Coronary artery bypass grafting is not a risk factor for dementia or Alzheimer disease

To the Editor: We read with interest the recent articles by Knopman et al.[1] and McKhann et al.[2] examining the possible relationship of coronary artery bypass surgery (CABG) and the subsequent emergence of Alzheimer disease (AD). Our group has also recently published on the issue of AD incidence following CABG surgery[3] and see this forum as an opportunity to discuss these results, especially in light of our conclusion that CABG surgery is associated with the early emergence of AD.

In our study, we retrospectively followed a large VA cohort for up to 6 years after either CABG surgery (n = 5,216) or percutaneous transluminal coronary angioplasty (PTCA; n = 3,954), noting an adjusted risk of AD associated with CABG vs PTCA of 1.71 (95% CI 1.02 to 2.87; p = 0.04). We did not observe separation of the two groups until more than 3 years following the procedure. Thus, it is not surprising that the study by McKhann et al., as well as an earlier study by Newman et al.,[4] did not reveal any evidence for cognitive decline at up to 1 year of follow-up. However, it is notable that Newman and colleagues' study did observe evidence of cognitive decline 5 years post CABG.

The study by Knopman et al., while well designed and having a longer follow-up period, still represents a relatively small sample size with only 34 cases of AD noted. The wide 95% CIs just barely exclude the OR that we observed in our study (1.56 vs 1.71), although we acknowledge their point estimate is 0.78. It is likely that the two populations studied differ in baseline comorbidities, with the VA cohort possibly being a sicker population at the time of their procedure. A difference in the cohorts' health status at baseline could have contributed to the incongruent outcomes observed between our study and the Knopman et al. study.

As we have discussed in our report, we acknowledge a number of weaknesses in our study design, but we are concerned that the short time frame and low statistical power of the current studies could provide a misleading assessment of the impact of CABG surgery on the emergence of AD.

Martin M. Bednar, MD, PhD, T.A. Lee, PharmD, PhD,
B. Wolozin, MD, PhD, K.B. Weiss, MD, MPH, *Groton, CT*

Disclosure: Dr. Ben Wolozin received honoraria from the sponsor during the conduct of the study (<$10,000 per year). Dr. Todd Lee received a grant from the same sponsor for other research or activities not reported in this research (research grant for a COPD project, $10,000/year). Dr. Kevin Weiss has nothing to disclose.

Reply from the Authors: We appreciate the interest of Bednar et al. in our study, and we restricted our reply to the comments pertinent to our results. Our study[1] examined the long-term effects of CABG surgery on the brain by identifying incident cases of dementia in a geographically defined population.

We matched our dementia cases to nondemented controls of the same age (± 1 year) and sex drawn from the same community. Our study had a longer time frame compared to that of Lee et al.,[3] with a median lag time between CABG and dementia of 5.5 years (range = 0.1 to 15.9). We found no differences between cases and controls in the frequency of preceding CABG surgery.

We acknowledged in our article that we could not exclude a small association; however, our results showed no trend in the direction of a risk for dementia after CABG.[1] Our case-control methodology avoided the difficulty of identifying a suitable reference group for a cohort study. Short of using a traditional randomized clinical trial, it is impossible to prevent a difference in severity of cardiovascular disease between patients with CABG and referent subjects (confounding by indication).[5]

The comparison group of Lee et al. included persons who underwent PTCA because they had a less severe form of vascular disease than the subjects who underwent CABG surgery.[3] For example, their PTCA patients were younger, had far shorter lengths of hospitalization following the surgery (6.5 vs 11.9 days), and far fewer hospitalization days prior to the surgery (1.4 vs 4.5 days) than the CABG patients. Five or more diagnoses were associated with the index hospitalization in 59% of the PTCA patients vs 63% of the CABG patients.

Constructing a suitable comparison group for people undergoing CABG surgery has greatly hampered analysis of the long-term effects of CABG. Thus, it can be argued that the difference in rate of dementia observed by Lee et al. reflected the severity of the underlying cardiovascular disease in the two arms of the cohort study rather than the effect of CABG surgery itself on the brain.

David S. Knopman, Walter A. Rocca, *Rochester, MN*

Disclosure: The authors report no conflicts of interest.

References

1. Knopman DS, Petersen RC, Cha RH, Edland SD, Rocca WA. Coronary artery bypass grafting is not a risk factor for dementia or Alzheimer disease. Neurology 2005;65:986–990.
2. McKhann GM, Grega MA, Borowicz LM, et al. Is there cognitive decline 1 year after CABG? Neurology 2005;65:991–999.
3. Lee TA, Wolozin B, Weiss KB, Bednar MM. Assessment of the emergence of Alzheimer's disease following coronary artery bypass graft surgery or percutaneous transluminal coronary angioplasty. J. Alzheimer Dis 2005;7:319–324.
4. Newman MF, Kirchner JL, Phillips-Bute B, et al. Longitudinal assessment of neurocognitive function after coronary-artery bypass surgery. N Engl J Med 2001;344:395–402.
5. Szklo M, Nieto FJ. Epidemiology. Beyond the basics. Gaithersburg: Aspen Publishers, Inc., 2000.

What do people at risk for Alzheimer disease think about surrogate consent for research?

To the Editor: Patients with Alzheimer disease (AD) face a cruel paradox when it comes to clinical trials: the moment that people are the most eager to enroll in treatment protocols, they may least be able to decide for themselves whether participation is appropriate. The resulting inability to recruit volunteers for vitally needed research can slow or even stifle the development of new methods to combat AD at a moment when scientists are becoming increasingly optimistic about creating effective disease-modifying treatments.

What if a person no longer has full capacity to decide? Can someone else make the right medical decision for another?

Those and other questions are raised in a provocative study by Kim et al.[1] The authors surveyed a cohort of those at heightened risk for AD by presenting them with 10 research scenarios ranging from low-risk studies to more experimental trials including vaccines or gene transfer.

When confronted with the question of whether a family member should be allowed to enroll a patient with AD in a study, 90% of respondents said that it was acceptable if the risk were minimal. However, even with a riskier treatment, most of those queried felt that they would trust a family member.

We believe the results of the study are encouraging for both scientific and ethical reasons. First, it shows that the people who are more likely to be patients have confidence that AD research will find answers, even if they cannot choose to participate in trials of new agents themselves. Secondly, the survey reveals that there is faith in loved ones to act with caution and conscience for those who no longer have a voice in their medical destiny.

Providers must take great care as well to determine a person's wishes and concerns in advance of committing an individual to any medical risk.

Finally, it is interesting that the survey respondents were most enthusiastic about offering themselves as research subjects with family consent. The clear message is that patients who understand the risks are willing to commit themselves to potentially

life-saving research, and they want those who mean the most to them to carry those wishes out as a gesture of love and understanding and perhaps with the hope of changing their own destiny in the process.

Dale B. Schenk, *South San Francisco, CA*, Sid Gilman, *Ann Arbor, MI*

Disclosure: Dale Schenk is employed and holds stock in Elan Pharmaceuticals, a company that is identifying potential therapeutic candidates for Alzheimer disease. Dr. Sid Gilman reports no conflicts of interest.

Reference

1. Kim SYH, Kim HM, McCallum C, Tariot PN. What do people at risk for Alzheimer disease think about surrogate consent for research? Neurology 2005;65:1395–1401.

Wernicke encephalopathy after bariatric surgery: Losing more than just weight

To the Editor: Foster et al. describe a complication well known to bariatric surgeons—acute thiamine deficiency.[1] This tremendously disabling complication is nearly always preceded by persistent vomiting weeks or months after bariatric surgery and is most often caused by a stricture of the gastrojejunal anastomosis.

While highlighting the irreversible aspects of this complication is important, preventative measures are equally important. Any patient who has persistent vomiting after gastric bypass surgery should have an upper endoscopy to diagnose and treat a stricture. In addition, routine thiamine infusion should be administered in any bariatric patient who is readmitted to the hospital.

Obese patients often have nutritional deficiencies as they overconsume calories of poor nutritional value. In a recent report, 15% of morbidly obese patients were found to have preoperative thiamine deficiency.[2] This group of patients may be especially sensitive to developing irreversible neurologic damage.

Gastric bypass surgery, especially when performed by experienced surgeons with a dedication to follow-up care, can be one of the most positive events in an obese person's life. The improvements in quality of life and weight-related medical problems are well documented.[3] All physicians involved in the care of these patients should be educated in the diagnoses and prevention of nutritional deficiencies such as thiamine, calcium, and iron that are associated with this operation.

Ramsey M. Dallal, *Philadelphia, PA*

Disclosure: The author reports no conflicts of interest.

References

1. Foster D, Falah M, Kadom N, Mandler R. Wernicke encephalopathy after bariatric surgery: losing more than just weight. Neurology 2005;65:1987.
2. Carrodeguas L, Kaidar-Person O, Szomstein S, Antozzi P, Rosenthal R. Preoperative thiamine deficiency in obese population undergoing laparoscopic bariatric surgery. SOARD 2005;1:517–522.
3. Buchwald H, Avidor Y, Braunwald E, et al. Bariatric surgery: a systematic review and meta-analysis. JAMA. 2004;292:1724–1737.

Pentoxifylline in ALS: A double-blind, randomized, multicenter, placebo-controlled trial

To the Editor: Meininger et al.[1] report discrepant trial results for survival and functional outcome measures for pentoxifylline in amyotrophic lateral sclerosis (ALS). Their discussion of functional measures, and particularly the Amyotrophic Lateral Sclerosis Functional Rating Scale–Revised (ALSFRS-R),[2] deserves attention.

The authors report a negative effect of pentoxifylline on survival. However, their a priori design was for a one-sided test of the hypothesis that pentoxifylline is beneficial. The primary conclusion should therefore be that the drug is not beneficial ($p > 0.90$),[3] although this is not stated. The authors' interpretation of the harmful outcome not allowed for in the original design as statistically significant is post hoc. While their analysis stresses adjusted rather than unadjusted results, the unadjusted result may be preferable. Adjustment for prognostic factors is unnecessary, since randomization balanced prognostic factors, and the stepwise adjustment procedure does not yield a replicable analysis. The unadjusted result is not significant ($p = 0.107$ on the required two-sided test).

Regarding the ALSFRS-R, in secondary analyses the authors confirm that it strongly predicts survival time[4] (hazard ratio for the dichotomized ALSFRS-R, adjusted for prognostic variables, is 0.46, $p < 0.001$, table 3). As with survival, the impact of pentoxifylline on the ALSFRS-R is also in the harmful direction, and not significant ($p = 0.35$). By conventional criteria, the results suggest compatible rather than discrepant outcomes for survival and the ALSFRS-R.

Taking qualitatively different results using two correlated outcome measures, such as survival and the ALSFRS-R, at face value would require equivalent statistical power to detect an effect of corresponding magnitude for each outcome, and equally reliable measurement. For example, what magnitude of effects for the secondary functional outcomes would correspond to the 15% survival rate difference for which the pentoxifylline trial had more than 90% power (appendix E-1), and what was the power to detect these corresponding effects?

The authors state that "All studies had the statistical power to detect a difference in functional or survival endpoints." However, since analyses for secondary, functional outcome measures are commonly underpowered, susceptible to missing data, and often less reliably measured than mortality, we doubt that most meet the requirement we describe. These problems may explain the apparent lack of qualitative agreement with survival which some of them report.

The current question of whether, despite being strongly associated, survival and the ALSFRS-R as outcomes may produce qualitatively discrepant results is unsettled.

B. Levin, J.L.P. Thompson, G. Levy, H. Mitsumoto, P. Kaufmann, *New York, NY*

Disclosure: The authors report no conflicts of interest.

Reply from the Authors: We thank Levin et al. for their interesting correspondence. We apologize for not clearly stating that the drug was not beneficial. However, the drug had a negative rather than a positive effect, so we assumed that it was obvious that the drug was not beneficial.

We agree that the original design was for a one-sided test of the hypothesis that pentoxifylline was beneficial. However, even if the trial was designed primarily to detect a beneficial effect of the drug, we considered it important to inform neurologists and physicians of the possible detrimental effect of the drug on survival.

We find it difficult to believe that Levin et al. would consider statistical fine points more important than clinical common sense and safety. Levin et al. consider that adjustment is unnecessary, even if they also used such an adjustment in their recent publication in *Neurology*.[4] In our trial, adjustment was planned a priori. Adjusted and unadjusted results are consistent, demonstrating a 28% increased risk of death in the unadjusted analysis (HR = 1.28, CI 0.94 to 1.71) and 43% in the adjusted analysis (HR = 1.43, CI 1.05 to 1.96), even if the unadjusted confidence interval includes 1.00.

The principle of using adjustment or not in the statistical analyses in randomized trials led to a large debate in the statistical community, but the majority of statisticians are now in favor of adjustment, if adjustment factors and the statistical procedures are of course a priori defined as in our trial.

Levin et al. suggest that in order to compare survival and

ALSFRS-R, we have to consider the equivalence of statistical power. However, as discussed in the article, the ALSFRS-R analysis in most trials (including our trial) is equally powered compared to the survival analysis. Figures 1 and 2 demonstrate that the treatment effect on the ALSFRS is less than the effect on survival.

Finally, Levin et al. state that "functional outcome measures are commonly underpowered, susceptible to missing data, and often less reliably measured than mortality." It seems that they provide a strong argument for survival analysis in ALS trials.

V. Meininger, B. Asselain, P.N. Leigh, A. Ludolph, L. Lacomblez, P. Guillet, *Paris, France*

Disclosure: ExonHit Pharma funded the study and participated in the design and conduct of the study being discussed in this correspondence; collection, management, analysis, and interpretation of the data; and preparation, review, and approval of the discussed manuscript. P.G. was an employee of ExonHit Pharma.

References

1. Meininger V, Asselain B, Guillet P, et al., for the Pentoxifylline European Group. Pentoxifylline in ALS: a double-blind, randomized, multicenter, placebo-controlled trial. Neurology 2006;66:88–92.
2. Cedarbaum JM, Stambler N, Malta E, et al. The ALSFRS-R: a revised ALS functional rating scale that incorporates assessments of respiratory function. J Neurol Sci 1999;169:13–21.
3. Fleiss JL, Levin B, Paik MC. Statistical methods for rates and proportions. Third edition. Hoboken: John Wiley & Sons, 2003.
4. Kaufmann P, Levy G, Thompson JLP, et al. The ALSFRSr predicts survival time in an ALS clinic population. Neurology 2005;64:38–43.

Cerebrovascular reactivity and vasospasm after subarachnoid hemorrhage: A pilot study

To the Editor: We read with interest the article by Frontera et al.[1] The authors demonstrated that bedside transcranial Doppler (TCD) carbon dioxide reactivity (CO_2R) testing could predict symptomatic vasospasm after aneurysmal subarachnoid hemorrhage (SAH) with 57 CO_2R studies in 20 patients.

A similar conclusion using transient hyperemic response test of cerebral autoregulation was previously published.[2] In that article, 20 aneurysmal subarachnoid hemorrhage patients with no immediate postoperative deficits were studied. Bedside transient hyperemic response test was done with 5 to 9 seconds of carotid artery compression and TCD criteria. Primary impairment (at day 1 after surgical clipping) was noted in six patients and five of them went on to develop delayed ischemic neurologic deficits (DIDs, equivalent to symptomatic vasospasm). The other 14 patients did not develop DID.

It would be interesting to have the data of primary impairment of cerebrovascular reactivity of the study by Frontera et al. to see whether a similar primary impairment would have similar predictive values. At the time of significant vasospasm, cerebrovascular reserve as predicted by CO_2R should always be decreased. Another option to perform the CO_2R, as in our hospital, would be through acetazolamide injection.

The pathophysiologic implication of primary impairment of autoregulation predictive of symptomatic vasospasm might also be interesting. It might be hypothesized that a primary brain injury (initial hemorrhage or surgery) was a prerequisite for DID caused by delayed vasospasm. This double injury model for DID might be worthwhile to explore for improvement in management for patients with aneurysmal subarachnoid hemorrhage.

George K.C. Wong, Stephanie C.P. Ng,
Wayne W.S. Poon, *Hong Kong*

Disclosure: The authors report no conflicts of interest.

Reply from the Authors: We appreciate the interest in our article[1] and the observations offered. The transient hyperemic response test (THRT) used by Lam et al. found a significant association between abnormal THRT and delayed ischemic deficits after SAH.[2] This method of assessing autoregulation, in which transient decreases in carotid blood flow stimulate a compensatory arteriolar vasodilation, simulates rapid blood pressure cuff deflation or pressure challenge techniques. Some limitations of this technique include the risk of emboli from carotid compression and there is evidence of limitations in accuracy.[3]

Mechanoregulatory responses to changes in blood pressure may be mechanistically different from chemoregulatory CO_2 challenges. Another option is dynamic cerebral autoregulation (dCA), which evaluates changes in middle cerebral artery mean flow velocity (MFV) in response to naturally occurring fluctuations in blood pressure. A direct correlation of MFV and blood pressure suggests a loss of autoregulation. This technique has been applied in SAH and does predict vasospasm diagnosed by transcranial Doppler parameters.[4,5]

It is unclear whether dCA predicts symptomatic vasospasm or delayed ischemic deficits after SAH, though this technique seems promising since it is noninvasive and does not require a blood pressure challenge or carotid compression. Dynamic cerebral autoregulation testing and CO_2 reactivity testing (or alternately acetazolamide challenge) may be complementary in determining the risk of vasospasm after SAH. Future studies comparing dCA, CO_2 reactivity, and other modalities of assessing autoregulation in SAH are warranted.

Jennifer A. Frontera, Randolph S. Marshall, *New York, NY*

Disclosure: The authors report no conflicts of interest.

References

1. Frontera JA, Rundek T, Schmidt JM, et al. Cerebrovascular reactivity and vasospasm after subarachnoid hemorrhage: a pilot study. Neurology 2006;66:727–729.
2. Lam JM, Smielewski P, Marek C, Pickard JD, Kirkpatrick PJ. Predicting delayed ischemic deficits after aneurysmal subarachnoid hemorrhage using a transient hyperemic response test of cerebral autoregulation. Neurosurgery 2000;47:819–826.
3. Smielewski P, Czosnyka M, Kirkpatrick P, Pickard JD. Evaluation of the transient hyperemic response test in head-injured patients. J Neurosurg 1997;86:773–778.
4. Lang EW, Diehl RR, Mehdorn HM. Cerebral autoregulation testing after aneurysmal subarachnoid hemorrhage: the phase relationship between arterial blood pressure and cerebral blood flow velocity. Crit Care Med 2001;29:158–163.
5. Soehle M, Czosnyka M, Pickard JD, Kirkpatrick PJ. Continuous assessment of cerebral autoregulation in subarachnoid hemorrhage. Anesth Analg 2004;98:1133–1139.

Progression of progressive multifocal leukoencephalopathy despite treatment with β-interferon

To the Editor: We read with interest the article by Nath et al.[1] Interferon-beta is neither the first choice nor a proven therapeutic option for the treatment of progressive multifocal leukoencephalopathy (PML).

IFN-alfa has been studied in the past with conflicting results. Viral infections promote IFN secretion, which counteracts the disease by its inhibitory effect on the virus replication.[2] Interferon-alfa has been used for treating viral infections more than IFN-beta, but the effects of both may be very similar. The immunomodulatory anti- inflammatory cytokine effect of IFN-beta minimizing T-cell migration into the CNS exerts a therapeutic effect in multiple sclerosis (MS).

Reactivation of a latent JC virus infection in an immunocompromised patient appears to coincide with an impairment of the Th1-type cell function, different from the aberrant activation of IFN-gamma-producing Th1 in MS. Recent observations[3] have shown activation of different interferon-inducible genes in the JCV infected host, with no significant change in the transcripts of

IFN-alfa and IFN-beta. The host response induced by JCV is comparable to those described for several other herpesviruses, and it is possible that this response restricts viral expansion in healthy hosts. The response in an AIDS-diseased immune system may be different, and the effects of interferon could also restrain the response to an infection in an already immunocompromised host.

Studies have demonstrated an inhibition of HIV-1 replication in vivo and in vitro induced by IFNs, particularly IFN-alfa. The possible benefit of this therapy has not been established by clinical trials. However, recent reports of PML development in patients receiving the humanized monoclonal antibody against alfa4 integrins (Natalizumab), which also prevents cellular migration into the CNS, in combination with interferon-beta 1A[4,5] raises concerns on the risk-benefit of using beta-interferon in a T-cell–depleted host.

Eli Skromne, Victor M. Rivera, Daniel Ontaneda, Laura Ordonez, *Houston, TX*

Disclosure: The authors report no conflicts of interest.

Reply from the Authors: We thank Skromne et al. for their interest in our case report.[1] They raise concern that beta-interferon may block T cell entry into the brain (which is one of the reasons for its use in MS). If T cell surveillance is important in controlling JCV replication in the brain, then beta-interferon may be detrimental to patients with PML.

However, while T cell surveillance has been shown to control the virus in the periphery, the same has yet to be shown once the virus reaches the brain. The recent occurrence of PML in two patients who were taking both beta-interferon and humanized monoclonal antibody against alpha4 integrin (Natalizumab), which also prevents cellular migration into the CNS, supports this argument. However, these two patients had an accelerated course of PML and one of them had a very fulminant form of PML.[4,5]

Although it is impossible to know in our patient what the course of PML would have been if he had not received the beta interferon,[1] it appears that his illness followed a predicted course of PML as seen in patients with HIV infection in the pre-antiretroviral era.[6] There was no clear evidence of acceleration of the disease.

While we do not advocate the use of beta-interferon in the treatment of PML, the effect of beta-interferon on JCV replication is worthy of exploration in in vitro studies.

Avindra Nath, Anita Venkataramana, Daniel S. Riech, Irene Cortese, Eugene O. Major, *Baltimore, MD*

Disclosure: The authors report no conflicts of interest.

References

1. Nath A, Venkataramana A, Reich DS, Cortese I, Major EO. Progression of progressive multifocal leukoencephalopathy despite treatment with β-interferon. Neurology 2006;66:149–150.
2. Sen GC. Viruses and interferons. Annu Rev Microbiol 2001;55:255–281.
3. Verma S, Ziegler K, Ananthula P, et al. JC virus induces altered patterns of cellular gene expression: interferon-inducible genes as major transcriptional targets. Virology (PMID 16297951) in press. Available at: www.elsevier.com/locate/yviro. Accessed November 17, 2005.
4. Kleinschmidt-DeMasters BK, Tyler KL. Progressive multifocal leukoencephalopathy complicating treatment with Natalizumab and interferon beta-1a for multiple sclerosis. N Engl J Med 2005;353:369–374.
5. Langer-Gould A, Atlas SW, Green AJ, Bollen AW, Pelletier D. Progressive multifocal leukoencephalopathy in a patient treated with Natalizumab. N Engl J Med 2005;353:375–381.
6. Berger JR, Levy RM, Flomenhoft D, Dobbs M. Predictive factors for prolonged survival in acquired immunodeficiency syndrome-associated progressive multifocal leukoencephalopathy. Ann Neurol 1998;44:341–349.

What is the risk of sham surgery in Parkinson disease clinical trials? A review of published reports

To the Editor: After nearly a century of uncontrolled neurosurgical efforts to ameliorate symptoms of parkinsonism, it is good to know of the evolving consensus that new research must provide reliable double-blind control strategies.[1,2] If the only distinction required of a phase 3 study were the difference between placebo suggestibility and certain biological proof of the injectate's theoretical mechanism, then a scalp incision/burr hole double-blind control would provide adequate protocol design.

But the stubborn complexity of the pathophysiologic circuitry of parkinsonism, along with the theoretical baggage of various invasive techniques, leads to the logical necessity for brain penetration control data.

Experience provides evidence for four possible classes of clinical effects; unfortunately, they are not mutually exclusive.

1. Psychogenic placebo effect, prejudicial tilted judgment, often shared by observers as well as subjects. Argument that such improvement is negligible is unjustified.

2. The theoretical biological effect, somehow equivalent to total restoration of normal functional neuronal circuitry, has been accomplished. Conceptually competent candidate agents have included natural or artificial trophic or growth substances that reverse cellular degeneration, resurrect sick synapses, or supplement transmitter substance; viable cells that passively extrude functional chemicals or become intimately involved in synaptic circuitry control; powerful new structural agents like genes and stem cells; carrier substances like viruses and gelatin globs. Clinical improvement alone is inadequate proof of mechanism.

3. Acutely or subsequently, there are positive symptoms and signs of tissue injury like intractable movements, dementia, Lhermitte phenomenon, nausea, anorexia, vomiting, weight loss, hyponatremia, and depression.[3,4] Mechanisms of injury are secondary problems.

4. Improvement of parkinsonian symptoms may be the direct consequence of nonspecific injury of neural tissue in many regions, a remarkable paradox of parkinsonian pathophysiology.[5,6] Some prematurely enthusiastic claims for cure by adrenal and embryonic brainstem transplantation were based upon effects too acute to be attributable to physiologic mutation. But now the long term efficacy of subthalamic nucleus inactivation/lesion is well established.

Possible injurious effects that must be considered are not only mechanical, but also immediate and delayed toxic, infectious, inflammatory, antigenic, and neoplastic phenomena.[7] It follows that control experiments must include full doses of all of the potentially injurious agents that accompany the putative curative stuff. The ethical risk for human subjects will be best limited by more thorough and prolonged primate model studies that have become common custom. The burden of prime prototypes must be a rigorous challenge of the therapeutic hypothesis using pertinent physiologic, pathologic, and histochemical methods that cannot be readily engaged in human subjects.

William Landau, *St. Louis, MO*

Disclosure: The author reports no conflicts of interest.

Reply from the Authors: We agree with Dr. Landau that the safety and efficacy evaluation of new interventions requires well-designed trials that include a placebo control condition. Even though the majority of Parkinson disease experts agree with the use of a placebo surgery in well-designed trials, there remains debate about the degree of invasiveness of the control.[2] In addition, potential research subjects need to have a say in what is permissible.

There is literature representing the opinion of neurologists and ethicists but little to formally represent patient opinions. Before we inject "the putative curative stuff," we should assess patients' willingness to participate, knowing they may receive a "potentially injurious agent." From previous trials, we know that at least a small number of people are willing to participate in such research.

Samuel A. Frank, Karl Kieburtz, Robert Holloway, Scott Y.H. Kim, *Boston, MA*

Disclosure: The authors report no conflicts of interest.

References

1. Frank S, Kieburtz K, Holloway R, Kim SYH. What is the risk of sham surgery in Parkinson disease clinical trials? A review of published reports. Neurology 2005;65:1101–1103.
2. Kim SYH, Frank S, Holloway R, Zimmerman C, Wilson R, Kieburtz K. Science and ethics of sham surgery: a survey of Parkinson disease clinical researchers. Arch Neurol 2005;62:1357–1360.
3. Anderson FH, Lehrich JR. Lhermitte sign following head injury. Arch Neurol 1973;29:437–438.
4. Kordower JH, Palfi S, Chen E-Y, et al. Clinicopathological findings following intraventricular glial-derived neurotrophic factor treatment in a patient with Parkinson's disease. Ann Neurol 1999;46:419–424.
5. Landau WM. Artificial intelligence: the brain transplant cure for parkinsonism. Neurology 1990;40:733–740.
6. Landau WM. Tissue transplants for PD [special correspondence, reply to letters to the editor]. Neurology 1994;44:573–577.
7. Folkerth RD, Rudso R. Survival and proliferation of nonneural tissues, with obstruction of cerebral ventricles, in a parkinsonian patient treated with fetal allografts. Neurology 1996;46:1219–1225.

Correction

Bilateral involvement of a single cranial nerve: Analysis of 578 cases

In this recent correspondence "Bilateral involvement of a single cranial nerve: Analysis of 578 cases" by Alan R. Hirsch, Stephanie Fulton, Thomas L. Wilding, Frances Groen, and James R. Keane (*Neurology* 2006;66:1284), Stephanie Fulton, Thomas L. Wilding, and Frances Groen were mistakenly listed as co-authors.

Alan R. Hirsch is the sole author of the original letter, and James R. Keane was the author on the reply.

Correction

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