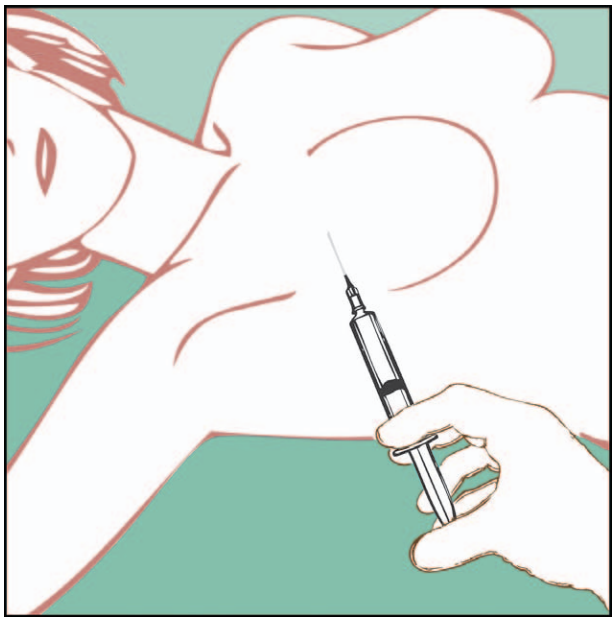
Prevention of Chronic Postsurgical Pain

The Ongoing Search for the Holy Grail of Anesthesiology



"The findings clearly demonstrate a short-term benefit for local wound infiltration in breast cancer surgery, but ... [failed] to definitively prove a long-term benefit ."

WE all know them. Perhaps it is the "funny uncle" you see only at family reunions, or the high-school friend who was sent away to live with relatives in a "better environment." Every profession has their share, those things that all too often get "tucked away into some closet," or "swept under a rug." In social work services, they might come under the guise of "domestic violence" or "sexual abuse." In the military, there are lots of them: "friendly fire" casualties for line officers, and nonbattle injuries (*e.g.*, back pain) for medical officers. For medicine in general, medical errors seem to occupy this exalted slot at the top of the publicity pyramid. It is our opinion that chronic postsurgical pain (CPSP) is the anesthesia equivalent of this phenomenon, the 800-pound gorilla in the room that everyone notices, but until recently few people acknowledged.

In this double-blind study by Albi-Feldzer *et al.*,[1] the authors sought to determine whether deep infiltration with local anesthetic could decrease the incidence of CPSP. A case in point for how our thinking about how CPSP has evolved is postamputation pain. In the aftermath of World War II, the most widely cited studies on postamputation pain routinely reported prevalence rates less than 5%, with many investigators attributing the phenomenon to concurrent psychosocial morbidity.[2] Today, the incidence of postamputation pain is generally considered to be between 50 and 80%.[3] The evolution of our understanding of postmastectomy pain parallels that of postamputation and other forms of CPSP, with the estimated prevalence rates having risen from approximately 25% in the 1980s,[4] to above 40% by current estimates.[5]

Part of this disparity has to do with the frequency and method of surveillance. Even my daughter in first grade (SPC) knows that the more frequently she asks a question, the more likely she is to hear an answer she likes. But as the number of surgical procedures and the operative mortality rate continue to move in opposite directions, the looming question about how to prevent CPSP takes on increasing importance. Previous studies evaluating membrane stabilizers, regional anesthesia, and *N*-methyl-D-aspartate receptor antagonists have all yielded mixed results to date.[6,7] This issue is even more paramount when one considers our poor track record in treating CPSP.

In this randomized, multicenter study,[1] the authors allocated 260 patients to receive local wound infiltration with either ropivacaine or saline approximately 1 h before the end of breast cancer surgery. What distinguishes this from other similar studies is the large number of patients enrolled (which should be sufficient to detect small differences), the different sites (which should enhance generalization), and the long-term surveillance using a wide array of validated instruments (which increases relevance). Not surprisingly, in the first 24 h postprocedure the treatment group reported lower pain scores than the saline group in the context of similar analgesic consumption. However, this pain reduction did not translate into lower pain scores after 24 h, less

Illustration: James P. Rathmell.

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◆ This Editorial View accompanies the following article: Albi-Feldzer A, Mouret-Fourme E, Hamouda S, Motamed C, Dubois PY, Jouanneau L, Jayr C: A double-blind, randomized trial of wound and intercostal space infiltration with ropivacaine during breast cancer surgery: Effects on chronic postoperative pain. ANESTHESIOLOGY 2013; 118:318–26.

opioid-related side effects, or a lower incidence of CPSP. Although patients who received ropivacaine experienced a trend toward less neuropathic pain as measured by DN-4 at 12 months, the significance of this finding under the umbrella of similar overall pain scores at 12 months and similar DN-4 scores at 6 months, is unclear. One way the authors could have done more to tease out any possible benefit in reducing the incidence of neuropathic pain would have been to separately survey the different types of postsurgical pain (*i.e.*, the intercostobrachial neuralgia/arm pain, scar pain, phantom pain), as each are mechanistically distinct. This has previously been done not only for CPSP,[5] but also for a host of other chronic pain conditions.

These findings are consistent with most,[8–10] but not all,[11] studies that failed to demonstrate even short-term meaningful benefit from pre- or intraoperative wound infiltration. This latter distinction is important, because the ability of an intervention administered before tissue injury to reduce the incidence of CPSP would likely come as a consequence of its ability to reduce the inflammatory cascade and resultant postoperative pain that follows tissue injury.[6,7,12] Yet in view of the clear-cut, short-term benefits demonstrated by this large, rigorously conducted multicenter study, the possible long-term benefits in select patients, and low risks associated with open wound infiltration in a monitored setting, one should be very cautious in flippantly dismissing this simple intervention as a possible tool in individuals at high risk for poorly treated postoperative pain. In those individuals who may be spared postoperative vomiting or posttraumatic neuropathic pain—which is associated with greater levels of disability than nonneuropathic pain states[13]—the advantages of this simple intervention by the surgical team might possibly outweigh the relatively low risks associated with the controlled administration of high amounts (3 mg/kg) of ropivacaine.

But we are still left with the seemingly Sisyphean task of how to prevent CPSP, and the question of whether or not the Holy Grail of preventive analgesia is even obtainable. These questions, and the search for this elusive magic bullet, are by no means unique to anesthesiologists. Currently, physicists are consumed by the search for the Higgs-Boson (a.k.a. "God") particle, and philosophers have wrestled with the "Meaning of Life" for at least as long as language has existed.

The factors that affect whether or not someone experiences CPSP include not only the magnitude of postoperative pain, but also the extent of preoperative pain, trauma during surgery, and a host of psychosocial variables, including but not limited to depression, psychological vulnerability, and anxiety[6,7,14]—all of which occur with increased frequency in cancer patients.[15] Whereas the effects of truly preemptive interventions such as gabapentinoid drugs and preoperative regional anesthesia are conflicting, the evidence supporting preemptive "treatment" is still more robust than for interventions performed after tissue injury has already occurred.[6,7] Another factor to consider is that postoperative pain scores were relatively low in this cohort. Not only will low pain scores decrease the likelihood of detecting a statistical difference between groups, but they will also mitigate the impact of any intervention designed to reduce pain. In addition, the fact that Brief Pain Inventory scores and pain interference actually increased over the course of this study—which defies the natural course of healing—suggests that undocumented confounding factors may have contributed to the lack of effect. These factors could include nonoperative interventions such as chemo- and radiation therapy and emotional factors such as depression and anxiety secondary to a prognosis that proved worse than anticipated.

So where does this study leave us with regard to postoperative analgesia in general and wound infiltration in particular? The findings clearly demonstrate a short-term benefit for local wound infiltration in breast cancer surgery, but taken in the context of the conflicting (though mostly negative) extant literature, they fail to definitively prove a long-term benefit. Similar to friendly fire, medical errors, "funny uncles" and other hot-button topics, our appreciation of the impact CPSP has on breast cancer survivors and other patients is just beginning to emerge, and the complete picture has not fully materialized. However, given the enormous impact that identifying a preventive anesthetic regimen that can reliably reduce CPSP would have on society, our search for the Holy Grail of Anesthesia will (and should) continue.

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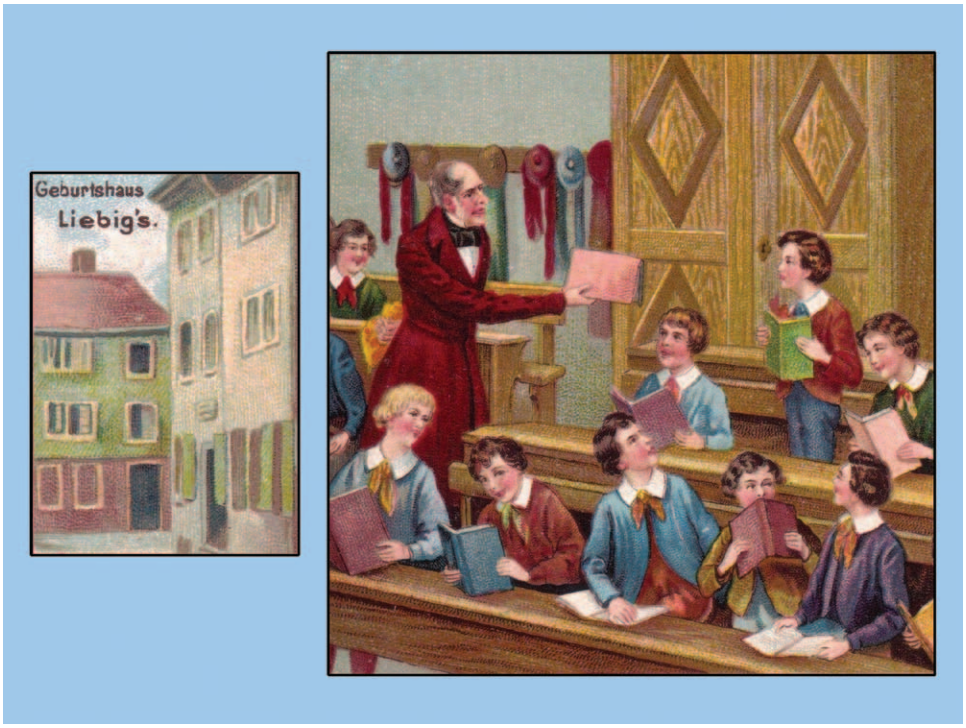
Darmstadt, Birthplace of Chloroform Pioneer Liebig



A German co-discoverer of chloroform, Justus Liebig was born in 1803 in a modest home (*left*) in the Hessian city of Darmstadt, a place noted for its sandy soil. Perhaps that soil helps explain young Liebig's future interests in agricultural chemistry and in formalizing organic chemistry. On the centennial of his birth, Liebig was depicted as "the genius at school" in "Liebig's Extract of Meat" advertising (*right*). Fortunately, Liebig's schoolboy aspirations of becoming "a chemist" were never derailed by his schoolmaster, who branded Justus as "hopelessly useless." Liebig's birthplace would later be immortalized by scientists there, who, after discovering the 110th chemical element, named it … "Darmstadtium."

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