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In Reply:—I thank Dr. Barasch for his insightful comments and for this opportunity to clarify my statement regarding the priority for confirmatory research. Actually, we agree that both laboratory and clinical research findings are strengthened, challenged, or refuted by further studies, and that subtle effects or those which are heavily dependent on the exact conditions of the experiment absolutely require confirmation. In my own field of interest, I note that it took very few studies to establish that the analgesic potency of epidural morphine greatly exceeded that of systemic delivery, but dozens of studies to establish that potency of epidural fentanyl differed little from that of systemic delivery. At this point, it would be very unlikely that yet another study comparing epidural to systemic morphine or fentanyl would meaningfully add to our understanding of analgesic potency, although other factors which were not previously examined in depth, such as opioid-induced immune modulation, might justify such a comparison. My point in the editorial[1] was not that confirmatory research was not wanted in this journal, but rather that we would consider articles addressing the study topics of the retracted papers as being entirely novel rather than confirmatory.

I also thank Dr. Barasch for the suggestion regarding electronic publication of selected articles, and we will discuss the advantages and disadvantages of creating this second class of article within our Editorial Board. As I have quickly observed, this journal, like others in medical science, must continuously and critically review its processes and products to better serve the research and clinical practice communities.

James C. Eisenach, M.D., Editor-in-Chief, ANESTHESIOLOGY. editor-in-chief@anesthesiology.org

Reference

1. Eisenach JC: Data fabrication and article retraction: How not to get lost in the woods (editorial). ANESTHESIOLOGY 2009; 110:955–6

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Concerns Regarding Ultrasound-guided Regional Anesthesia

To the Editor:—Although nerve injuries, including plexopathies, have long been reported, it is time to reflect on situations in which ultrasonic guidance has been used.[1] We are seeing reports of plexopathies after ultrasound-guided regional anesthesia and surgery, despite visualization of the injecting needle tip well away from neural elements.[2,3] At our institution, a case of brachial plexopathy after ultrasound-guided regional anesthesia recently occurred, resolving without sequelae. This disquiet has been increased by the knowledge that ultrasonic guidance for regional anesthesia is being accepted without any safety studies, efficacy studies, or equivalence studies for this particular application. For those of us involved in medical device development, these three steps are essential in assuring patient safety. So, we ask, are there effects heretofore unrecognized in exposing nerves—as in the case of panplexopathies, in particular—to the combination of ultrasound and regional anesthesia?

Nor is this concern limited to anesthesia. The accelerating use of routine sonograms since the 1980s and the accelerating incidence of autism in the 1990s, in light of Ang *et al.*, is troubling and deserving of investigation.[4] The letter of Davies may prove prescient.[5]

Almost 40 yr ago, when ultrasound was in its infancy, I worked in an ultrasound laboratory making and evaluating transducer equipment. There I learned that ultrasound is a nifty but high-energy technology with attendant effects, notably cavitation-related mechanical actions and free radical generation. These effects are demonstrably cytotoxic and combine with other cytotoxic agents to produce enhanced cell killing.[6,7]

So what is the concern? Personally, it is that operating room personnel gird their loins as if Armageddon is imminent when the C-arm image intensifier rolls into the room, but use ultrasound for regional anesthesia with little apparent concern for what we do not know: The effects of exposing neural structures to two different sources of neurotoxicity; *e.g.*, local anesthetics and ultrasound.

Ultrasound equipment used for regional anesthesia is described as "low-intensity," but it's still a lot of energy.[7–12] This, for those of us old enough to remember, is why x-ray machines are no longer found in shoe stores: While it may have been fun to see the bones of our feet on the screen, structures north of the feet should not have been exposed to unnecessary x-rays. *In vitro* studies describe ultrasound outputs of 5-50 W/cm^2 as "high-intensity." Inspection of product data for one system reveals derated average pulse intensity at maximal mechanical index of 439.3 W/cm^2.[13] What the apples and oranges comparisons between these values may be is not apparent; however, it is unclear what the low-intensity claim means. This quoted probe value is a calculated quantity derived from data in water and applying an assumed attenuation factor, because no one knows the actual tissue attenuation value.

Ultrasound demonstrates its cytotoxicity in municipal water purification systems and other applications. Thermal effects of high-intensity, focused ultrasound are employed in cancer therapy. However, in our application the cavitation-related shear forces and free-radical production attendant on the very high pressures and temperatures achieved when microbubbles implode in the high-frequency acoustical field are more concerning.[7] The pulse durations and pulse repeat frequencies used for ultrasound-guided regional anesthesia are quite capable of causing both of these effects. For example, ultrasound induces optimal apoptosis in cultured lymphoma cells with a 1 megahertz setup, intensity of 0.3 W/cm^2, 10% duty cycle, and 100-hertz pulse repeat frequency.[7] These values are entirely within the operational range of our equipment.

How local anesthetic toxicity and ultrasound mechanisms of cellular injury interact is unknown, not to mention the effects of adding, for example, chemotherapeutic agents to the mix. The folate inhibitor methotrexate is a risk factor for plexopathies after total shoulder arthroplasty, and there is a report of a patient on cisplantin sustaining brachial plexopathy after an ultrasound-guided interscalene block.[1,3] Cisplatin, like ultrasound, generates free-radicals.[8] Rather than the pharmacologic double crush the authors describe, perhaps it was in fact a triple crush.

Then there is the question of how tissue response to sonication changes with fluid-filling. Alteration of soft tissue attenuation characteristics by fluid injection is completely unknown, though the assumed

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attenuation factor probably underestimates the acoustic exposure in fluid-filled tissue.

A homogeneous tissue model with attenuation coefficient of 0.3 decibels/cm megahertz throughout the beam path is commonly used when estimating exposure levels. The model is conservative in that it overestimates the *in situ* acoustic exposure when the path between the transducer and site of interest is composed entirely of soft tissue. When the path contains significant amounts of fluid, as in many first- and second-trimester pregnancies scanned transabdominally, this mode may underestimate the *in situ* acoustic exposure. The amount of underestimate depends on each specific situation.[13]

So as, we gaze appreciatively at the "donut" surrounding the nerves, what is that increased exposure time doing on a cellular basis? We do not know. But the injection of fluid may alter tissue acoustic attenuation factors to more closely resemble *in vitro* conditions favorable to inertial cavitation, the effects of which increase with exposure time. The same product literature notes that we should structure the performance of studies to minimize exposure times.

In addition, bubbles represent an acoustical interface where energy release occurs. These bubbles may be iatrogenic or produced in the rarefaction phase of the acoustical wave.[14,15] Are practitioners assiduous about avoiding bubbles in the injected local anesthetic? What happens to a room-temperature, nondegassed liquid injected into a body-temperature subject? What of bubbles in a local anesthetic to which sodium bicarbonate has been added? Data show that bubbles decrease the cavitation threshold from 1.9-2.4 MPa to less than 0.65 MPa (filtered water data).[12] Product information for the SonoSite L38×/10-5 probe (SonoSite, Inc., Bothell, WA) shows an acoustical pressure of 2.345 MPa in the PW/Doppler mode or 2.89 MPa in the CPD mode. We have no information on the effect(s) of these potential sources of ultrasound cytotoxicity/neurotoxicity enhancement.

Ongoing studies in which thousands of ultrasound-assisted regional anesthetics have been performed without notable adverse effects are reassuring.[16] However, we remember other reports wherein the remarkable safety of spinals in tens of thousands of cases were discussed, and then a complication shows up; *i.e.*, transient neurologic symptoms. The flip side to those observations is that if effects do occur, such as those I have been discussing above, they are unusual events with high significance. Again, for those of us familiar with product development, one would want to specifically identify and mitigate just such occurrences through risk analysis. However, we have not performed or obtained that risk analysis for ultrasound-guided regional anesthesia.

In lieu of an outright moratorium on ultrasound-guided regional anesthesia, we must at least take reasonable precautions until additional research results are available: Limiting local anesthetic concentration to that necessary for achieving the desired result, limiting ultrasound exposure times, eliminating bubbles in injection solutions, not carbonating local anesthetics, warming local anesthetic solutions before use (degassing), and not spending time admiring the "donut." Until safety questions have been definitively answered, ultrasound-guided regional anesthesia deserves a continued high level of scrutiny.

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References

1. Lynch NM, Cofield RH, Silbert PI, Hermann RC: Neurologic complications after total shoulder arthroplasty. J Shoulder Elbow Surg 1996; 5:53–61
2. Koff MD, Cohen JA, McIntyre JJ, Carr CF, Sites BD: Severe brachial plexopathy after an ultrasound-guided single-injection nerve block for total shoulder arthroplasty in a patient with multiple sclerosis. Anesthesiology 2008; 108:325–8
3. Hebl JR, Horlocker TT, Pritchard DJ: Diffuse brachial plexopathy after interscalene blockade in a patient receiving cisplantin therapy: The pharmacologic double crush syndrome. Anesth Analg 2001; 92:249–51
4. Ang ES Jr, Gluncic V, Duque A, Schafer ME, Rakic P: Prenatal exposure to ultrasound waves impacts neuronal migration in mice. Proc Natl Acad Sci U S A 2006; 103:12903–10
5. Davies P: Hazards of ultrasound (letter). BMJ (Clin Res Ed) 1984; 289:559
6. Yoshida T, Kondo T, Ogawa R, Feril LB Jr, Zhao QL, Watanabe A, Tsukada K: Combination of doxorubicin and low-intensity ultrasound causes a synergistic enhancement in cell killing and an additive enhancement in apoptosis induction in human lymphoma U937 cells. Cancer Chemother Pharmacol 2008; 61:559–67
7. Feril LB Jr, Kondo T: Biological effects of low intensity ultrasound: The mechanism involved, and its implication on therapy and on biosafety of ultrasound. J Radiat Res 2004; 45:479–89
8. Jernberg A: Ultrasound, ions and combined modalities for increased local tumour cell death in radiation therapy [thesis]. Karolinska Institutet, Stockholm, Sweden: 2007; 1–35
9. Miyoshi N, Tuziuti Z, Yasui K, Iida Y, Riesz P, Sostaric JZ: Ultrasound-induced cytolysis of cancer cells is enhanced in the presence of micron-sized alumina particles. Ultrason Sonochem 2008; 15:881–90
10. Milowska K, Gabryelak T: Reactive oxygen species and DNA damage after ultrasound exposure. Biolmol Eng 2007; 24:263–7
11. Riesz P, Kondo T: Free radical formation induced by ultrasound and its biological implications. Free Radic Biol Med 1992; 13:247–70
12. American Institute of Ultrasound in Medicine: Consensus Document Section 6. Mechanical bioeffects in the presence of gas-carrier ultrasound contrast agents. J Ultrasound Med 2000; 19:120–68
13. M-Turbo Ultrasound System User Guide. SonoSite 2008
14. Juffermans LJ, Dijkmans PA, Musters RJ, Visser CA, Kamp O: Transient permeabilization of cell membranes by ultrasound-exposed microbubbles is related to formation of hydrogen peroxide. Am J Physiol Heart Circ Physiol 2006; 291:595–601
15. Skyba DM, Price RJ, Linka AZ, Skalak TC, Kaul S: Direct *in vivo* visualization of intravascular destruction of microbubbles by ultrasound and its local effect on tissue. Circulation 1998; 98:290–3
16. Swenson JD, Davis JJ: Ultrasound-guided regional anesthesia: Why can't we all just stay away from the nerve? Anesthesiology 2008; 109:748–9

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Green Breast Milk after Propofol Administration

To the Editor:—We would like to report an unusual observation of green breast milk after propofol administration. A 33-yr old woman underwent emergency laparoscopic removal of an ectopic pregnancy under general anesthesia with 474 mg propofol as a target-controlled infusion, fentanyl, remifentanil, mivacurium, and metamizole.

Preoperative medication included dimenhydrinate, metamizole, and piritramide, with additional metamizole, butylscopolamine, and metoclopramide postoperatively.

About 8 h after surgery, the patient reported that the first breast milk pumped showed a bluish green color, which changed to green during the course of the day, and which resolved 48 h postoperatively. Urine color was not monitored. Metabolites of phenoles like propofol (2, 6-diisopropylphenol) are a known cause of green urine.[1] The exact chromophoric compound responsible is not known. As propofol is also excreted into the breast milk,[2] it was suspected as a cause in this case.

A breast milk sample obtained 30 h after the initial color change was evaluated for possible propofol conjugated metabolite content. The sample was acid hydrolyzed, extracted with ethyl acetate, and analyzed by gas chromatography/mass spectroscopy, but there was no significant differ-

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