

Correspondence



Intimidation of Researchers by Special-Interest Groups

To the Editor: As the complainant in the example involving multiple chemical sensitivity syndrome discussed in “The Messenger under Attack” Sounding Board article by Deyo et al. (April 14 issue),¹ I wish to correct some of the authors’ many errors that grossly misrepresent this case and its applicability to their thesis.

At issue in the study by Simon et al. of the immunology of multiple chemical sensitivity² was not the investigators’ published results but what they withheld from peer review and publication — namely, a split-sample analysis of the reliability of their immune laboratory, showing, as Dr. Simon himself later disclosed, that “the reliability on most of their measures is no better than chance.”³ All the inquiries into this case confirmed, as I alleged, that the authors withheld this information. We differed only on whether the withholding of this information combined with the authors’ published conclusion that their findings “strongly militated” against an immunologic basis for multiple chemical sensitivity² constituted scientific misconduct.

As for inhibiting research by intimidating investigators and funding agencies, my complaint actually led directly to new funding by the Washington Department of Labor and Industries of a more comprehensive multicenter study of the immunology of multiple chemical sensitivity, which is now under way at Johns Hopkins — a study designed in part to address the very questions of test reproducibility at the core of my complaint.

Other errors of fact and misrepresentations include the following: First, the unsubstantiated claim that “the investigators were attacked by parties whose financial interests

depended on immunodiagnostic testing: plaintiffs’ attorneys, advocacy organizations for people with chemical sensitivity, representatives of immunologic-testing laboratories, and prominent expert witnesses.” Only I filed a complaint, and neither I nor MCS Referral & Resources (the advocacy organization I direct) has any financial interest in diagnostic testing. Second, neither I nor anyone else requested that the “investigators’ [medical] licenses be revoked.” Third, no patients were “encouraged to attack” Dr. Simon’s credibility.

Only the University of Washington’s inquiry process took longer than allowed, owing to an unprecedented review by three deans, including Dr. Omenn. They took three months to overrule two faculty members whose independent initial inquiries had both resulted in a recommendation for a full investigation. One of these anonymous faculty members wrote: “This paper is weak and should not have been published as it stands. Retraction of the paper should be considered as an option. Publication of further papers on these matters could destroy the reputations of the authors [underlining in original].” How prescient — and still true.

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1. Deyo RA, Psaty BM, Simon G, Wagner EH, Omenn GS. The messenger under attack — intimidation of researchers by special-interest groups. *N Engl J Med* 1997;336:1176-80.

2. Simon GE, Daniell W, Stockbridge H, Claypoole K, Rosenstock L. Immunologic, psychological, and neuropsychological factors in multiple chemical sensitivity: a controlled study. *Ann Intern Med* 1993;119:97-103.

3. Simon GE. In: Proceedings of the Conference on Low-Level Exposure to Chemicals and Neurobiologic Sensitivity, Baltimore, April 6-7, 1994. *J Toxicol Industrial Health* 1994;10:526-7.

To the Editor: As the treating physician for all 41 of the patients in the study by Simon et al., I am uniquely situated to bring to the attention of my colleagues issues of concern regarding the design and context of this study. I was asked by one of the researchers to select patients for evaluation. Believing the study planned to refine diagnostic criteria for multiple chemical sensitivity, I wanted to see

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how my assessments corresponded with the panel's conclusions. After only a desultory inquiry, the researchers erroneously assumed that all 41 patients had multiple chemical sensitivity. In fact, a majority (23 of 41) did not, in my assessment as treating physician, fit the profile for multiple chemical sensitivity; 18 did fit the profile, 10 did not, and in the case of 13 the results were uncertain. Moreover, the control subjects were patients from the musculoskeletal-pain clinic, in which case it might be expected that the inclusion of patients with autoimmune diseases (e.g., lupus and rheumatoid arthritis) would obfuscate the significance of autoimmune test findings. Not surprisingly, the study found no meaningful correlations.

Additional issues arose when the unpublished study was released to the defense counsel in a major toxic-injury case, who used it for cross-examination. At that time, I learned the study had been underwritten financially, at least in part, by the defendant. When, as here, research yields outcomes consistent with the interests of the entity funding the study, issues of increasing importance within the medical and scientific community are raised.^{1,2}

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1. Thompson DF. Understanding financial conflicts of interest. *N Engl J Med* 1993;329:573-6.

2. Kassirer JP, Angell M. Financial conflicts of interest in biomedical research. *N Engl J Med* 1993;329:570-1.

To the Editor: Deyo et al. infer that the North American Spine Society (NASS) criticized the clinical practice guidelines for acute low back pain in adults devised by the Agency for Health Care Policy and Research (AHCPR) because "nonsurgical approaches were recommended in most circumstances." The NASS, whose membership and leaders include spine care physicians in both operative and nonoperative specialties, promotes appropriate care for acute and chronic back pain, which for the vast majority of patients is nonoperative. The NASS questioned how the guidelines were derived and how they were to be applied, not what was said about surgery.¹

Deyo et al. reason as follows: Of the 32 authors of the guidelines, 2 had published articles critical of spinal-surgery fusion. The NASS criticized the guidelines. Therefore, the society was vengeful because its members had special interests in fusion surgery. Using similarly flawed logic, Deyo et al. mention the Center for Patient Advocacy, which lobbies for patients' interests over a wide spectrum of health care issues including maternity rights, because its founder was a NASS board member. The NASS neither funds nor participates in policy setting of the Center for Patient Advocacy. We should pause to consider whether legitimate critics should be censored on the basis of such reasoning.

The NASS vigorously supports peer-reviewed and bias-free research as well as government funding of research. In fact, it has been supportive of some initiatives of the AHCPR. The formulation of data-supported clinical guidelines is a difficult task. However, criticism is important, especially when the work is generously supported by taxpayer funds. Rather than aiming at imagined inappropriate

ideologues, the authors should concern themselves with valid points about the guidelines raised by the NASS and by the politicians who objected to funding similar projects. It is grossly improper in today's society to suggest that investigators whose work is funded by a government grant should be shielded from open scientific critical reviews by professional societies.

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1. North American Spine Society statements regarding the AHCPR's clinical practice guideline: acute low back pain in adults. Rosemont, Ill.: December 7, 1994.

The authors reply:

To the Editor: Mr. Donnay implies that investigators are attacked only in formal complaints. We pointed out that attacks take many forms. Simon et al. were attacked by several other parties, including attorneys and representatives of immunologic-testing firms, one of whom complained to the state medical disciplinary board. Mr. Donnay repeatedly violated institutional policies regarding confidentiality of inquiry proceedings, attempted to circumvent appeals processes, and filed personal complaints against local and federal officials who found against his claims.

The claim that Simon et al. withheld data that undermined their conclusions was unambiguously dismissed by inquiries at the University of Washington, Group Health Cooperative, the Washington Department of Labor and Industries, and the federal Office of Research Integrity. The reliability data in question were distributed to scientists in the field, including the medical director of Mr. Donnay's organization, 21 months before the paper was published.¹ No issues of concern were raised. The remark by Simon referred to the clinical use of immunologic data to classify patients, a topic far from that of the paper.

The faculty member quoted had seen only the misleading accusations, not the response. A thorough inquiry reversed this cursory impression. We note that special-interest groups can make groundless accusations faster than scientists can refute them.

Dr. Baker consulted in designing the eligibility questionnaire, and his billing and chart diagnoses were used. Only after the publication of the paper¹ did he question the diagnoses. He never responded to repeated requests to "re-diagnose" the chemically sensitive group. As reported,¹ the control group included patients with "musculoskeletal injury" but excluded those with systemic rheumatologic illnesses. The study was jointly funded by Boeing and the International Association of Machinists, representing defendants and plaintiffs in the lawsuit mentioned.

We never suggested that scientists or funding agencies should be protected from criticism, but rather from unwarranted political attacks. When the NASS encouraged protests to Congress, its letterhead listed 12 board members, of whom 11 were surgeons. That letter attacked only two articles published by our research team, both concerning spinal-fusion surgery,^{2,3} repeatedly charging the re-

search team with “anti-surgery bias.” An orthopedist member of the NASS wrote to the American Academy of Orthopaedic Surgeons (AAOS) that the article by Turner et al.³ “is, I think, designed as a resource for people to deny authorization for spinal fusion surgery. . . . [T]he North American Spine Society is taking this on.” The AAOS reviewed both articles, judging one² to be of “exceptionally high quality” and the other³ to be a “fair representation of the literature for spinal fusion for low back disorders.” The NASS currently faces lawsuits alleging that some of its continuing-education activities were largely promotional activities for pedicle-screw devices.⁴

It remains true that a NASS board member founded the Center for Patient Advocacy. In its fundraising letter, the center cited restrictions on pedicle screws as a reason for attacking the Food and Drug Administration FDA. Thoughtful criticism is an important part of science, but cutting or eliminating the budgets of federal agencies discourages disinterested investigation.

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1. Simon GE, Daniell W, Stockbridge H, Claypoole K, Rosenstock L. Immunologic, psychological, and neuropsychological factors in multiple chemical sensitivity: a controlled study. *Ann Intern Med* 1993;119:97-103.
2. Deyo RA, Cherkin DC, Loeser JD, Bigos SJ, Ciol MA. Morbidity and mortality in association with operations on the lumbar spine: the influence of age, diagnosis, and procedure. *J Bone Joint Surg Am* 1992;74:536-43.
3. Turner JA, Ersek M, Herron L, et al. Patient outcomes after lumbar spinal fusions. *JAMA* 1992;268:907-11.
4. Borzo G. Societies caught in fraud cases: product liability lawsuits raise questions about CME vs. promotion. *American Medical News*. May 12, 1997;1, 24-5.

The article by Deyo et al. elicited other letters from readers. Two are published below with responses.

To the Editor: Deyo and colleagues describe attacks by industry on scientists who publish data relevant to “hot-button” policy issues or large liability claims. The epidemic of tryptophan-associated eosinophilia–myalgia syndrome exemplifies both these issues.

In 1989, over 1500 cases of eosinophilia–myalgia syndrome and approximately 40 deaths were reported in the United States among persons ingesting tryptophan. Epidemiologic, chemical, and toxicologic studies showed that impure tryptophan produced by a large Japanese petrochemical company, Showa Denko K.K., caused the syndrome.^{1,2} As a result of these studies, the FDA removed tryptophan from the market, Showa Denko was sued for approximately \$2 billion, and congressional hearings were held on the safety and regulation of dietary supplements.

The scientists whose studies implicated the company and unregulated tryptophan in the pathogenesis of eosinophilia–myalgia syndrome were attacked by the company and industry-related interests. These attacks included frequent prepublication Freedom of Information Act lawsuits and the spreading of rumors of nonreproducibility of scientists’ peer-reviewed studies, whose major findings³ were

in fact replicated in peer-reviewed papers.^{4,5} The numerous claims against scientists from seemingly independent sources were facilitated by a Showa Denko research advisory council, which paid consulting fees and “was almost the sole source of funds for research on [eosinophilia–myalgia syndrome] since 1990.”⁶

These claims, based on one flawed study funded by Showa Denko (data on 2 male and 2 female rats studied at 12 time points were reported as the sum of data on 48 rats; Showa Denko’s attorneys refused the FDA’s offer to confirm the test material’s chemical identity), were eventually published in a supplement to the *Journal of Rheumatology*, “sponsored entirely by Showa Denko K.K.”⁶ The editors and most authors in this sponsored supplement received grant support and consulting fees from the company, belying the editors’ claims that the “peer review process of the supplement . . . was entirely independent of Showa Denko K.K.”⁶

Publication of papers given the guise of unbiased peer review in journal supplements sponsored by corporations involved in litigation over large liability claims undermines the credibility derived from the publication of scientific findings after truly unbiased peer review. To avoid this, the standards of peer review should be clear and consistent, and full disclosure should be made regarding the source and amount of sponsorship in the citation of the supplement.

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1. Slutsker L, Hoesly FC, Miller L, Williams LP, Watson JC, Fleming DW. Eosinophilia–myalgia syndrome associated with exposure to tryptophan from a single manufacturer. *JAMA* 1990;264:213-7.
2. Belongia EA, Hedberg CW, Gleich GJ, et al. An investigation of the cause of the eosinophilia–myalgia syndrome associated with tryptophan use. *N Engl J Med* 1990;323:357-65.
3. Love LA, Rader JI, Crofford LJ, et al. Pathological and immunological effects of ingesting L-tryptophan and 1,1'-ethylidenebis [L-tryptophan] in Lewis rats. *J Clin Invest* 1993;91:804-11.
4. Silver RM, Ludwicka A, Hampton M, et al. A murine model of the eosinophilia–myalgia syndrome induced by 1,1'-ethylidenebis (L-tryptophan). *J Clin Invest* 1994;93:1473-80.
5. Emslie-Smith AM, Mayeno AN, Nakano S, Gleich GJ, Engel AG. 1,1'-Ethylidenebis[tryptophan] induces pathologic alterations in muscle similar to those observed in the eosinophilia–myalgia syndrome. *Neurology* 1994;44:2390-2.
6. Clauw DJ, Pincus T. The eosinophilia–myalgia syndrome: what we know, what we think we know, and what we need to know. *J Rheumatol Suppl* 1996;46:2-6.

The editor of the *Journal of Rheumatology* replies:

To the Editor: Dr. Sternberg comments that the “publication of papers given the guise of unbiased peer review in journal supplements . . . undermines the credibility derived from . . . truly unbiased peer review.” She questions the *Journal of Rheumatology*’s standards of peer review and disclosure as exemplified in the publication of our supplement on eosinophilia–myalgia syndrome.¹

In our supplement, however, we made a formal disclosure statement that listed the names of all those invited to the symposium, those who attended, and the relationship of all authors to Showa Denko K.K.² (Dr. Sternberg declined an invitation to attend.) With my help and that of the journal’s editorial committee, our peer-review process was directed by our guest editors Clauw and Pincus.^{2,3}

Critical discussion of each presentation was also included.¹ Moreover, Kilbourne et al., from the Centers for Disease Control and Prevention, as well as editorialists Belongia and Gleich, from the Mayo Clinic, contributed their independent views.^{4,5} None of these authors had any relationship with Showa Denko K.K.

In my opinion their reports and our editorial process qualify as unbiased peer review.³⁻⁵ Thus, despite Dr. Sternberg's concern, I believe that our supplement informed our readers about this medical event better than if we had not published it.

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1. Clauw DJ, Pincus T, eds. Eosinophilia-myalgia syndrome: review and reappraisal of clinical, epidemiologic and animal studies symposium, December 7-8, 1994, Georgetown University, Washington, DC. *J Rheumatol Suppl* 1996;46.
2. *Idem*. The eosinophilia-myalgia syndrome: what we know, what we think we know, and what we need to know. *J Rheumatol Suppl* 1996;46:2-6.
3. Gordon DA. The peer review process and sponsored supplements. *J Rheumatol* (in press).
4. Kilbourne EM, Philen RM, Kamb ML, Falk H. Tryptophan produced by Showa Denko and epidemic eosinophilia-myalgia syndrome. *J Rheumatol Suppl* 1996;46:81-8.
5. Belongia EA, Gleich GJ. The eosinophilia-myalgia syndrome revisited. *J Rheumatol* 1996;23:1682-5.

To the Editor: The article by Deyo and colleagues¹ on the intimidation of researchers by special-interest groups was timely. Unfortunately, such intimidation continues.^{2,3}

Dr. David Kern is an occupational-medicine physician who has taught at Brown University's medical school for over a decade. Between 1994 and 1996, Dr. Kern evaluated 6 workers at a Microfibres nylon flocking plant who were given a diagnosis of interstitial lung disease; in a work force of 150, this represented an exceedingly high prevalence and a finding of clear public health importance.

Dr. Kern prepared an abstract for presentation at an upcoming meeting, describing his findings from the investigation. The company demanded that it be withdrawn, threatening legal action. Consequently, Dr. Kern withdrew from his consulting relationship with the company and consulted officials at Brown University and its affiliate, Memorial Hospital of Rhode Island, where the occupational-medicine clinic is based. The university and its affiliate urged that he comply with the company's demand, and later the president and physician-in-chief of Memorial informed Dr. Kern that the occupational health service had closed.

The hospital administration has insisted that because Dr. Kern submitted his abstract, his academic freedom was not violated, ignoring the fact that Dr. Kern's clinical program was abolished. A confidentiality agreement that Dr. Kern signed a year before the workplace investigation began has been cited by the administration as justifying Dr. Kern's censure. In fact, the confidentiality agreement pertained only to the disclosure of commercial trade secrets, not to health data, and was signed in the context of a plant visit, not a research project.

Conflicts such as these are unfortunately not rare in occupational medicine. Dr. Kern investigated an outbreak of interstitial lung disease and communicated objectively

with management, labor, and the scientific community. As a result, Dr. Kern's academic freedom has been threatened, his doctor-patient relationships undermined, his public health-reporting responsibilities blocked, and his livelihood and reputation jeopardized.

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SANDRA MOHR, M.D., M.P.H.

HOWARD FRUMKIN, M.D., DR.P.H.

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1. Deyo RA, Psaty BM, Simon G, Wagner EH, Omenn GS. The messenger under attack — intimidation of researchers by special-interest groups. *N Engl J Med* 1997;336:1176-80.
2. Roush W. Publishing sensitive data: who calls the shots? Secrecy dispute pits Brown researcher against company. *Science* 1997;276:523-4.
3. Freyer FJ. Doctor: hospital tried to silence health-risk findings. *Providence Journal-Bulletin*. April 25, 1997:1, 11.

A spokesperson for Brown University School of Medicine replies:

To the Editor: Brown University School of Medicine fully recognizes the importance of research conducted by its faculty members, including Dr. David Kern, and recognizes their right — even their responsibility — to publish their results. Although Dr. Brodtkin and his colleagues are also supportive, they provide an incomplete description of Dr. Kern's situation and create the erroneous perception that Brown University School of Medicine provides less than steadfast support of academic freedom. In fact, Dr. Kern's dispute with his employer — Memorial Hospital — and with the textile-processing company at which he conducted investigations involved several matters, only one of which was his publication of an abstract at a national meeting. Memorial Hospital is a separate and independent entity and is neither owned nor controlled by Brown University.

Brodtkin et al. are mistaken in their belief that a confidentiality agreement signed by Dr. Kern at the outset applied only to commercial trade secrets. Trade secrets was but one item in a series of terms in that agreement; subsequent paragraphs in the agreement placed even tighter restrictions on the dissemination of information derived during work at the company. By signing the agreement, Dr. Kern indicated his concurrence with these restrictions.

Brown goes to great lengths to protect academic freedom, particularly the freedom to publish. Our faculty rules prohibit classified research for that very reason, and Brown's Office of Research Administration reviews all contracts, grants, and other agreements to be certain that they do not pose unacceptable restrictions. Dr. Kern persisted in working at the company without a written contract, leaving him with no prior understanding about the right to publish and no mechanism for conflict resolution.

That Dr. Kern chose to frame the current controversy as a struggle over academic freedom is unfair to Brown. The controversy was already full-blown when Dr. Kern first involved the university. Neither he nor the hospital consulted Brown before entering into an agreement with the company or signing the broadly worded confidentiality agreement. Although academic freedom is a core value of Brown University, we also expect all members of our community to honor the commitments they make and not to make

commitments they cannot honor. The sole question on which Dr. Kern sought advice from an associate dean of medicine was whether the agreement he had signed would interfere with his right to publish. The associate dean's concern was that by signing the confidentiality agreement, Dr. Kern might have compromised the academic freedom he later wanted the university to guarantee him.

I am in complete agreement with Brodtkin et al. that disputes such as these are all too common in the field of occupational medicine. The solution, it seems to me, is for all parties — particularly physicians, who have a societal duty to report threats to the public health — to be rigorous, honest, and absolutely clear about their requirements at the outset and to support projects such as Dr. Kern's with carefully negotiated written agreements.

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A spokesperson for Memorial Hospital of Rhode Island replies:

To the Editor: Dr. Kern's public health-reporting responsibilities were never blocked. I fully supported his reporting the cluster of interstitial lung disease to the Rhode Island Department of Health. Such reporting was required by state law. His report included an abstract, which was submitted through the Department of Health to *Morbidity and Mortality Weekly Report*. This remains under editorial review and has yet to appear. I also wrote to and spoke with the director of the Department of Health to express my concern about the health problem and to request that the agency monitor the situation closely. The director agreed to do this.

Legal counsel informed the hospital that presentation of the abstract at the annual meeting of the American Thoracic Society put the hospital at risk of breach of contract. This risk occurred not only because of the signed confidentiality agreement but also because there was no formal consulting contract between Dr. Kern and the company. In the absence of a specific stipulation that gave Dr. Kern discretion over the dissemination of information about the disease cluster, the attorneys told us that contract law would support the idea that any information generated by Dr. Kern belonged to the company and that the company had the right to control dissemination of the information. Ignoring these legal constraints put the hospital at serious financial risk — a risk that if judged by a court to be a breach of contract would not be covered by any of the hospital's insurance policies. I thought it reasonable to request that Dr. Kern withdraw his abstract from the American Thoracic Society. And as noted above, we could and did respond to the public health concern under the statutory requirements of state law.

Dr. Kern's occupational program has run at a financial loss of \$30,000 to \$50,000 per year since its inception in the late 1980s. Since 1991 the hospital has considered canceling the program. Ironically, this particular consultancy brought the first promise of financial solvency to the program. When the company and Dr. Kern felt they could no longer work together, the hospital judged that the future was bleak and elected to terminate the program for

financial reasons. The action was not in retaliation for Dr. Kern's publication of the abstract at the American Thoracic Society meeting.

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A spokesperson for Microfibres responds:

To the Editor: Unfortunately, public discussion to date of our investigations into lung cases at our Pawtucket, Rhode Island, plant has been fraught with misrepresentations, misunderstandings, misconceptions, and outright falsehoods.

From the time we first learned that there might be a connection between our plant and two patients with unusual lung conditions, we have pursued an aggressive, responsive, and responsible investigation into environmental conditions at the plant and the health problem among our associates. As part of this effort, we hired Memorial Hospital and Dr. Kern and invited the National Institute of Occupational Safety and Health (NIOSH) to assist in determining what was causing the maladies. Extensive medical testing of virtually all associates revealed four additional cases. Detailed examination of environmental conditions within the plant yielded specific recommendations that would allow us to meet or significantly exceed all known environmental standards for elements such as air quality. Even though the exact cause of the health problems has eluded researchers, we have already made an investment of over \$1 million in equipment and investigative costs to address this problem.

Our associates have been involved from the very start in nearly all aspects of the investigation. They have also been active partners in responding to recommendations provided by Memorial Hospital, NIOSH, and other health consultants hired by us.

As a contractor with Microfibres, Dr. Kern was given access to a wide variety of information, including proprietary information that might have competitive implications. Dr. Kern's voluntary signature on the agreement — which we require of all associates and contractors — to protect that information required him to obtain written company approval for release of any data related to Microfibres. Our request that Dr. Kern abide by this agreement was to ensure that he did not inadvertently reveal proprietary details of our manufacturing process. There has never been any attempt nor a desire to keep important health information from the public. Indeed, the very involvement of NIOSH in the investigation guarantees public release of critical health information, a fact that seems to elude Dr. Kern.

Our first priority continues to be the health of our associates and possible public health ramifications. The termination of our contractual relationship with Dr. Kern in no way diminishes our commitment to identify the health problem at hand. We have since contracted with one of the nation's foremost occupational physician-scientists, Dr. Frederick Fung of the University of California at Irvine, to carry on this important research.

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Dr. Kern and a colleague reply:

To the Editor: The experiences of Dr. Deyo and his colleagues remind us that when a special-interest group is threatened, its first victims typically are truth and the messenger, even should the latter be a physician.¹ Dr. Brodtkin and his colleagues accurately summarize our somewhat similar predicament.²⁻⁴ However, the ways in which our case appears to differ from those recently reported both here and elsewhere⁵ are worth highlighting.

First, we were investigating an evolving occupational-disease outbreak among a unionized industrial work force. Our primary focus was the health of these workers rather than academic research. Second, our hospital and medical school administrators have actively participated in the special-interest group's efforts to undermine both our credibility and the generation, dissemination, and application of scientific findings. Third, the combined interference of the company, the hospital, and the medical school administration has placed workers at risk both here and, potentially, elsewhere. Fourth, this interference threatened a basic responsibility of all physicians, that of reporting and describing new disease phenomena, and may have jeopardized an opportunity to advance the understanding of disease causation. Fifth, throughout, there has been a callous disregard for truth, professional integrity, and the public health by institutions charged with honoring these ideals. Finally, we have been fortunate in that there has been an outpouring of outrage both locally and nationally from colleagues, students, patients, and professional organizations; formal statements have been generated thus far by the Association of Occupational and Environmental Clinics, the American College of Occupational and Environmental Medicine, the American Thoracic Society, and the president of the American Public Health Association.

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KATE T.H. DURAND, M.H.S., C.I.H.
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1. An enemy of the people (1882). In: Ibsen H. The complete major prose plays: Henrik Ibsen. Fjelde R, trans. New York: Farrar, Straus, & Giroux, 1978.

2. Knox R. R.I. firm wanted doctor silent on lung research. *Boston Globe*. May 12, 1997:A1, B12.

3. *Idem*. Brown public health researcher fired. *Boston Globe*. July 6, 1997: B1, B5.

4. Fine M. Not about academic freedom: Dr. Kern and professional integrity. *Providence Journal-Bulletin*. July 18, 1997:B4.

5. Rennie D. Thyroid storm. *JAMA* 1997;277:1238-43.

Granulocyte Colony-Stimulating Factor in Afebrile Patients with Neutropenia

To the Editor: Hartmann et al. (June 19 issue)¹ apparently assumed that a neutrophil count of zero per cubic millimeter has the same implications as a count of 499 per cubic millimeter, an assumption we all know is not correct. Failing to stratify according to the degree of neutropenia at the time of randomization fails to acknowledge this

point. Furthermore, we are not told how many patients who were potentially eligible for this study refused to undergo randomization or how many were rejected for the study by their physicians because of extremely severe neutropenia. Since ethical considerations can skew the population of patients enrolled in randomized studies in favor of less seriously ill patients, it is possible that this study did not include a large proportion of patients with neutrophil counts below 100 per cubic millimeter. Even if it did, we are not told how many of them were treated in each group. Finally, there was no attempt to analyze whether granulocyte colony-stimulating factor (G-CSF) was of any advantage in patients with extremely severe neutropenia.

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1. Hartmann LC, Tschetter LK, Habermann TM, et al. Granulocyte colony-stimulating factor in severe chemotherapy-induced afebrile neutropenia. *N Engl J Med* 1997;336:1776-80.

The authors reply:

To the Editor: We compared G-CSF with placebo in a group of 138 afebrile patients with absolute neutrophil counts of 500 or less per cubic millimeter. Dr. Cabanillas questions the severity of the neutropenia in our study population. The distribution of absolute neutrophil counts among our patients at entry into the study was as follows: 19 percent had counts of 0 to 99 per cubic millimeter, 26 percent had counts of 100 to 199 per cubic millimeter, 15 percent had counts of 200 to 299 per cubic millimeter, 25 percent had counts of 300 to 399 per cubic millimeter, and 15 percent had counts of 400 to 500 per cubic millimeter. Among the patients in the lowest quintile (absolute neutrophil count, <100 per cubic millimeter), 15 received G-CSF and 11 received placebo ($P=0.5$).

We are not aware of a randomized study of a colony-stimulating factor used therapeutically for post-chemotherapy neutropenia that has stratified for the absolute neutrophil count at base line, nor have subgroup analyses of these studies demonstrated an effect of the base-line count on the length of hospitalization.¹ We did not perform or report subgroup analyses according to base-line absolute neutrophil counts, because our study was not designed to do so.

Dr. Cabanillas hypothesizes that physicians are less likely to enroll seriously affected patients in randomized trials. The degree of neutropenia in the majority of patients enrolled in our study does not support that hypothesis. Moreover, his premise assumes that G-CSF will positively affect clinical outcomes when used in the treatment of established neutropenia. Such efficacy has not been demonstrated in the randomized trials of the agent used therapeutically — namely, in studies of febrile neutropenia.^{1,2}

Dr. Cabanillas would also like to know how many patients who were potentially eligible for the study refused to undergo randomization and how many were rejected for study entry by their physicians because of extremely severe neutropenia. Although we agree that such information would be ideal for every reported randomized, controlled trial, to place results in their proper context, such

information is not routinely obtained for clinical trials and was not recorded in this study.

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Granulocyte Colony-Stimulating Factor in Children with Acute Lymphoblastic Leukemia

To the Editor: The conclusion of Pui et al. (June 19 issue)¹ that “whether the benefits of G-CSF [granulocyte colony-stimulating factor] therapy justify its use in individual cases is ultimately a matter of clinical judgment” is surprising. Their study showed that G-CSF use halved the median duration of hospital stays (from 10 days to 6 days, $P=0.011$) and the incidence of documented infections (from 27 to 12, $P=0.009$). Children receiving G-CSF had fewer episodes of bacteremia, disseminated fungal infections, cellulitis, central venous catheter-associated infections, otitis media, *Clostridium difficile* enterocolitis, and lymphadenitis. Nevertheless, the editorial in the same issue² also concludes that “since there was no clear-cut clinical benefit of treatment with G-CSF and the median total costs of supportive care were similar in the G-CSF and placebo groups, the results of the study have to be considered negative.”

Formal quality-of-life evaluations in this and similar studies are lacking. But surely the instruments and criteria used to make a quality-of-life assessment in very young children would be purely conjectural, based on projections of our values as adults; for how could we ever look at the world through the eyes of an infant? Common sense suggests that if they could, infants would tell us that hospital stays and infections of the kind listed above are distressing and that they would be grateful if physicians could prevent such events. While event-free survival and cost-benefit analysis may be more important measures from a scientific and economic standpoint,³ let us remember that our primary role as physicians is to alleviate and prevent patients' suffering. When outcomes we consider important differ from those that our patients might consider important, let us defer to our patients. Compassionate clinical judgment suggests that G-CSF as used by Pui et al.¹ does have clear-cut clinical benefit. Moreover, the price of G-CSF therapy was adequately offset by reductions in the cost of supportive care, so that the clinical benefit observed was achieved at no extra cost.

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To the Editor: We were impressed with the clinical benefits of G-CSF given after induction chemotherapy in children with acute lymphoblastic leukemia reported by Pui et al. They reported a statistically significant reduction in the duration of grade 3 and 4 neutropenia, a reduction of the duration of hospital stays, and a reduction of more than 50 percent in documented infections. This study supports our results in children with high-risk acute lymphoblastic leukemia who received nine courses of intensive chemotherapy, with G-CSF administered between courses.¹ We found additional clinical benefits, including reductions in the incidence and duration of febrile neutropenia and in the use of intravenous antibiotics. Similar benefit has been reported in adult patients with acute lymphoblastic leukemia when G-CSF was used concomitantly with chemotherapy.²

The benefits of G-CSF in pediatric acute lymphoblastic leukemia may be underestimated if the interpretation of the clinical results is based on only one chemotherapy cycle per patient as in the study by Pui et al. We achieved our results by using G-CSF after repeated cycles.¹ In addition, Pui et al. chose to emphasize such clinical end points as the rate of hospitalization and disease-free survival, which not surprisingly did not show statistically significant differences. The elected study design might not have allowed a better result. In our study there were also only minor effects of G-CSF on the frequency of febrile neutropenic episodes after the first chemotherapy cycle. The real benefit of G-CSF treatment started at chemotherapy cycle 3 (7 percent febrile neutropenia episodes in the G-CSF arm vs. 53 percent in the control arm) and continued throughout cycle 9. This supports the hypothesis that the beneficial effects of G-CSF are more pronounced when the damage to hematopoietic progenitor cells is more severe (e.g., after repeated cycles of chemotherapy³) and explains the lack of reduction of febrile neutropenia in the study by Pui et al. Patients and their families may value these clinical benefits of G-CSF, especially when they are attained without an increase in costs.

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The authors reply:

To the Editor: We agree with Dr. Gupta that quality-of-life considerations in the young children we studied are conjectural at best; hence, we focused on more objective end points in our study. In this regard, G-CSF therapy did not significantly reduce the frequency of hospitalization or severe infection in comparison with treatment with normal saline. Moreover, a third of the patients presumably did not derive any clinical benefit from G-CSF, since 32 percent of the placebo group did not require hospitalization. Although the median duration of hospitalization was reduced by four days among G-CSF-treated patients who had febrile neutropenia, it was shortened by only two days if the analysis included all the patients receiving G-CSF. Thus, whether a child would prefer daily injections of G-CSF for nine days, without any guarantee of benefit, over two extra days in the hospital is a matter of conjecture. These remarks notwithstanding, we believe that G-CSF treatment does produce modest clinical benefits for some children who receive intensive induction chemotherapy for acute lymphoblastic leukemia, but the magnitude of these effects does not appear to justify routine use of the growth factor in all patients. Clearly, elucidation of factors that would identify the patients at greatest risk of febrile neutropenia and prolonged hospitalization is needed to improve the cost:benefit ratio of G-CSF therapy. We also agree with Dr. Gupta that "our primary role . . . is to alleviate and prevent patients' suffering," a role that involves the appropriate use of medications based on proper interpretation of well-designed clinical trials.

With regard to Drs. Welte and Riehm's comments, we did in fact cite the interim report of his study and suggested that G-CSF treatment might prove advantageous in the treatment of malignant diseases that require repeated courses of intensive chemotherapy (e.g., advanced-stage Burkitt's lymphoma and B-cell leukemia). However, administration of G-CSF has not yet been shown to improve leukemia-free survival in a randomized, placebo-controlled study.

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Immediate Coronary Angiography in Survivors of Out-of-Hospital Cardiac Arrest

To the Editor: Spaulding and colleagues (June 5 issue)¹ present important information regarding coronary morphology and outcome after angioplasty in survivors of out-of-hospital cardiac arrest. They found coronary occlusions in 48 percent of their patients and consider this to be supportive evidence of the role of acute coronary thrombosis in sudden death. The authors further report that only 42 percent of their patients had ST-segment elevation on admission. Finally, the authors' analysis suggests that immediate angioplasty is associated with an improved outcome.

A number of methodologic issues merit consideration. First, no information is given on the neurologic status of the patients. The level of consciousness on admission and the score on the Glasgow Coma Scale have been shown to

be important predictors of outcome after out-of-hospital cardiac arrest.² The patients' outcomes should be related to an accepted neurologic measure. It is unclear what factors were entered into the logistic-regression model, but neurologic status should be one of them. Second, the exclusion criteria are unclear. The authors state that they included patients who were "successfully" resuscitated and excluded hundreds of patients "because of late arrival of the medical team." Both terms require definition. The authors' recommendation for immediate angiography is difficult to assess and implement without knowledge of these variables, as well as the neurologic status of the patients on admission. Do the authors recommend immediate angiography regardless of the patient's neurologic status? Third, no information is given regarding the complications of coronary intervention in this very sick group of patients. Fourth, the identification of a coronary occlusion in a survivor of out-of-hospital cardiac arrest, in the absence of localizing electrocardiographic changes, does not necessarily point to that occlusion as the cause of the cardiac arrest. Therefore, the authors' conclusions about the poor predictive accuracy of the electrocardiogram for (presumably acute) coronary occlusion is unwarranted. Finally, as the authors recognize, coronary angiography and angioplasty were performed in an uncontrolled fashion in a very small, highly selected subgroup of patients surviving out-of-hospital cardiac arrest. The applicability of these findings to consecutive patients admitted after cardiac arrest remains to be determined. Meanwhile, caution should be exercised before immediate coronary intervention is offered after cardiac arrest to patients who do not have clear evidence of evolving myocardial infarction.

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The authors reply:

To the Editor: We thank Dr. Zahger for his comments. Consciousness on admission was assessed with the Glasgow Coma Scale,¹ and the median score was 3 (10th to 90th percentiles, 3 to 8). In-hospital death was not predicted by this variable (odds ratio, 0.68 for each point over a score of 3; 95 percent confidence interval, 0.36 to 1.26; $P=0.21$). Forty-two patients were admitted with a Glasgow score of 3; 11 survived with no major neurologic complication. Dr. Zahger's reference to the study of Grubb et al.² is inaccurate: as in our study, deep coma on admission or even 48 hours after the arrest did not always predict a hopeless prognosis. Therefore, decisions about coronary angiography should be made regardless of the patient's neurologic status on admission.

Patients were excluded if the time between the onset of cardiac arrest and the arrival of the emergency medical team was more than 20 minutes with no basic cardiac life support performed by a bystander.

No deaths occurred during coronary angiography; ven-

tricular fibrillation or tachycardia recurred in 14 patients who were successfully defibrillated. Monitoring and stabilization procedures were continued in the cardiac catheterization laboratory by the emergency medical team and an intensivist who then treated the patients in the medical intensive care unit. Cardiac procedures were performed by senior interventional cardiologists with extensive experience in emergency angioplasty.

Coronary occlusion was considered recent if thrombus was present and the guidewire easily crossed the occlusion. As suggested by Dr. Zahger, recent coronary occlusion was not necessarily the cause of the arrest in nine patients with no ST-segment elevation but could have been the consequence of prolonged low cardiac output and a preexisting coronary stenosis. However, in both cases, coronary occlusion results in acute myocardial ischemia. Immediate coronary angiography regardless of preadmission electrocardiographic data therefore allowed reperfusion therapy in this subgroup.

Since our study was nonrandomized and involved a small number of patients, we obviously cannot recommend a systematic approach of immediate coronary angiography in all survivors of out-of-hospital cardiac arrest. However, if no obvious noncardiac cause of arrest is found, our strategy of immediate coronary angiography regardless of preadmission clinical and electrocardiographic data is safe and may improve the long-term outcome if it is available and is performed by teams with extensive experience in preadmission and in-hospital management of cardiac arrest and emergency interventional cardiology.

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Minocycline for Symptomatic Neurosyphilis in Patients Allergic to Penicillin

To the Editor: Treatment of symptomatic neurosyphilis is an increasingly common clinical problem because of its rising incidence, particularly in patients coinfecting with the human immunodeficiency virus type 1 (HIV-1).¹ The mainstay of treatment remains intravenous penicillin G at high dosage, ranging from 12 million to 24 million units given six times a day for 10 to 14 days.¹ Treatment options for patients with neurosyphilis who are allergic to penicillin are limited. Such patients should undergo a skin test and hospitalization for a penicillin-desensitization protocol before intravenous penicillin administration.^{2,3} We know little, however, about the outcomes of high-dose penicillin G treatment for neurosyphilis in penicillin-allergic patients after desensitization.

Long-acting oral tetracyclines are recommended for patients with primary or secondary syphilis who are allergic to penicillin.¹ Sufficient cerebrospinal fluid concentrations are obtained in healthy subjects and in patients with latent neurosyphilis.⁴

Three HIV-seronegative men were given a diagnosis of neurosyphilis. All three had extensive cutaneous rash consistent with a hypersensitivity reaction to penicillin, refused to undergo a desensitization procedure, and provided informed consent to be treated with minocycline according to the present protocol. They were given oral minocycline at a dose of 100 mg twice a day for 14 consecutive days per month for 9 months, with clinical, serologic, and cerebrospinal fluid examinations 6, 12, and 24 months after beginning treatment.

There were no drug-related side effects. Clinical symptoms and signs improved after only one month. Cerebrospinal fluid examination showed the disappearance of pleocytosis at 6, 12, and 24 months, as well as progressive normalization of protein concentrations in two cases. A Venereal Disease Research Laboratory test in cerebrospinal fluid became negative in two patients at six months (Table 1). Patient 3 was noncompliant and only completed three cycles of treatment during the first 12 months.

Oral administration of long-acting tetracyclines according to the present protocol may represent an effective alternative treatment to penicillin desensitization for patients with neurosyphilis who are allergic to penicillin G.

Treatment of neurosyphilis in patients coinfecting with HIV-1 may require the presence of treponemidal concentrations in the central nervous system for longer periods than those provided by standard, high-dosage, intravenous penicillin G regimens. Given the poor response to

TABLE 1. RESULTS OF CEREBROSPINAL FLUID TESTS IN THREE PATIENTS ALLERGIC TO PENICILLIN WHOSE NEUROSYPHILIS WAS TREATED WITH ORAL MINOCYCLINE.

PATIENT No.	MONTH	VDRL*	CELL COUNT	PROTEIN	TPHA INDEX†
			cells/mm ³	g/liter	
1	0	1:4	31	0.92	65
	6	++	5	0.52	30
	12	—	3	0.47	78
	24	—	3	0.43	17
2	0	++++	73	1.07	18
	6	+++	2	0.51	32
	12	—	4	0.58	4.9
	24	—	5	0.44	10.5
3	0	++++	73	1.26	9
	6	1:32	1	1.37	11
	12	++	1	1.0	25
	24	1:2	1	0.7	5

*The last positive dilution is indicated. Plus signs indicate semiquantitative evaluations. VDRL denotes Venereal Disease Research Laboratory.

†TPHA denotes *Treponema pallidum* hemagglutination. The index was calculated as follows: (cerebrospinal fluid TPHA titer ÷ cerebrospinal fluid IgG) ÷ (serum TPHA titer ÷ serum IgG).

standard intravenous penicillin G in some HIV-infected patients,⁵ intermittent, oral administration of long-acting tetracyclines may be a useful therapeutic strategy in patients with recurrence after a full course of intravenous penicillin G.

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