

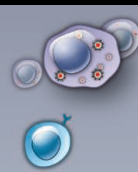
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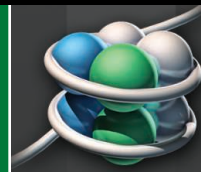
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LETTERS

edited by Jennifer Sills

Consent Contraindicated?

THE POLICY FORUM BY B. A. LIANG AND T. MACKEY ("REFORMING OFF-LABEL promotion to enhance orphan disease treatment," 15 January, p. 273) provides a thoughtful and provocative roadmap for the rational development of drugs that are approved for one indication and prescribed "off-label" for another.

However, we wonder whether the preclinical toxicological assessment, combined with the post-marketing safety assessment, provides adequate assurance of safety for the proposed off-label use. We are particularly concerned about the intrathecal and epidural (spinal), and perineural (next to a nerve) delivery of drugs developed for systemic administration. Preclinical research and human experience have taught us that such neuraxial drugs can evoke tissue toxicity unique to the spinal space (1, 2).

We agree that clinical trials are necessary to determine the efficacy of off-label uses. However, a universal requirement of such trials is that the subjects are permitted to make an informed risk assessment. Yet if preclinical safety data by the proposed route of drug administration do not exist—as is frequently the case for neuraxial and perineural administration—then there are no data to guide the subject in making the informed decision. In our experience, local institutional review boards (IRBs) often do not realize the unique risks of neuraxial or perineural administration, and studies are approved that cannot have provided subjects with required information.

The journals *Anesthesiology* and *Anesthesia and Analgesia*, where two of us are editors-in-chief (J.C.E. and S.L.S., respectively),

have frequently received submissions describing studies, approved by local IRBs, that involve neuraxial or perineural drugs not previously assessed for safety by these routes. It has raised the journals' concerns, leading to editorial policies requiring regulatory approval for all studies of off-label neuraxial administration, unless there is overwhelming evidence of safety through accepted or widespread use (e.g., intrathecal fentanyl) (3).

Liang and Mackey's recommendations are rational and will provide physicians with better therapies and more informed treatment decisions for many illnesses. However, in expanding off-label use, adequate preclinical safety data must exist when route, dose, indication, or population (e.g., adult versus neonate) are fundamentally different from those for which the drug has been approved. **TONY L. YAKSH,^{1*} JAMES C. EISENACH,² STEVEN L. SHAFER³**

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Response

YAKSH, EISENACH, AND SHAFER RAISE AN important issue associated with off-label drug use. As they point out, many IRB-approved studies do not take into account populations or route of administration when assessing disclosure adequacy and informed consent. Basing clinical drug research project approvals on work that uses different routes of administration or patient populations than that proposed cannot and should not be the basis for safety evaluations. If they are, IRBs are acting on inappropriate information, and through such faulty project approval would not be fulfilling their key role of ensuring study participant safety. We applaud *Anesthesiology* and *Anesthesia and Analgesia* for their policies addressing IRB limitations, and would strongly advocate

that all journals adopt similar policies.

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Polystyrene Overestimated

THE RANDOM SAMPLES PIECE "MAGIC MUSHROOM" (11 December 2009, p. 1463) cited data that polystyrene is now 25% of landfill volume. Overestimates of polystyrene (PS) in the waste stream have abounded since in the mid-1980s. Various surveys of waste generators and disposal facilities have found

that PS is actually a very small part of the overall waste stream. The latest survey we found (1) reported that expanded PS was 0.8% of wastes disposed in Connecticut, by weight. EPA's modeling (2) estimated that there were 2.6 million tons of PS discarded in 2008, which is a substantial amount. However, that tonnage is only 1.6% of all estimated discards. Even though PS is a low-density material, it is hard to believe that these relatively small masses could amount to 25% of the volume of discards in landfills. That's a good thing, because the stability of those landfills depends on more massive, cohesive materials comprising most of the wastes.

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2. U.S. Environmental Protection Agency, "Municipal solid waste generation, recycling, and disposal in the United States: Detailed tables and figures for 2008" (EPA, 2009), Tables 2 and 7; www.epa.gov/osw/nonhaz/municipal/pubs/msw2008data.pdf.

Suitability of Artificial Nests

THE REPORT "LOWER PREDATION RISK FOR migratory birds at high latitudes" by L. McKinnon *et al.* (15 January, p. 326) describes a massive artificial nest experiment spanning 29 degrees of latitude in the high Arctic. The authors suggest that artificial nests are appropriate for this sort of investigation because they allow a controlled study of predation risk. However, several studies show that artificial nests are not rep-

resentative of real nests (1–4), including one by the authors of the Report, which found that predators of artificial nests included arctic foxes, jaegers, and gulls, whereas predators of real nests were confined to foxes (4). The studies in *Conservation Biology* (1–3), which compare artificial nests and real nests in the same location, show different predation rates and completely different dominant predators. Such substantial differences indicate that meaningful ecological or conservation statements cannot be made on the basis of artificial nest studies. McKinnon *et al.* did not even attempt to correlate their findings with data from real nests from that region [e.g., (5, 6)].

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Response

FAABORG PRESENTS A VALID CONCERN THAT ARTIFICIAL NESTS SHOULD NOT BE USED TO INFER REAL NEST SUCCESS. For our study, we chose artificial nests to provide a controlled measure of relative predation risk across latitudes, not to infer real nest success. In real nests, success is not determined by predation risk alone, but by a combination of factors including nest defense capabilities (1), the degree of parental care (2), incubation duration (3) and break frequency (4), and nest density. Artificial nest experiments permit us to control for these sources of heterogeneity to make meaningful ecological statements concerning predation risk in arctic-nesting birds (5, 6)

It is true that when artificial nests are not physically representative of real nests, differences in predation rates and dominant predators may arise (7–9). This critique has merit in temperate and tropical regions where bird nest structure is often complicated and difficult to mimic and the diversity of potential predators is high. On the Arctic tundra, where we conducted our study, this critique is not compelling. Arctic-nesting shorebirds excavate a small depression (scrape) in the tundra, upon

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which uncovered eggs are laid. To mimic a real nest, artificial shorebird nests require no structural material, just eggs placed upon a depression with a small marker hidden underneath. In addition, the diversity of potential predators is low in the Arctic. Limited camera monitoring at both real and artificial shorebird nests in the Arctic has revealed the arctic fox (*Alopex lagopus*) as the dominant predator (10–12), with avian predators such as jaegers (*Stercorarius spp.*) and gulls (*Larus spp.*) depredating both real (11) and artificial nests (12) in smaller proportions. That detection of avian predators can be higher at artificial nests (12) could demonstrate that shorebirds' defense of their nests from

avian predators is more effective (13).

Estimates of real nest success may permit us to evaluate the effectiveness of anti-predator strategies, but the underlying risk of predation may remain masked if these strategies are indeed efficient. Measurements of anti-predator behavior along with the full suite of factors influencing the survival of real nests would be a better complement to our study than would measures of real nest success alone.

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CORRECTIONS AND CLARIFICATIONS

News of the Week: "Polish science reforms bring fear and hope" by E. Pain (19 March, p. 1442). Stanisław Karpiński's name was incorrect. The name has been corrected in the online HTML version.

Random Samples: "Magic mushroom" (11 December 2009, p. 1463). The statistic that polystyrene is now 25% of landfill volume was incorrectly attributed to the EPA. The EPA does not measure volume, only weight. The data were from a San Francisco State University study.

Letters to the Editor

Letters (~300 words) discuss material published in *Science* in the previous 3 months or issues of general interest. They can be submitted through the Web (www.submit2science.org) or by regular mail (1200 New York Ave., NW, Washington, DC 20005, USA). Letters are not acknowledged upon receipt, nor are authors generally consulted before publication. Whether published in full or in part, letters are subject to editing for clarity and space.