

Infections Associated with Musculoskeletal-Tissue Allografts

TO THE EDITOR: We are grateful to the *Journal* for putting on the record¹ the undisclosed conflicts of interest of two of the authors of the report by Kainer et al. (June 17 issue).² Specifically, the associations were Dr. Archibald's employment with Regeneration Technologies (the manufacturer of BioCleanse, which was mentioned in the article) and Dr. Kainer's retention as an expert witness on behalf of plaintiffs' counsel in lawsuits against CryoLife (Tissue Bank A in the article). It is critical for readers to review the work in light of this context.

BioCleanse has yet to be clinically proven as a sterilizing method for soft-tissue musculoskeletal allografts. No documented evidence supports short-term or long-term maintenance of the structural integrity of BioCleanse-processed soft-tissue grafts. Given the poor clinical history of previous soft-tissue musculoskeletal-allograft "sterilization" methods, to, in effect, promote the use of BioCleanse in the absence of critically assessed clinical data is irresponsible and ethically questionable.

The authors' implication that Tissue Bank A knowingly released tissue with a positive culture result after processing (Table 1 of the article) is inaccurate and misleading. They report one culture result as negative, eight results as unknown, and five as positive. Tissue Bank A certifies that every one of the cultures after processing was negative, and this information was provided to the Centers for Disease Control and Prevention (CDC). Tissue Bank A has never intentionally released tissue contaminated with any organism. Furthermore, there have been reports of clostridial infections associated with musculoskeletal allografts from other tissue banks, and the data appear to have been presented selectively in a manner that omits all but those connected to Tissue Bank A.^{3,4} The report by Kainer et al. is based on data published two years ago.³ Since then, Tissue Bank A has developed and validated numerous new procedures to enhance safety. The recommendations listed in Table 4 of the report ("Recommendations to Reduce the Risk of Allograft-Associated Infections") have been substantially put into practice by Tissue Bank A.

J. Robin De Andrade, M.D.

Gregory S. Ray, M.D.

CryoLife
Kennesaw, GA 30144

1. Kainer MA, Archibald LK. Correction: infections and musculoskeletal-tissue allografts. *N Engl J Med* 2004;351:397-8.
2. Kainer MA, Linden JV, Whaley DN, et al. Clostridium infections

associated with musculoskeletal-tissue allografts. *N Engl J Med* 2004;350:2564-71.

3. Update: allograft-associated bacterial infections — United States, 2002. *MMWR Morb Mortal Wkly Rep* 2002;51:207-10.

4. Food and Drug Administration. Manufacturer and user facility device experience database. (Accessed August 26, 2004, at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/Detail.CFM?MDRFOI_ID=400733.)

TO THE EDITOR: We agree with Kainer et al. that standardized sterilization procedures for musculoskeletal allografts are necessary to reduce the risk of allograft-associated infections. Validating the sterilization of bone-tissue transplants with peracetic acid-ethanol, we showed that spores of *Bacillus subtilis* and *Clostridium sporogenes*, as well as enveloped and nonenveloped viruses, were inactivated effectively. Only hepatitis A virus appeared to be resistant.¹ We observed no bacterial or viral infection with the use of allografts treated with peracetic acid-ethanol in approximately 100,000 transplantations.² Tissues that do not allow sufficient penetration of chemical sterilization solutions (i.e., massive allografts) should be gamma-irradiated whenever possible; the minimal doses are 25 kGy for inactivation of nonviral microorganisms³ and 34 kGy for viral inactivation.⁴ For validation of the tissue-sterilization process, we recommend a reduction of 5 log₁₀ colony-forming units per milliliter for bacteria, spores, and fungi and 4 log₁₀ tissue-culture infectious doses (50 percent) per milliliter for viruses. In addition, testing of the donors for viral markers and single polymerase-chain-reaction analysis for at least the human immunodeficiency virus, hepatitis C virus, and hepatitis B virus are mandatory.

Axel Pruss, M.D.

Ulf B. Göbel, M.D., Ph.D.

Charité, University Medicine Berlin
D-10098 Berlin, Germany
axel.pruss@charite.de

Georg Pauli, Ph.D.

Robert Koch Institute
D-13353 Berlin, Germany

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3. IAEA Code of Practice for the radiation sterilisation of tissue allografts: requirements for validation and routine control. In: Phillips GO, ed. *Advances in tissue banking 2004*. Vol. 7. Cardiff, United Kingdom: World Scientific Publishers, 2004:211-65.
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fects of gamma irradiation on human cortical bone transplants contaminated with enveloped and non-enveloped viruses. *Biologicals* 2002;30:125-33.

TO THE EDITOR: Kainer et al. recommend the monitoring of allograft-associated adverse events; we would like to explain how to report them. Health care providers are encouraged to report adverse events (including infections) for which there is a reasonable possibility that the transplanted tissue caused the event. Reports should be made to the laboratory that made the tissue available for distribution; to the Division of Health Care Quality Promotion, CDC (telephone, 800-893-0485); and to the Food and Drug Administration (FDA). The FDA MedWatch reporting form and instructions are available at www.fda.gov/medwatch/report/instruc.htm and at the back of the Physicians' Desk Reference.¹ It has been proposed that manufacturers of tissue available for distribution be required to report to the FDA certain adverse events involving a communicable disease.²

Jacquelyn A. Polder, M.P.H.
Jennifer J. Wood, Ph.D., M.P.H.
M. Miles Braun, M.D., M.P.H.

Food and Drug Administration
Rockville, MD 20852
polder@cber.fda.gov

1. Physicians' desk reference. Montvale, N.J.: Thompson PDR, 2004.
2. Food and Drug Administration. Current good tissue practice for manufacturers of human cellular and tissue-based products; inspection and enforcement; proposed rule. 66 FR 1508. January 8, 2001.

THE AUTHORS REPLY: Polder and colleagues provide information on reporting adverse events associated with transplanted tissue. Detailed guidelines should also be developed for the process that tissue banks use after receiving such reports (e.g., what information is provided to surgeons who have implanted tissue from the same donor and how tissue banks ensure that clinicians receive that information).

Our letter¹ outlines the circumstances regarding the perceived conflicts of interest referred to by De Andrade and Ray. We did communicate Dr. Archibald's new affiliation to the *Journal* in revised manuscripts; unfortunately, it failed to appear in print. The retention of Dr. Kainer as an expert witness by patients and Dr. Archibald's affiliation with Regeneration Technologies did not constitute conflicts of interest, in our view, since these events oc-

curred after the completion of the manuscript and after their tenures with the CDC.

We identified only two other cases of musculoskeletal-tissue allograft-associated clostridium infection (in 1986).² We chose our study period (January 1998 to March 2002) because of available denominator data for estimating risks and because of concerns regarding the accuracy of case ascertainment before this period. Culture results of tissue from any anatomical site are presented in Table 1 of our article and were compiled with inspection reports from New York state regulatory authorities, the FDA, and warning letters. Although Tissue Bank A discarded tissue from anatomical sites that yielded a positive culture, it distributed tissue from implicated donors, despite the isolation of clostridium or bowel flora from other anatomical sites.

De Andrade and Ray are correct in suggesting that there are few published data on the efficacy of new sterilization methods. We determined that some tissues from implicated donors were processed with the use of gamma irradiation or Bio-Cleanse. No infections developed in recipients of tissue that was subjected to either of these sterilization methods. We reported the results of the public health investigation of this naturally occurring experiment to contribute to the scientific literature.

Pruss and colleagues describe the use of peracetic acid-ethanol to sterilize bone. They correctly state that chemical solutions must penetrate adequately to be effective. Gamma irradiation has excellent penetration; other methods also effectively penetrate tissue.³

Testing of donors for viral markers is important. Transmission of hepatitis C from an antibody-negative donor has been described⁴; tissues that underwent gamma irradiation did not transmit the virus. This finding constitutes further evidence that tissue sterilization provides an additional safety barrier when the donor-screening process does not identify contaminated tissue because of testing limitations. Patients and providers expect tissue to be safe and sterile; informed consent should be obtained before the implantation of nonsterile tissue.

Marion A. Kainer, M.B., B.S., M.P.H.

Tennessee Department of Health
Nashville, TN 37247
marion.kainer@state.tn.us

William R. Jarvis, M.D.

135 Dune Lane
Hilton Head Island, SC 29928

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2. Update: allograft-associated bacterial infections — United States, 2002. *MMWR Morb Mortal Wkly Rep* 2002;51:207-10.
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4. Hepatitis C virus transmission from an antibody-negative organ and tissue donor — United States, 2000–2002. *MMWR Morb Mortal Wkly Rep* 2003;52:273-4, 276.

Rheumatoid Arthritis

TO THE EDITOR: The data reported by O'Dell (June 17 issue)¹ and by Olsen and Stein (May 20 issue)² on biologic drugs for the treatment of rheumatoid arthritis reveal many points of uncertainty. First, the number of randomized trials that have compared new biologic agents plus methotrexate with methotrexate alone is small — a single, unreplicated trial of infliximab and adalimumab and two trials of etanercept. (The latest trial is very recent³ and is not mentioned by Olsen and Stein.) In addition, the number of patients who were enrolled in these trials is small (83 in the infliximab group, 67 in the adalimumab group, and 59 and 231 in the two etanercept groups). Furthermore, no head-to-head trial has been conducted that compares biologic agents.

Regulatory agencies that approve these drugs when the evidence of their effectiveness is preliminary do a disservice to the scientific community by discouraging drug manufacturers from undertaking confirmatory studies and trials that directly compare the new drugs. In this way, practitioners are led to prescribe these agents widely, despite limited evidence of their effectiveness.

Giulia Burchini, Pharm.D.

Cecilia Orsi, Pharm.D.

Azienda Ospedaliera Careggi
50134 Florence, Italy

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3. Klareskog L, van der Heijde D, de Jager JP, et al. Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. *Lancet* 2004;363:675-81.

TO THE EDITOR: O'Dell's update on rheumatoid arthritis provides insight into new therapeutic advances. However, these therapies appear to be suited for well-to-do patients with medical insurance, especially those who live in Western, developed countries. The author has not mentioned the treatment options for specific coexisting problems or compli-

cations of rheumatoid arthritis, such as associated vasculitis, activation of subclinical tuberculosis, restrictive lung disease, renal parenchymous disease, hypothyroidism, altered glucose tolerance, frank diabetes, and cardiomyopathy. The problem of rheumatoid arthritis is compounded in countries with inadequate resources¹ as a result of economic constraints, malnutrition, and a limited number of specialists. Most affected patients initially go to a primary care physician, and if the patient's condition worsens, with complications such as bone destruction, severe pain, and the development of fibrous or bony ankylosis, the primary care physician may refer the patient to an orthopedic surgeon or a consultant physician. Physicians and patients alike will benefit if inexpensive yet effective therapies are discussed, so that the progress of science may also reach the poor.

Niranjan Bhattacharya, D.Sc., M.D.

Bijoygarh State Hospital
Calcutta 700029, India
niranjanb@vsnl.net

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DR. O'DELL REPLIES: I certainly agree with Drs. Burchini and Orsi that more studies comparing tumor necrosis factor (TNF) inhibitors with active therapies and with each other would be very helpful to clinicians trying to make critical decisions about these expensive therapies. However, the evidence that TNF inhibition is an extremely effective strategy for a subgroup of patients with rheumatoid arthritis is overwhelming. Although I eagerly await comparative trials, as outlined in my review, I do not believe that this is the responsibility of the regulatory agencies.

The meta-analysis of data on the efficacy of anti-TNF drugs, presented in the recent letter by Messori et al. (August 26 issue),¹ is severely flawed by the fact that it combined three studies in which patients