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Too Limited a View of What Clinical Anesthesiology Could Become

To the Editor:—Dr. Bernards' conclusion that gene therapy may be in our future, albeit in a very limited way, may be based on too limited a view of what clinical anesthesiology could become.[1] For example, several laboratories in departments of anesthesiology are looking for new classes of biopharmaceuticals that target gene expression, not to mention viral vectors and other means of inserting novel genes, for the purpose of preconditioning vital organs that are likely to be jeopardized during pending surgery. How many of us could have foreseen the confluence of gene therapy and cerebral preconditioning 10 yr ago? And how many unforeseen applications of gene therapy in anesthesiology will be under investigation in 2011?

Regarding Dr. Bernards' argument that the economics of anesthetic drugs is such that drug companies will not be rushing to market with novel gene therapies for our use because the world-wide value of all anesthetic drugs is less than the value of the United States' salsa market—if the application of gene therapy in anesthesiology were one-tenth the value of the United States' salsa market we would have more salesmen in our offices than we have patients in our operating rooms. Besides, since when is anesthesiology a passive vessel whose progress depends on what drug companies market for our use? Clinicians and researchers in anesthesiology delineate new problems, which define new needs, which generate new markets for new solutions. Pharmaceutical companies need our problems as much as we need their solutions. The relationship is synergistic, but it starts with us.

A "why bother?" attitude toward gene therapy and the view that it may not offer clinical anesthesiology as much as it offers other medical disciplines could become a self-fulfilling prophecy. Anesthesiology would do better to view itself and gene therapy as endeavors whose combined and separate future application is unlimited.

John Hartung, Ph.D., Department of Anesthesia, Downstate Medical Center, Brooklyn, New York. jhartung@downstate.edu

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In Reply:—Dr. Hartung makes several interesting points, although I find I cannot agree with them. His observation that "several laboratories in departments of anesthesiology are looking for new classes of biopharmaceuticals. . ." is probably an underestimate. Numerous departments, my own included, are involved in "gene-related" research that might someday have relevance to human pathobiology, but that is a far cry from these techniques becoming routine in the practice of medicine in general or anesthesiology in particular.

In some ways, our differences of opinion on this point may reflect differences in our view of what constitutes the practice of anesthesia. Because Dr. Hartung is not a physician this is understandable. But, it is an unfortunate fact that anesthesiologists, particularly those in the United States, have largely (though not uniformly) withdrawn form anything but very short-term involvement with patients. This fact is sadly documented in a recent article in this journal that underscored the marked decrease in the number of anesthesiologists practicing critical care medicine.[1] Because gene-based therapies require longer-term (*i.e.*, days to weeks or even life-long) involvement with patients it is unlikely that anesthesiologists will be routinely involved unless the unfortunate pattern of anesthesiologists withdrawing exclusively into the operating room environment reverses itself. This is not to say that we will not administer gene-directed drugs to our patients while they are in the operating room, but this is likely to be no more a part of the practice of anesthesia than is our administering an antibiotic before every surgical procedure.

I also think Dr. Hartung's suggestion that the availability of pharmaceuticals for our use need not be dependent on pharmaceutical companies, and the financial aspects of drug development is a bit naïve (admittedly my view may be a bit jaded). The Orphan Drug Act exists because pharmaceutical companies would not produce some drugs that people need if they could not make money doing so. More directly relevant to anesthesiology is the fact that we have known since the 1970s that xenon may be superior to any other "volatile" anesthetic currently in use; but we do not have it for our patients because no pharmaceutical company can figure out how to patent an element and make money selling it. Too, fentanyl and sufentanil have never been approved by the Food and Drug Administration for intrathecal use, despite the overwhelming evidence that their use benefits patients, because no drug company sees a financial value in doing the necessary work to get them approved.

Deep-throat's admonition to Woodward to "follow the money" is as true when trying to figure out what pharmaceutical companies may choose to develop as it was in trying to understand what was going on in Richard Nixon's Whitehouse. Like it or not, the financial aspects of pharmaceutical development will determine what gene-directed products are available for our use. Dr. Hartung is correct that we can participate in the process by identifying problems that might benefit from gene-directed pharmaceuticals, but doing so will not guarantee that such products will come to fruition.

Finally, I do not mean to suggest that my view of how this issue may evolve in the future is the preferred path. Rather, I sincerely hope Dr. Hartung's view prevails. But I would be disingenuous if I said I thought he was correct.

Christopher M. Bernards, M.D., Department of Anesthesiology, University of Washington, Seattle, Washington. chrisb@u.washington.edu

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Versatility of *LMA-ProSeal*™ for Probe-Passage

To the Editor:—We appreciate Dr. Hemmerling's idea that the esophageal Doppler probe can be used through the drainage port of the *LMA-ProSeal*™.[1] We have tried to insert a similar probe (Arrow International, Reading, PA, USA; diameter: 6.5 mm) through the port of *LMA-ProSeal*™ size 5. First, we could successfully put the well-lubricated probe down into the drainage port with a slight resistance. Next, we tried to insert the probe with a condom-type disposable probe jacket for preventing infection into the lubricated drainage port. We found, however, in this case, the probe jacket did not allow the probe to pass through because of its relatively large diameter.

We are concerned that our ability to use the esophageal Doppler with the *LMA-ProSeal*™ may be limited. However, the drainage port can easily be used to pass a thermometer and a stethoscope into the esophagus.

Rumiko Uda, M.D., Ph.D., Department of Anesthesiology, Osaka Medical College, Osaka, Japan. ane003@poh.osaka-med.ac.jp

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In Reply:—We thank Dr. Uda for her comment and interest in our letter. We believe that Dr. Uda refers to the Hemosonic® Doppler monitor (Arrow International, Reading, PA, USA) which uses a reusable Doppler probe. To use this probe repetitively, a sterile "jacket" has to be placed over the probe. This makes it impossible to insert the probe into the *LMA* port. The Hemosonic® Doppler probe cannot be used with the *LMA-ProSeal*™; the single-use esophageal Deltex® (Deltex Co., Branford, CT) Doppler probe, however, can be used with both *LMA* sizes (No. 4, 5). If one intends to frequently use the esophageal Doppler monitoring with the *LMA-ProSeal*™, one should take into account that this is only possible with the Deltex® system.

Thomas M. Hemmerling, M.D., Department of Anesthesia, CHUM, Montreal, Quebec, Canada. thomashemmerling@hotmail.com

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Local Administration of Morphine for Analgesia after Iliac Bone Graft Harvest

To the Editor:—I was very interested to read the article "Local Administration of Morphine for Analgesia after Iliac Bone Graft Harvest" and would like to commend the authors on a good article.[1] I would, however, like to mention two points that may have adversely influenced the resultsof the study discussed.

The patients were scheduled for elective decompressive cervical laminectomy; however, it is not recorded whether these patients were on opioids or nonsteroidal anti-inflammatory drugs (NSAIDs) for preoperative pain management. Chronic persistent cervicogenic pain can be a preoperative presenting complaint and preoperative analgesic usage can influence postoperative analgesic requirements.[2]

The authors also do not adequately describe the method of harvest site injection. Was contact with the donor site bone made or was this merely a local infiltration into the surrounding tissues? In trying to reproduce the local injection technique we were unable to avoid local tissue injection. This unfortunately would result in a third space tissue depot injection of 5 mg of morphine with slower systemic absorption, and hence a more prolonged effect. This morphine effect would be present during the first 24 h of the study period. Unfortunately, the authors did not report pain scores beyond the first 24 h.

Richard J. Sawyer, M.D., Department of Anesthesia, Toronto Western Hospital, Toronto, Ontario, Canada. rjsawyer@hotmail.com

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In Reply:— We appreciate the comments by Dr. Sawyer and would like to address the two issues he has raised. All patients enrolled in our study discontinued the use of nonsteroidal anti-inflammatory drugs (NSAIDs) 7 days before surgery. In addition, patients were excluded from this study if they required long-term (≥ 6 months) preoperative opioids with a history of chronic pain.

The autogenous bone was harvested through a lateral oblique incision just cephalad to the iliac crest using a similar surgical technique described in the literature.[1,2] The dissection then proceeded through the subcutaneous tissue down to the level of the iliac crest. After obtaining adequate exposure, an osteotome was used to cut through the crest in a sagittal direction exposing the bone marrow cavity. After

bone was collected using curettes, morphine 5 mg in 10 ml normal saline was infiltrated directly into the exposed cancellous bone and bone marrow cavity using a 22-gauge spinal needle. Care was taken not to merely inject the morphine into the local surrounding tissues. The cortical iliac crest was then closed with interrupted suture and the soft tissue was closed in layers.

We believe the analgesic effect observed in our study was probably mediated through local opiate receptors because patients given the same dose of morphine intramuscularly failed to demonstrate any significant analgesic effect compared with saline treatment. Although previously performed in a rat model of bone damage,[3] future human studies should also address the local administration of a μ-opioid receptor antagonist to further delineate the role of peripheral morphine for analgesia after iliac bone graft harvest surgery.

Scott S. Reuben, M.D., Department of Anesthesiology, Baystate Medical Center, Springfield, Massachusetts. scott.reuben@bhs.org

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Suggesting an Alternative to the Term "Double-blind"

To the Editor:—We read with interest about the randomized controlled trial by Kotani *et al.*, suggesting that preoperative insertion of intradermal acupuncture may reduce postoperative pain.[1] The authors concluded that the intervention "is easy to use, safe, and markedly improves postoperative analgesia." We would like to raise a few methodological concerns, such as the double-blind terminology, credibility testing of the subject blinding, and the location of acupuncture points.

The definition of double-blind design varies (table 1).[2–5] This study may or may not be double-blind, depending on which definition one follows. Considering the fact that it is not possible to mask the acupuncturist, their method is indeed of high quality. However, having seen clear discordance in the usage of the term "double-blind" in the reports, we believe it is more appropriate to use the phrase "subject- and assessor-blind."[6]

The authors are to be applauded for testing the credibility of sham control in a pilot study in a separate group of 40 patients. However, the sample size was almost certainly not large enough to test the equivalence of the two different intervention modalities. In addition, we feel that it is not valid to assume that the credibility of subject blinding is same in all circumstances; it requires checking in each study. For this task, the investigators could have simply asked the participating patients which type of acupuncture they believed they received, either real, sham, or "do not know."

Researchers are in general agreement that information given to the patient on random allocation of real or sham treatment influences subject's expectations. The authors "explained to each patient that insertion of intradermal needles is virtually painless and that they may or may not feel slight pain during insertion." Yet they failed to report whether patients were informed of the possibility of receiving either of two modalities. This may confound subject blinding.

It is questionable whether 2.5 cm to the left and right of the T9–L3 spinal vertebrae are acupuncture points equivalent to BL18–BL24, because in a widely accepted acupuncture textbook, the *cun* or "body inch" is a measure that is individual for each person.[7] The insertion of an intradermal needle on the location would be better understood as segmental dermatome stimulation.

Table 1. Definitions of Double-blinding

First Author	Definition	Comments
Pocock[2]	Subjects, physicians, and assessors	—
Altman[3]	Subjects and assessors	—
AMA[4]	1. Subjects, therapists, and assessors 2. Any two groups	—
Jadad[5]	Two groups of individuals involved.	Triple-blind: three groups of individuals involved (either subjects, therapists, and assessors, or subjects, assessors, and data analysis).
	Usually the two groups include the subjects and the assessors	Quadruple-blind: four groups of individuals involved (subjects, assessors, and data analysts)

AMA = American Medical Association.

Jongbae Park, K.M.D., Ph.D.,* Hyejung Lee, K.M.D. Ph.D., Adrian White, M.B. B.Ch., Edzard Ernst, M.D. Ph.D. F.R.C.P., *Department of Complementary Medicine, University of Exeter, Exeter, United Kingdom. j.b.park@ex.ac.uk

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In Reply:—The new term proposed by Park *et al.,* "subject- and assessor-blind," is reasonable. However, our study was well within the conventional meaning of double-blind, based on Jadad's criteria.[1] Although a physician in charge of acupuncture treatment could not be blinded, patients participating in the study, the anesthesiologists providing intraoperative care, the physicians evaluating pain and morphine-related side effects, and the investigators measuring various biochemical mediators were fully blinded to the group assignment.

A more serious concern is whether the patients were really blinded. We accurately explained the nature of the study to each patient. We emphasized that insertion of these tiny intradermal needles is nearly painless. Furthermore, patients could not see the procedure because the needles were inserted on the backs while they were in the prone position. The needles were secured with opaque adhesive tape and remained in position for the entire study period. Because it is rarely possible for patients to detect insertion of these painless needles, it is thus unlikely that individuals were able to determine whether they were in the active treatment group. Placebo effects that are the most critical bias in acupuncture studies were thus minimal in our study. In fact, postoperative analgesic effects were supported by significant differences in various objective parameters including supplemental morphine requirement, incidence of side effects, and endocrinologic responses.

Our study would have been strengthened by contemporaneously asking patients to guess to which group they were assigned. However, the preliminary study reported in our paper demonstrated that 50–60% of the patients were unable to guess to which group they had been assigned; 20–30% guessed acupuncture, and the remaining 20% thought they were in the control group. These findings clearly indicate that patients were really blinded to treatment assignment.

Park *et al.* asked about our identification of acupoints in the bladder meridian. We agree that there are no established methods to identify acupoints or to detect individual differences of localization.[2] Furthermore, gentle and strong acupuncture has a different effect.[3] We thus defined a specific distance to minimize individual variety in the acupuncture procedure. Inaccurate needle placement would be a major concern had we failed to demonstrate a treatment effect. But in our case the technique was successful, suggesting appropriate positioning of the intradermal needles.

Naoki Kotani, M.D.,* **Daniel I. Sessler, M.D.,** *Department of Anesthesiology, University of Hirosaki School of Medicine, Hirosaki, Japan. nao@cc.hirosaki-u.ac.jp

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Common Substrates for Pain and Analgesia

To the Editor:—Drs. Woolf and Max should be commended for their excellent article, "Mechanism-based Pain Diagnosis."[1] This article provides a rational contextual framework for the diagnosis and treatment of painful conditions, and a philosophical approach to drug discovery and evaluation. These guidelines will be indispensable for scientists developing new drugs, clinical researchers testing them, and also for clinicians, who will ultimately decide when and how to use new drugs in practice. In addition to the author's points, I would like to suggest a therapeutic focus that was not emphasized in the article, namely that of intracellular messengers conveying painful signals.

As pointed out by the authors and others,[2] a wide variety of receptors and ion channels are involved in transmitting painful stimuli. It is possible that signals generated by these systems converge on a more limited set of intracellular second messenger systems. For example, previous work by Woolf has identified one such potential integrative target, the extracellular signal-related kinase (ERK) signaling cascade.[3] Studies have also suggested that opioids could modulate ERK activity.[4,5] Other such integrative signals have also been proposed.[6] Therefore, a more parsimonious approach might be to focus on identifying changes in various intracellular signaling systems modulated in appropriate neural targets after painful stimulation. Also, potential analgesic compounds could initially be screened in *in vitro* systems designed to test for blockade of specific signals. Subsequently, candidate drugs could be identified for further testing in appropriate animal models, thus minimizing animal use.

It is conceivable that such an approach may aid in the effective mechanistic classification of painful conditions, and perhaps help improve the prediction of therapeutic response to particular analgesics.

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Howard B. Gutstein, M.D., The University of Texas—MD Anderson Cancer Center, Houston, Texas. hgutstein@mdanderson.org

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