Recombinant hepatitis B vaccine and the risk of multiple sclerosis: A prospective study

To the Editor: Hernán et al. report an association between hepatitis B vaccine (HBV) and multiple sclerosis (MS) in a study mislabeled as “prospective.” Although the source data were recorded prospectively, this is a retrospective nested case control study. This introduces potential biases, such as ascertainment of HBV status when vaccinations were recorded in the notes but not in the computerized database.

The UK HBV program is targeted at people at high risk of infection. However, uptake of HBV is suboptimal in these groups, so that vaccinated individuals are those at highest risk. This means that HBV status was highly likely to be confounded by risk factors such as IV drug use (IVDU) and sexual practice, neither of which were adjusted for by Hernán et al.

IVDU is associated with immune-mediated diseases, which may include MS. The subanalysis excluding the 2% of subjects with “risk factors” was inadequate, as it excluded only people whose records indicated a history of occupational risk, alcoholism, drug abuse, or chronic renal failure. Most of this information on these and other critical variables was not in the database or medical records. The inclusion of influenza and tetanus vaccinations does not rule out bias, which could operate selectively for exposure to HB vaccination.

Only 163 of the 438 eligible cases were included in the study, creating the potential for bias in ascertaining cases, and in selectively determining onset and severity of symptoms for vaccinated cases. The principal analysis was based on only 11 vaccinated patients with MS. This may explain an association between HBV and MS when analyzed by date of symptom onset, but not by date of diagnosis. The diagnosis was made in the past, independently of the study investigators, while the investigators determined date of symptom onset. Data for cases came from both the database and notes, whereas data on controls were obtained only from the database.

Upper respiratory tract infections exacerbate or trigger MS within a few weeks, so why would HBV trigger MS 3 years after vaccination? HBV is a subunit of the HB virus, which is not one of the many viruses previously implicated in MS. Using the Bradford Hill criteria for causation, the criteria of biological plausibility, consistency, coherence, and dose-response are not met. The temporal association reported in this study requires one to assume a long lead-time, and is perhaps the strongest single argument in favor of a spurious association. The large body of negative evidence and the methodologic weaknesses of the study indicate no need for change in vaccination policy.

C.R. MacIntyre, MBBS, PhD, H. Kelly, MBBS, MPH, D. Jolley, PhD, H. Butzkueven, MBBS, PhD, D. Salmon, PhD, N. Halsey, MD, PhD, L.H. Moulton, PhD, Sydney, Australia

To the Editor: Hernán et al. found a puzzling increased risk of MS within 3 years of a HBV. No previous epidemiologic study has found a significantly increased risk and a review by the US Institute of Medicine determined that the evidence favors rejection of a causal association between HBV and MS. We conducted one of the studies that did not find an increased risk. Differences between our study, which was conducted in three large US health maintenance organizations, and the General Practice Research Database (GPRD) study included the fol-
Sporadic Creutzfeldt-Jakob disease: Magnetic resonance imaging and clinical findings

To the Editor: We read with interest the article by Meissner et al. They reported 97 out of 157 patients with Creutzfeldt-Jakob disease (CJD) had hyperintense signal in the basal ganglia on T2-weighted images. They also addressed the possibility link with spongiform or gliotic changes in the brain tissues.

We had two cases with autopsy-proven CJD who exhibited low signal intensity in the putamen. Autopsies revealed typical findings in CJD including spongiform, neuronal loss, and gliosis. Clinical findings were characterized by dementia and myoclonus. Pyramidal signs were not seen in either case. Both of our cases also showed typical periodic sharp wave complexes on EEG. Both patients died nearly a year after onset. Molecular studies were not performed.

We would like to know if there was low signal intensity in basal ganglia in the T2-weighted images in their series. Basal ganglia hyperintensity in CJD has been reported. They hypothesized that spongiform or gliotic changes could contribute to display hyperintense signal in the basal ganglia in T2-weighted image. Our cases had gliosis and spongiform changes similar to the cases studied by Meissner et al. but our MRIs showed low signal changes. Taken together, high or low signal intensity could occur despite the same pathologic conditions. Iron deposition, hemosiderin, and lipid deposits may produce hypointense signal but accumulation of these substances are not considerable in the brains of patients with CJD. Further pathologic and biochemical analyses are needed to clarify the MRI signal in CJD.

Yasuo Iwasaki, MD, Osamu Igarashi, MD, PhD, Yasumitsu Ichikawa, MD, PhD, Ken Ikeda, MD, PhD, Tokyo, Japan

Reply from the Authors: We read with interest Iwasaki et al.’s correspondence regarding two CJD patients displaying low signal of basal ganglia on MRI. In their series, no such abnormalities have been reported so far. The aim of our study, however, was the detection of high signal changes of the basal ganglia. It is possible that some cases of low signal changes might have been overlooked. A study including all MRI abnormalities is currently underway.

As Iwasaki et al. mentioned, iron deposition may lead to low signal intensity with increasing age. Unfortunately, we have no information on the age of the patients nor if any iron deposits could be found in the neuropathologic examination given. In prion diseases signal increase on DWI (diffusion weighted imaging) has been supposed to be due to spongiform changes leading to reduced water diffusion as the vacuoles measure only 5 to 20 μm. Signal increases on T2- and fluid-attenuated inversion recovery-weighted images have been described in the deep gray structures—an observation best underlined by the pulvinar sign of the new variant of CJD (vCJD), showing high signal of the pulvinar based on intense astrocytosis in this area.

Miguel A Hernán, MD, DrPH, Susan S. Jick, DSc, Boston, MA

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References


Staining: we evaluated neuritic neuropil as well as MS; we included information from personal interviews in addition to medical record data; and we evaluated different time intervals. To determine if these differences could account for the different findings we reanalyzed our data using similar methods as the GPRD study.

In the re-analysis, we included only MS cases (according to the International Panel criteria), assessed relative risks by single years after vaccination, and further restricted the analysis to documented data. We restricted to medical records data, we identified 119 eligible MS cases, of which only three had been vaccinated. The ORs were 0.4 (95% CI, 0.1 to 1.5) for ever vs never vaccinated, and 1.4 (0.1 to 23.6) for 0 to 1 year and 0.8 (0.1 to 8.9) for >5 years after vaccination; in the intervening years ORs could not be estimated due to lack of vaccinated cases or controls. When we supplemented the medical record data with information from the standardized personal interviews, we were able to include 276 cases of MS in the analysis; the OR for ever vs never vaccinated was 0.8 (0.4 to 1.4). According to timing of vaccination, the ORs were 0.7 (0.3 to 2.0), 0.7 (0.2 to 2.5), and 0.6 (0.1 to 3.1) for 0 to 1, 1 to 2, and 2 to 3 years after vaccination. The main concern with the analysis is that included is a privileged preferential recall of vaccinations by the cases. That all the OR point estimates were <1.0 argues against this possibility.

We found no increased risk of MS overall or at any time during the first 3 years after HB vaccination. Restricting the analysis to data from medical records did not alter this conclusion.

Frank DeStefano, MD, MPH, Eric S. Weintraub, MPH, Robert T. Chen, MD, MA, Atlanta, GA

Reply from the Authors: We welcome the reanalysis by DeStefano et al., which not only constitutes a methodologic improvement, but also allows for a more direct comparison with our estimates. Unfortunately, the stricter criteria used in the reanalysis resulted in period-specific estimates with CIs too wide to draw firm conclusions. This sample size problem would have only been aggravated had the authors mimicked our eligibility criteria more closely by restricting their cohort to individuals who were members of the health maintenance organizations for at least, say, 3 years before the start of follow-up (see below).

MacIntyre et al. do not consider ours to be a prospective study. We believe this is a semantic disagreement. In our study, the exposure information was collected before first symptoms of MS. This key feature of fully prospective investigations prevents recall bias. Whether the investigators made the decision to conduct this study in 1990 or in 2000 is irrelevant: the information was presented from case-control studies nested in these cohorts were 2.7 for cohort 1 and 3.1 for cohort 2. As a further clarification, our exposure information came from the computerized records only. Paper medical records were used to confirm the cases’ diagnosis and to help determine their date of first symptoms.

Finally, MacIntyre et al.’s questions about the time between HB and MS onsets are crucial. Future research efforts should be directed toward answering them.

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References

Statin therapy and risk of dementia in the elderly

To the Editor: We commend Li et al.1 for using robust methodology, especially a time-dependent Cox model. They argue that one reason for the potential biased results of previous case-control studies may have been in the method of selection of the controls. Controls may have been selected in such a way that a control may have had more opportunity to have been prescribed a statin. This may have spuriously shifted the OR toward a protective effect. The authors further elaborate that a nested-case-control study may have spuriously shifted the OR toward a protective effect. Immortal time bias can therefore occur in a classical cohort study or a nested-case-control study.

Immortal time bias refers to a phenomenon where failure to account for the time-dependency of exposure in a cohort study can affect the rates in the exposed and unexposed groups and therefore bias to rate ratio (RR = rate exposed/rate unexposed). It is possible that a person who entered the cohort in that study did not receive a statin until many months after cohort entry. In a time-independent analysis, this person would have been considered as exposed when in reality the true person time contribution in the cohort for this individual should have been unexposed person time. Subsequently, the rate in the unexposed group could artificially be made larger potentially biasing the rate ratio towards a protective effect. Because the OR may approximate a rate ratio when the disease of interest is rare, the OR obtained from the nested-case-control study may also be shifted towards a protective effect. Immortal time bias can therefore occur in a classical cohort study or a nested-case-control study. This bias may be avoided when a time-dependent Cox model is used in the analysis of cohort studies as shown by Li et al.

Mahyar Etminan, PharmD, MSc, Mark Fitzgerald, JM, MB Chb, MRCPI, FRCP, Ali Samii, MD, FRCP, Vancouver, Canada

Reply from the Authors: We thank Etminan et al. for their thoughtful comments. We believe that the immortal bias suggested by them is consistent with our explanation, rather than being an alternative explanation, regarding how the failure to account for timing of exposure in a case-control study could result in a biased estimation of the OR towards detecting a “protective” effect of statins. In a conventional case-control study, the failure to account for time of exposure is mainly due to the failure to establish a comparable time of exposure in the controls. For example, a case entered the follow-up study at age 65, developed dementia at age 70, started taking a statin at age 71, and exited the study at age 72. In this case, the use of a statin would not be counted as an exposure because statin use occurred after onset of dementia. When selecting a control for this case, the exposure time should be also limited to the same time period by using a “reference” or “index” time, i.e., from age 65 to 70, rather than at any time beyond the reference time point (age 70). If the control starts a statin at age 71, he should be correctly classified as non statin-exposed, because he did not actually use a statin in that exposure time period. Thus, both cases and controls have equal exposure time with respect to both length of exposure and calendar time.

The study by Jick et al.2 did use the “index date” as a criterion in the selection of matched controls to determine timing of exposure, although there was no explanation of how the index date was determined. The difference in our findings compared to those of Jick et al. is not likely due to this type of bias. However, the immortal time bias discussed by Etminan et al. in classic cohort studies justifies the rationale for choosing a time-dependent covariate over a fixed covariate in modeling statin exposure in the Cox regression model in our study. We observed a biased estimate of hazard ratio (HR) when modeling statin use as a fixed covariate (HR = 0.53, 95% CI 0.32 to 0.87), in contrast to modeling the statin exposure as a time-dependent covariate (HR = 0.90, 95% CI 0.54 to 1.51) in the Cox regression model. We believe the points raised by Dr. Etminan are valid and important, particularly for the design and analysis of future studies.

G. Li, MD, R. Higdon, PhD, W.A. Kukull, PhD, E. Peskind, MD, D. Tsuang, MD, E.B. Larson, MD, MPH, Seattle, WA

References


Interestingly, in a hamster model, high signal on T2-weighted MRI correlated with marked gliosis and only little vacuolation, whereas low signal was found in brain areas showing moderate to severe vacuolation and only little gliotic changes. Both kinds of lesions in an outweighed measure tended to show a normal signal in T2.5 The authors, furthermore, reported high signal at initial stage (matching predominant gliotic changes) followed by a signal hypointensity during the course (matching increasing vacuolation). These findings might explain the observation of low signal in the two reported patients with CJD.

In contrast to this hypothesis, there have been cases reported showing increasing signal on T2 during the disease course, whereas DWI signal (depending on vacuolation) was high already in the beginning.6 It is important to consider that the MRI signal caused by the underlying neuropathologic lesion pattern actually depends on a certain disease phenotype determined by the methionine-valine polymorphism of the prion protein gene and the type of prion protein (PrPSc type1 or 2, Sc = Scapie) and, possibly, also on the disease stage.

Further studies correlating MRI findings, neuropathologic lesion patterns, and phenotype will have to be performed.

Bettina Meissner, MD, Inga Zerr, MD, Göttingen, Germany

References


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Economic evaluation of donepezil in moderate to severe Alzheimer disease

To the Editor: Although the authors reported a well-designed economic evaluation,1 they misleadingly concluded that treatment with donepezil is economically beneficial. The authors state that they used standard χ² and t tests to compare costs. Nevertheless, no statistical test was presented to show the statistical significance of the cost saving.

None of the differences were statistically significant. Therefore, the conclusion of the authors in the original article was incorrect and misleading. There is no evidence of economic benefit of donepezil compared to placebo in the treatment of moderate to severe Alzheimer disease (AD).

Hein P.J. van Hout, PhD, Judith E. Bosmans, MSc, Wim A.B. Stalman, MD, PhD, Amsterdam, The Netherlands

Reply from the Authors: Van Hout et al. have expressed their reservations over aspects of the methodology and the conclusions of our economic evaluation of donepezil in moderate to severe AD. They indicate that there was no statistical test presented to show the significance of the cost saving. We stated in the Methods that we used a direct statistical comparison of costs, and in table 4 reported that there were no statistically significant differences at the 0.05 level between groups in mean costs over 24 weeks.1

Similar methodological approaches to ours have been used within the field of health economics.2 Our analysis did not include patient-specific adjusted costs as would be needed to construct a bootstrapped CI. In any event, we do not think that this would alter the lack of statistical significance between groups.

There are some discrepancies between the numbers in the table provided by van Hout et al. and the data reported in our study that make comparisons difficult. It is not clear why their adjusted total costs were different from that in table 4 of the manuscript. The difference in costs of unpaid caregiver time reported by van Hout et al. should be a negative value.

With respect to our conclusion, the determination of health economic benefits has been previously recognized as an issue not readily approached using conventional tests of statistical significance because health resource utilization and cost data are typically much more variable than efficacy.3 Achieving statistical significance would therefore require extremely large sample sizes and longer durations for adequate powering.4 A recognized alternative is to piggyback on the design of a trial of efficacy and safety, thus minimizing problems of internal validity and bias.4

Our economic analysis was conducted as an add-on study to the primary aim of the trial, which investigated the efficacy and safety of donepezil in moderate to severe AD with a sample size determined on the basis of a CIBIC plus primary outcome.5 We did not anticipate that we would achieve statistically significant differences. Nevertheless, we were able to show a net cost-savings in mean aggregate costs, independent of the previously demonstrated clinical benefits.3

It is important to understand that in cost evaluations designed to inform payers, it is total healthcare cost that is most relevant, and it is from this perspective that this analysis was performed.5

Howard Feldman, MD, Margaret Hux, MSc, Elias M. Schwam, PhD, Vancouver, British Columbia, Canada

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References

Table Patient and caregiver cost differences to society over a 24-week evaluation period

<table>
<thead>
<tr>
<th></th>
<th>Donepezil, n = 143a</th>
<th>Placebo, n = 146a</th>
<th>Difference (95% CI)†</th>
</tr>
</thead>
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<tr>
<td>Total patient costs</td>
<td>2,453 ± 3,626</td>
<td>2,837 ± 4,104</td>
<td>−384 (−1,281; 513)</td>
</tr>
<tr>
<td>Total caregiver costs</td>
<td>113 ± 209</td>
<td>92 ± 146</td>
<td>21 (−21; 63)</td>
</tr>
<tr>
<td>Cost of unpaid caregiver time</td>
<td>3,689 ± 3,267</td>
<td>3,847 ± 3,043</td>
<td>158 (−889; 573)</td>
</tr>
<tr>
<td>Total costs society</td>
<td>6,824 ± 4,985</td>
<td>6,774 ± 4,979</td>
<td>50 (−1,104; 1,204)</td>
</tr>
<tr>
<td>Adjusted total costs society‡</td>
<td>6,662 ± 4,497</td>
<td>6,885 ± 4,648</td>
<td>−223 (−1,282; 836)</td>
</tr>
</tbody>
</table>

* Values are mean ± SD.
† None of the differences are significant as all 95% CIs comprise zero.
‡ Adjusted for initial baseline costs.

Cosmetic neurology: The controversy over enhancing movement, mentation, and mood

To the Editor: The healthy human has vast, untapped potential. Neurologists do not need to create new neural capability or alter individual essence. In the military, we would be remiss if we did not seek to improve performance in sleep-restricted environments. When American warriors cannot sleep, when their lives are at stake, and when battles may be won or lost based upon ability to sustain performance, it would be unethical for the military not to provide a rational and well-researched fatigue countermeasure doctrine. Dextroamphetamine can lead to dependence. However, there are no reports of dependency or abuse with operational use, and there are no reports of flight surgeons overseducing or forcing countermeasures upon service members. There are no accidents or performance errors associated with the correct use of countermeasures. The incident of the US Air Force pilots erroneously firing on Canadian forces in Afghanistan, while alleged by
legal defense, was not substantiated as a contributing factor linked to their use of dextromethorphan.

Chatterjee refers to research with sleep-deprived helicopter pilots, and comments that only the tip of this research may reach the public domain. Chatterjee is correct, much of the work is published in technical reports (see www.usaarl.army.mil) rather than in peer-reviewed literature, and much is not published at all. However, a vast amount of peer-reviewed information on pharmacological interventions to sustain performance in healthy humans is available through a literature search of John Caldwell.

Chatterjee questions the safety of modafinil for use in healthy individuals, commenting that it may improve performance in some areas while impairing it in others. This is a serious concern. Application of countermeasures must balance cost with benefit. If judgments of leadership taking, and other sensitive neurologic functions are impaired rather than improved, the cost of using the countermeasure may outweigh the benefits. This is a topic of current study.

Military practitioners are among the most carefully regulated physicians. We understand the responsibility to assure the health and safety of our military members and of our nation. Research to tap into the healthy human's underutilized capacity may be called enhancement. This form of enhancement is an important contribution to not only society, but also to aging individuals who experience naturally-occurring cognitive declines. Cosmetic neurology is not what military neurologists practice; this implies our efforts are shallow or superficial.

Rather, neurologists may ethically and honorably help healthy individuals optimize their cognitive potential.

Lieutenant Colonel Michael Russo, MD, Colonel Cornelius Maher, MD, Colonel William Campbell, MD, Fort Rucker, Alabama

Reply from the Author: I appreciate Drs. Russo et al.'s comments about cosmetic neurology and their confirmation of my speculation that much research conducted on soldiers will not reach the public domain. I am also heartened that there are no reports of amphetamine dependency or abuse within any of the services, no reports of coercive prescribing practices among flight surgeons, and that military research shows that the benefits of modafinil outweigh the risks.

I do not consider what military practitioners do, or cosmetic neurology for that matter, to be shallow or superficial. While the term cosmetic has come to be associated with appearance rather than essence, it is rooted in the Greek word "kosmetikos," which refers to skill in arranging. My point was to discuss ways in which cosmetic neurology involves skilled neurologic arrangements that penetrate our very notions of personhood, and the promise and predicaments that follow. The questions I pose: Can you be more than you can be? Should you?

Anjan Chatterjee, MD, Philadelphia, PA

To the Editor: The use of neuroenhancements in the military noted by Drs. Russo et al. is an unwitting case study in the concerns about safety, coercion, and the role of physicians that Dr. Chatterjee, Dr. Hauser, and P raised in our articles.

Although the military may have good reasons for maintaining secrecy, the rest of us should not be expected to rely on what the military chooses to make our judgments about the safety of a drug or a procedure. The authors argue that the use of dextromethorphan is safe, because they have seen no reports of adverse effects, of dependency with "operational" use, or of flight surgeon's overprescribing them. We have to take their word for it because the data are not available outside the military—assuming that they are available within the military. We should never accept the unwavering commitment of any government and we should be especially skeptical when the institution involved, be it the military or a pharmaceutical company, has strong reasons to make the rest of us accept a particular finding.

Second, the military is a coercive institution. I suspect that if the soldiers are not actually ordered to take these drugs, their superiors let it be known that they are expected to do so. At minimum, they are compelled to take these drugs, and the members of their unit are at stake if they fail to take these drugs. The soldiers thus do not have a meaningful choice about whether they can take the drugs or not. Such coercion is perhaps justifiable, but only if an important ethical goal cannot be achieved in any other way. In addition, the drugs could easily be subject to "mission creep." While situations in which these drugs are needed may sometimes be unavoidable in war, the availability of such drugs makes the assignment of sleep-depriving missions easier. With these drugs available, the military is likely to assign missions to fewer soldiers rather than build in the sleep requirements that humans normally require. As a result, the use of these drugs will simply become a routine part of their job.

Third, the authors' role in prescribing neuroenhancing drugs for soldiers under their care raises general questions about the doctor-patient relationship. The authors believe that, as military physicians, they have responsibilities to both the health of "our military members and of our nation." These two responsibilities may conflict, especially if the desires of the military become equated in some people's minds with the needs of the nation. In that spirit, some military doctors at Abu Ghraib and Guantánamo Bay thought it ethical to advise interrogators about their prisoners' vulnerabilities. The authors, of course, claim a much more modest use of this principle: they only claim that "when battles may be won or lost," that it would be unethical not to provide performance-enhancing drugs for the "warriors" in their care.

Nevertheless, the doctors do not prescribe these drugs to better their patients' health, but to enable the soldiers to perform their lethal jobs better and thereby to advance what they perceive to be the greater good. When doctors begin to act on their own perception of the greater good, they can begin to treat their patients not as the individuals that need care, but as cogs in a war machine. Even if the war in which they are participating is a just war—even if it is a war for survival—doctors violate the deepest duties of their profession when they lose sight of the individuals they are supposed to help. If physicians keep their focus squarely on their patients, they will be better off ethically, and the rest of us will be better off medically.

Acknowledgment: The author thanks Jonathan Mink, David Goldblatt, and Jennifer Kwon for comments on earlier drafts of this response.

Richard H. Dees, PhD, Rochester, NY

Reply from the Editorialist: Dr. Russo's comments, and the reactions elicited by my colleagues, highlight again the need for active engagement by the neurologic community in the use of neurologic enhancement technologies. The problem here, as with many bioethical issues, is that reasonable people will often disagree. Our community has two obligations. I think, the first, as stated eloquently by Dr. Dees, must be to support the traditional view of the physician—patient relationship which required that the physician always act in the best interest of the individual patient. Even this mandate is not black and white, however. Consider the situation in which acting in the best interest of the patient may conflict with the goal of improving public health. Would it be ethically justifiable to vaccinate our patients against polio for the purpose of maintaining herd immunity (rather than providing individual protection), even though vaccination carries a risk—albeit miniscule—of neuroparalytic complications. From his military vantage point, Dr. Russo provides an interesting and important example in which the greater good is not that of public health but that of combat readiness, public welfare, and the national interest. Perhaps the military should distinguish between a personal physician and a combat physician whose role is to prepare troops for battle. In such a situation one would hope that the personal physician is given the final say over any therapeutic option suggested (or imposed) by the combat physician. By analogy, professional athletes have long been aware of the potential conflict of interest inherent in their relationship with team physicians. They usually seek the opinions of independent experts before undergoing treatment for sports injuries. They recognize that team physicians may be subtly (or not so subtly) incentivized to return the player to the field as soon as possible. An egregious example of this type of potential conflict occurred several years ago in professional baseball; in this case the team physician was also a member of the ownership group.

Our second obligation, and the purpose of the editorial, was to suggest that we must as a profession provide expert and evidence-based data on the risks and benefits of interventions that enhance neurologic functions.

Stephen Hauser, MD, San Francisco, CA

April (1 of 2) 2005 NEUROLOGY 64 1321
Correction

Report from the Neurology Scientific Integrity Advisor: Year 1

In the Editorial “Report from the Neurology Scientific Integrity Advisor: Year 1” by Robert B. Daroff, MD (Neurology 2005;64:588–589), there are two errors in the printed publication. The URLs in references 3 and 7 are incorrect. The references should read as follows:


The publisher regrets the errors.
Report from the Neurology Scientific Integrity Advisor: Year 1
Neurology 2005;64;1322
DOI 10.1212/WNL.64.7.1322

This information is current as of April 11, 2005

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