather than drug delivery. Toxic reactions to the catheter itself insured that silicone catheters replace the more reaction-provoking polyethylene tubing.[13] Today, the spinal lesions occurring in cancer pain patients and laboratory animals could ultimately implicate catheter materials, and the spinal and vertebral anatomy of the particular animal model used, as well as the drug delivered! One must sort out whether the effects are from each element alone, or whether they are synergistic.

In comparison to opioids, which could theoretically overload receptor systems without producing a toxic effect, local anesthetics are membrane pump poisons at high concentrations. The clinical syndrome of spinal cord injury following intrathecal injection of 2 chloro-procaine has been studied by Gissen and colleagues.† They attributed this agent's intrathecal toxicity at accepted pharmacological concentrations to the combined effects of low *p*H and bisulfite in the solutions. Damage need not happen in an altered environment, however. In a series of studies, Kalichmann *et al.* have shown that swelling of the neuron is produced hours after exposure of the isolated rat sciatic nerve to most local anesthetics.[14] While Kroin *et al.* did not see light microscopic changes involving the cell body of the neuron or myelinated axons, they did not report early signs of injury, such as swelling of cytoplasmic organelles, like endoplasmic reticulum or mitochondria.

Though expensive and technically demanding, *in vivo* experiments are essential to answer unresolved questions. What duration and magnitude of spinal exposure in the animal is adequate to indicate reasonable safety before proceeding to humans? Is injection of a bolus of a drug comparable to continuous infusion of drugs? Which is the best animal model? Despite its limitations, the study by Kroin *et al.* is a welcome toxicologic step in the right direction. The clinical demand for alternative spinal agents to deal with spinal analgesic tolerance and resistant types of pain does not preclude the need to assess the toxic potential of even the most promising agents.

† Gissen AJ, Datta S, Lambert D: The chloroprocaine controversy. II. Is chloroprocaine neurotoxic? Regional Anesth 9:135–145, 1984.

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Axillary Plexus Block: Paresthetic or Perivascular

In this issue of Anesthesiology, Partridge *et al.*[1] present an interesting study on the functional anatomy of the brachial plexus sheath and its implications for anesthesia. To correctly understand the importance of their results and conclusions regarding the technique for axillary plexus blocks, it is necessary to briefly review the evolution of this blockade.

Several modifications of the technique for axillary plexus blockade have been proposed since it was introduced by Hirschel[2] in 1911. Although simple and with fewer complications than the supraclavicular technique, the axillary block did not become popular until its reintroduction by Burnham[3] in 1959. He described how the major brachial nerves were arranged around the axillary artery and how this neurovascular bundle was surrounded by "a sturdy fascia." Blockade of these nerves could be achieved by "bathing" them in a local anesthetic solution, and the landmarks for injection were the arterial pulse and the "pop" as the needle pierced the neurovascular fascia. Burnham injected only 16 ml of local anesthetic (8 ml on each side of the artery) in the average adult, but, in 42 cases, reported complete anesthesia with this volume. Based on dissections of seven cadavers, de Jong[4] calculated that 40–50 ml must be injected into the axillary neurovascular sheath (NVS) in the adult to obtain a sufficient "bath" of all major nerves, including the musculocutaneous, before it disappears into the coracobrachial muscle high up in the axilla. De Jong described the axillary neurovascular sheath, which surrounds the neurovascular bundle, as a "sturdy tube of deep fascia derived from the cervical prevertebral fascia," and that "thin areolar septa within the sheath support the individual nerves and vessels." Still, de Jong recommended one injection on each side of the artery, preferably after eliciting paresthesia or the aspiration of blood to verify a correct needle position.

The perivascular arrangement of the axillary plexus within a fascial tube was the basis for the single injection techniques later described by Eriksson[5] and Winnie[6,7]. Winnie suggested blocking the brachial plexus at various levels along the NVS by merely injecting the local anesthetic at a suitable level through a single centrally directed "immobile" needle. In 1977, Selander[8] presented the use of a 4–5 cm long catheter-over-the-needle that could be introduced into the NVS without searching for paresthesia. This flexible catheter could then be left for longer periods, allowing the block to be prolonged without further needling.

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