

studies. However, the point that Daley fails to see is that scientific considerations should never trump the ethical considerations of society.

Jurek G. Grabowski, M.P.H.

Johns Hopkins University School of Medicine
Baltimore, MD 21205
ggrabows@jhmi.edu

DR. DALEY REPLIES: Human embryonic stem cells provide unique opportunities for science and medicine, enabling researchers to investigate basic mechanisms of human development and clinicians to formulate cell-based therapies. In my Perspective article, I outline specific scientific directions facilitated by new human embryonic stem-cell lines that the federal government is not supporting, so as to illustrate how current policy is hindering progress in biomedicine.

I find it curious that Dr. Petros suggests that I have changed my position of advocacy of embryonic stem-cell research “to make a political statement,” given my “previous enthusiasm” for the use of adult (somatic) stem cells. In numerous public lectures and scientific articles, I have consistently expressed my conviction that fundamental knowledge and lifesaving cell-based therapies will emerge from research into both embryonic and adult stem cells and that neither avenue should be excluded in favor of the other. In my own laboratory, I maintain active research programs on both classes of stem cells.

Dr. Petros is correct in highlighting my hope that one day we will learn to reprogram somatic cells directly by methods that are less cumbersome

than nuclear transfer in order to “confer upon adult somatic cells the pluripotency of embryonic stem cells.”¹ Though promising, such speculative cellular-engineering research does not obviate the need for expanded access to new human embryonic stem cells. Adult stem cells are not equivalent to embryonic stem cells and cannot satisfy all scientific and medical needs. Dr. Petros chose not to highlight the following statement from the same review he cites: “The biological fact of life that some adult tissues lack stem cells has bolstered the argument that cell replacement for some disorders must tap a source within the embryo, or alternatively from differentiated products of ES [embryonic stem] cell lines.”¹

Dr. Grunt correctly warns us that restrictions on stem-cell research can have a chilling effect on scientific progress and put scientists in the United States — and possibly patients in this country as well — at a disadvantage.

Rather than distracting readers from the ethical debate, as Mr. Grabowski suggests, I attempt in my article to provide legislators, physicians, biomedical scientists, and the public with credible details of the missed scientific opportunities under the current governmental policy, so that all might exercise sound ethical and pragmatic judgment about medical priorities in our pluralistic society.

George Q. Daley, M.D., Ph.D.

Children’s Hospital
Boston, MA 02115
george.daley@childrens.harvard.edu

1. Daley GQ. Prospects for stem cell therapeutics: myths and medicines. *Curr Opin Genet Dev* 2002;12:607-13.

Combat Duty in Iraq and Afghanistan and Mental Health Problems

TO THE EDITOR: Hoge et al. (July 1 issue)¹ assessed mental health problems in members of the U.S. Army and Marine Corps who were involved in combat operations in Iraq and Afghanistan. Additional analyses might further elucidate their interesting findings.

First, a large proportion of the participants were positive for more than one disorder on screening. It is important to learn about the frequency of multiple disorders² and whether deployment and com-

bat experiences were independently associated with depression and anxiety.³ Also, roughly one quarter of the deployed personnel reported alcohol misuse, which has been shown to be associated with combat-related post-traumatic stress disorder in previous research.⁴ Untreated affected combatants might use alcohol as self-medication for psychological symptoms.⁵ It would be instructive to know whether such a relationship between lack of treatment and alcohol abuse exists in the present study.

Second, the authors compared perceived barriers to mental health care between respondents who met screening criteria for a mental disorder and those who did not. A more informative approach, in terms of public health implications, might be to compare perceived barriers to care between service members with mental health problems who received care and those who did not.

Raz Gross, M.D., M.P.H.
Yuval Neria, Ph.D.

Columbia University
New York, NY 10032
rg547@columbia.edu

1. Hoge CW, Castro CA, Messer SC, McGurk D, Cotting DI, Koffman RL. Combat duty in Iraq and Afghanistan, mental health problems, and barriers to care. *N Engl J Med* 2004;351:13-22.
2. Forbes D, Creamer M, Hawthorne G, Allen N, McHugh T. Comorbidity as a predictor of symptom change after treatment in combat-related posttraumatic stress disorder. *J Nerv Ment Dis* 2003;191:93-9.
3. Neria Y, Bromet EJ. Comorbidity of PTSD and depression: linked or separate incidence. *Biol Psychiatry* 2000;48:878-80.
4. Neria Y, Koenen KC. Do combat stress reaction and posttraumatic stress disorder relate to physical health and adverse health practices? An 18-year follow-up of Israeli war veterans. *Anxiety Stress Coping* 2003;16:227-39.
5. Bremner JD, Southwick SM, Darnell A, Charney DS. Chronic PTSD in Vietnam combat veterans: course of illness and substance abuse. *Am J Psychiatry* 1996;153:369-75.

TO THE EDITOR: Hoge et al. identified substantial barriers to treatment of psychological distress in combat personnel returning from Iraq and Afghanistan. The authors recommended providing mental health services within the primary care setting to overcome the perceived barriers of mistrust, poor access, and stigma. In 1996, to encourage use of such services by our veterans, mental health providers were situated in one primary care clinic. By doing so, mental health providers assessed four times as many patients as did a similar primary care clinic following the usual referral procedures. In our current study, we are examining the two-year outcome of treating psychological symptoms with this model in a sample of 48 referred patients (unpublished data). Of these, 40 (83 percent) have indicated that the availability of a mental health professional in primary care is helpful; 15 patients (31 percent) have specifically cited the lack of stigma or the easier access as benefits. Among the participants who were interviewed, there were 19 (40 percent) who refused treatment or dropped out.

Veterans are more likely to use mental health services in primary care settings. Such programs for

returning combat veterans have the potential to meet an important need.

Anna G. Engel, M.D.
Cheryl A. Aquilino, Ph.D.

Stratton Veterans Affairs Medical Center
Albany, NY 12208
anna.engel@med.va.gov

THE AUTHORS REPLY: Drs. Gross and Neria point out areas for further analysis as we continue to evaluate the mental health impact of current combat operations, including risk factors, multiple psychiatric disorders, and barriers to care. We are grateful to Drs. Engel and Aquilino for providing data that support an important strategy to reduce barriers to care. Mental health services are typically delivered in hospital- or office-based specialty clinics. On the basis of our experience with members of the Army and Marine Corps, we believe that the delivery of mental health services in primary care clinics would establish these services as routine, facilitate screening for mental health problems, and improve awareness and treatment of these problems by primary care professionals.

Primary care has been referred to as the de facto mental health service system.¹ In the military, mental disorders are the sixth leading illness category (as defined by the *International Classification of Diseases, Ninth Revision*) for ambulatory treatment, are nearly as common as respiratory conditions, and frequently occur along with other medical conditions.^{2,3} However, specialty treatment for mental health problems is associated with unique barriers to care, particularly stigma. It is plausible that mental health specialty clinics contribute to stigmatization through separate clinics, entrances, and medical records, particularly in a military environment where soldiers often live and work together and may not have privacy when they use a clinic on post.

The military offers unique opportunities to study new models of service delivery. These include having one location to go to for "sick call" (the term that soldiers use for an urgent or walk-in primary care visit) that offers care for both medical and mental health problems; providing mental health services on a walk-in basis (no appointment necessary); establishing procedures to document care for mental health problems in the regular medical record; and ensuring confidentiality, starting with not having to state the reason for a primary care visit until the patient is face to face with the health professional.

We hope that our study will energize further research and testing of new models for mental health services.

Charles W. Hoge, M.D.
Stephen C. Messer, Ph.D.
Carl A. Castro, Ph.D.

Walter Reed Army Institute of Research
Silver Spring, MD 20410
charles.hoge@na.amedd.army.mil

1. Regier DA, Narrow WE, Rae DS, Manderscheid RW, Locke BZ, Goodwin FK. The de facto U.S. mental and addictive disorders service system: Epidemiologic Catchment Area prospective 1-year prevalence rates of disorders and services. *Arch Gen Psychiatry* 1993;50:85-94.
2. Army Medical Surveillance Activity, Department of Defense. Ambulatory visits among active component members, U.S. Army Forces, 2003. *Med Surveill Monthly Rep* 2004;10:9-14. (Also available at <http://amsa.army.mil>.)
3. Hoge CW, Lesikar SE, Guevara R, et al. Mental disorders among U.S. military personnel in the 1990s: association with high levels of health care utilization and early military attrition. *Am J Psychiatry* 2002;159:1576-83.

PSA Velocity and Prostate Cancer

TO THE EDITOR: There are some basic methodologic flaws in the work by D'Amico et al. (July 8 issue).¹ In their multivariate analyses, the prostate-specific antigen (PSA) velocity was modeled as a binary variable on the basis of a threshold of 2.0 ng per milliliter per year. This threshold was selected on the basis of a univariate analysis of the same data, and hence the P values for all the multivariate analyses are overly optimistic. The multivariate analyses are central to the report, since they are the basis for claims that the PSA velocity provides prognostic information beyond that provided by the standard prognostic variables. Hilsenbeck and Clark² and Altman et al.³ have previously discussed statistical errors that result from the analysis of data with optimally selected cutoff points determined on the basis of the same set of data. Although the cutoff point of 2.0 ng per milliliter per year was the optimal quartile for the data presented by D'Amico et al., further validation with independent data, with other known prognostic variables taken into account, is necessary before this index can be recommended for clinical use or for risk stratification in clinical trials.

Lori E. Dodd, Ph.D.
Richard Simon, Sc.D.

National Cancer Institute
Rockville, MD 20852
dodd@mail.nih.gov

1. D'Amico AV, Chen MH, Roehl KA, Catalona WJ. Preoperative PSA velocity and the risk of death from prostate cancer after radical prostatectomy. *N Engl J Med* 2004;351:125-35.
2. Hilsenbeck SG, Clark GM. Practical p-value adjustment for optimally selected cutpoints. *Stat Med* 1996;14:103-12.
3. Altman DG, Lausen B, Sauerbrei W, Schumacher M. Dangers of using "optimal" cutpoints in the evaluation of prognostic factors. *J Natl Cancer Inst* 1994;86:829-35.

TO THE EDITOR: The provocative implications of the report by D'Amico et al. raise concerns about the use of a single, nonvalidated prognostic variable to select patients for adjuvant systemic therapy after radical prostatectomy. Some 68 to 75 percent of patients have no evidence of cancer (i.e., undetectable PSA levels), and only 7 percent die of cancer within 15 years after surgical treatment.^{1,2} The key questions with regard to adjuvant therapy after surgery are what level of risk justifies the potential side effects and how best to quantify the risk. Furthermore, the prognostic value of a PSA level that rises at a rate of more than 2.0 ng per milliliter per year before radical prostatectomy is clouded by biologic and interassay variations that average 30 percent in men without cancer.³ Some men could have an increase of 2.0 ng per milliliter per year by chance alone. Nomograms that incorporate all known risk factors to estimate probabilities of an event over time (e.g., recurrence) perform better than any single risk factor or risk group.⁴ A rapid rate of rise in the PSA level before surgery may be associated with a more advanced stage of cancer. However, it has not been validated by independent cohort studies as a prognostic factor to be applied in clinical trials (Fig. 1, facing page).

Fernando J. Bianco, Jr., M.D.
Michael W. Kattan, Ph.D.
Peter T. Scardino, M.D.

Memorial Sloan-Kettering Cancer Center
New York, NY 10021
scardinp@mskcc.org

1. Walsh PC. Surgery and the reduction of mortality from prostate cancer. *N Engl J Med* 2002;347:839-40.
2. Bianco FJ Jr, Dotan ZA, Kattan MW, Fearn P, Easthan JE, Scardi-