

ed free cortisol index ( $r=0.55$  and  $r=0.68$  in patients with serum albumin concentrations of 2.5 g per deciliter or lower and those with concentrations above 2.5 g per deciliter, respectively). We examined neither the need for, nor the advantages of, glucocorticoids in critical illness; therefore, we made no additional recommendations. Instead, our study addressed serious limitations of tests used routinely to assess adrenal function in critically ill patients.

Dr. Polderman and colleagues raise a frequently cited limitation of the standard-dose cosyntropin test. Although the low-dose (1- $\mu$ g) cosyntropin test provides improved sensitivity and specificity, recent data show that it is still imperfect.<sup>2</sup> Although use of the low dose has advantages over use of the standard dose test in ambulatory patients, this point has not been adequately investigated in critically ill patients in whom adrenal function is already highly stimulated, as indicated by baseline serum free cortisol concentrations that are at least double the cosyntropin-stimulated concentrations in healthy volunteers. Considering the extensive published experience with the standard cosyntropin test, particularly during critical illness, and acknowledging its known limitations, we elected to use this test in our study.

We agree with Dr. Polderman and colleagues and Drs. Jackson and Shorr that clinical judgment should always be exercised in making decisions about the use of glucocorticoid therapy during crit-

ical illness. We also agree with Drs. Jackson and Shorr that the severity of illness might not be the sole determinant of the adrenal response to critical illness. A large prospective study would be necessary to address that question.

Finally, we appreciate the comments of Drs. Vogeser and Briegel and regret that we did not refer to their study, which appeared after our article was submitted for publication. Newer assay methods such as the one they suggest should provide reliable data in a timely manner.

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1. Vogeser M, Groetzner J, Küpper C, Briegel J. Free serum cortisol during the postoperative acute phase response determined by equilibrium dialysis liquid chromatography-tandem mass spectrometry. *Clin Chem Lab Med* 2003;41:146-51.

2. Nasrallah MP, Arafah BM. The value of dehydroepiandrosterone sulfate measurements in the assessment of adrenal function. *J Clin Endocrinol Metab* 2003;88:5293-8.

**DR. LORIAUX REPLIES:** I agree completely with the comments of Drs. Jackson and Shorr on diagnosing adrenal insufficiency in critically ill patients. Additional study is needed to clarify the clinical usefulness of the plasma "free cortisol" concentration in these patients. That was my thesis.

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## Correction: Infections and Musculoskeletal-Tissue Allografts

**TO THE EDITOR:** Our article on clostridium infections associated with musculoskeletal-tissue allografts (June 17 issue)<sup>1</sup> describes an epidemiologic investigation that was initiated by the Division of Healthcare Quality Promotion, Centers for Disease Control and Prevention (CDC), in November 2001 and concluded in April 2002. Dr. Marion A. Kainer carried out the investigation and was supervised by Dr. Lennox K. Archibald. A manuscript describing the investigation was completed in August 2002. After clearance by the director of the Division of Healthcare Quality Promotion, the manuscript was submitted to the *Journal* for publication in December 2002. There were no changes to the discussion relating to the BioCleanse process, which was mentioned in the article, between the time the manuscript was submitted and publication.

On January 20, 2003, Dr. Archibald became an employee of Regeneration Technologies, the manufacturer of BioCleanse. Stock options were granted to Dr. Archibald subsequent to his employment at Regeneration Technologies, subject to a vesting program over a period of five years.

The article was accepted for publication, pending revision, by the *Journal* in March 2004. Dr. Archibald signed a financial-disclosure form on August 1, 2003, attesting in good faith that the investigation had been conducted and completed while he was employed by the CDC. Dr. Archibald did not indicate on that financial-disclosure form that he was now employed by Regeneration Technologies. In March 2004, Dr. Archibald orally discussed his new affiliation with staff at the *Journal*. It was his understanding that no further revision of

his financial disclosure was required. Although Dr. Kainer noted in revised manuscripts that Dr. Archibald was no longer affiliated with the CDC and was now working for Regeneration Technologies, this point was not separately addressed in an accompanying letter to the editor, and Dr. Archibald's new affiliation failed to appear in the publication.

We regret any perception of impropriety that might have resulted from Dr. Archibald's subsequent employment with Regeneration Technologies after his tenure with the CDC.

At no stage has Dr. Kainer been a paid expert witness on behalf of any tissue bank. However, after having left the CDC she was retained late in 2002 as an expert witness on behalf of patients affected by Tissue Bank A and shareholders who are filing a class-action lawsuit. In the article, per CDC policy, the use of trade names and commercial sources is for identification only and does not imply endorsement by the Department of Health and Human Services.

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*Editor's note:* When we publish a research report, our policy is to disclose to readers any relevant financial ties of the authors. To accomplish that, we rely on disclosure forms that all authors complete and sign. It is essential that we receive this information in writing; we cannot rely on telephone communication. In this case, Dr. Archibald's disclosure form, completed on August 1, 2003, stated that he had no relevant financial associations. Specifically, his form did not indicate that after the research was completed, he became an employee of Regeneration Technologies, an association that is relevant because Regeneration Technologies makes BioCleanse, a product that is mentioned in the article. It is our policy that disclosure forms must reflect the most current information. If this author's new affiliation had been indicated on the disclosure form, it would have been printed in the article according to our policy. The above letter with the financial disclosure has been linked permanently to the article as a correction, both on the *Journal* Web site and in the Medline database.

1. Kainer MA, Linden JV, Whaley DN, et al. Clostridium infections associated with musculoskeletal-tissue allografts. *N Engl J Med* 2004;350:2564-71.

## Trends in Assisted Reproductive Technology

**TO THE EDITOR:** Jain et al. (April 15 issue)<sup>1</sup> report growing restraint in the practice of transferring numerous embryos after in vitro fertilization. This reassuring news should not, however, distract attention from the fact that other assisted reproductive techniques (i.e., ovarian stimulation, followed by artificial insemination) also contribute to the increasing problem of multifetal pregnancies in this country. Earlier recourse to in vitro fertilization would give physicians a better opportunity to reduce the likelihood of triggering such dangerous pregnancies,<sup>2</sup> but ovarian stimulation alone remains the preferred first-line treatment for many types of infertility because of its relative cost-effectiveness.<sup>3</sup>

The technological milieu has changed dramatically in the four decades since the first fertility drugs became available. More primitive first-generation technology competes with refined and now more responsibly used second-generation technologies (i.e., in vitro fertilization and embryo transfer). The

original risk-benefit calculus for first-generation treatments for infertility warrants reassessment.<sup>4</sup>

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1. Jain T, Missmer SA, Hornstein MD. Trends in embryo-transfer practice and in outcomes of the use of assisted reproductive technology in the United States. *N Engl J Med* 2004;350:1639-45.
2. Gleicher N, Oleske DM, Tur-Kaspa I, Vidali A, Karande V. Reducing the risk of high-order multiple pregnancy after ovarian stimulation with gonadotropins. *N Engl J Med* 2000;343:2-7.
3. Guzick DS, Carson SA, Coutifaris C, et al. Efficacy of superovulation and intrauterine insemination in the treatment of infertility. *N Engl J Med* 1999;340:177-83.
4. Noah L. Assisted reproductive technologies and the pitfalls of unregulated biomedical innovation. *Fla Law Rev* 2003;55:603-65.

**THE AUTHORS REPLY:** Noah is correct in pointing out that, in addition to in vitro fertilization, other infertility therapies that promote superovulation contribute to multiple gestations in the United States.