References

Response
We thank Drs Hart, Halperin, and Miller and Ms Pearce for their interest in our article on the factors associated with the failure of aspirin treatment after stroke.

Unfortunately, the small sample size of patients with atrial fibrillation does not allow us to further stratify the patients to perform multivariate analysis (Cox proportional hazards model).

As for the second point, we indeed found that ischemic heart disease is a significant risk factor for aspirin failure, since even after Bonferroni correction the odds ratio for this risk factor remain statistically significant.

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Neurobiology of Passive Avoidance Impairment After Ischemia
Karasawa et al.1 report that passive avoidance impairment after ischemia is related to damage of CA1 neurons of the hippocampus related to memory and habituation. The neurobiology is suggested by the release of dopamine1 lateralized to the right hemisphere2 subserving passive avoidance.3 This hypothesis is supported by optimal response organization at intermediate dopamine tone in a medial-frontal-striatal activation system2 and by operant conditioning of CA1 bursting at different concentrations of dopamine, showing a sharp peak at 1 mM and falling abruptly when this optimal concentration was either halved or doubled.4 The fact that delay-dependent speeding of reaction time, indicating motor readiness, is abolished by depletion of dopamine subserving mood prompts the evaluation of ischemia-induced behavioral changes by monitoring behavioral correlates of mood, ie, speech hesitation and switching pausess. This method is supported by the contribution of articularatory rehearsal to short-term memory5 and by the association of >2-second speech pauses with prearticularatory repair6 and competitive and courtship activity.7 These findings suggest a causal relationship between impairment in passive avoidance and neuronal damage in the hippocampus,8 thus tending to confirm powerful isomorphisms between mind and body and the existence of deep and lawful mental structures governing human cognitive and emotional functioning reflecting properties of neuronal activity and firing.9

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References

Response
We thank Dr Friedman for his comments on our article.1 In our study, passive avoidance impairment was apparent even on day 28 after 5 minutes of induced ischemia. On that day, locomotor activity in the group subjected to the 5-minute ischemia neither increased nor decreased; rather, it was the same as in the sham-operated group. This indicates that motor function was normal on day 28 and that passive avoidance could be impaired only by mental dysfunction. In clinical studies, mental or motor dysfunction can be induced by cerebral ischemia or by stroke.2,3 However, whether the motor dysfunction in our study on ischemic gerbils reflects clinical motor dysfunction after stroke is unclear. Furthermore, passive avoidance impairment after ischemia, which may be attributed to mental dysfunction and to CA1 neuronal damage, warrants further attention for possible links to clinical symptoms. The dopaminergic system is no doubt a factor related to various behaviors. Our ongoing studies on behavioral changes after ischemia include factors related to dopaminergic systems.

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Experimental Stroke Treatment With High-Dose Methylprednisolone
We read with interest the recent article by de Courten-Myers et al.1 There are several parallels between this study and a study we recently published.2 Because ischemia is a primary pathophysiological mechanism in epidural brain compression,3 both studies involve transient regional cerebral ischemia. Both the steroids in the study by de Courten-Myers et al and the hypothermia in our study are considered to protect and resuscitate by affecting several sites along the ischemic cascade.4 In both studies treatment was initiated early, 30 minutes into the insult by de Courten-Myers et al and 15 minutes into the insult in our study. The results of the two studies are remarkably similar. In neither study did treatment decrease mortality, but in both studies treatment significantly decreased the cerebral infarct size (P<.05 in the de Courten-Myers study and P=.07 for infarct and P=.03 for overt histological damage in our study). In the de Courten-Myers study treatment clearly improved cerebral blood flow during ischemia (P<.005),...
and in our study hypothermia clearly delayed increased intracranial pressure and thereby prolonged a higher cerebral perfusion pressure (P=0.1).

We propose that even in a well-controlled experimental study, and despite prolonged postinsult control of extracerebral variables, 2 with an adequately severe cerebral focal ischemic insult small animal-to-animal variations will lead to the inevitable death of a certain percentage of the animals. Present treatment modalities are inadequate in preventing this mortality from diffuse brain swelling and herniation. Prolonged moderate hypothermia (31°C) but not mild hypothermia (35°C) postpones intracranial hypertension while the hypothermia lasts, but it does not prevent the delayed intracranial hypertension that leads to herniation and brain death during rewarming in some of the animals. 25 The modalities that are effective decrease the cerebral ischemic damage of surviving animals, as expressed by the brain infarct size and cerebral perfusion.

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References

Statistical Significance Versus Clinical Importance

The article by Walzl et al 1 describes the results of heparin-induced extracorporeal low-density lipoprotein precipitation (HELP) treatment in patients with acute embolic stroke and multi-infarct dementia. The authors conclude that “the apheresis causes an immediate and significant improvement of the hemorheologic pattern, obviously followed by an improvement of clinical symptoms, which has so far not been achieved by any hemorheologically active substance to a comparable degree and time.” I seriously doubt the validity of the conclusion on several grounds.

1. It is not clear how bias was controlled in selecting the control group of 30 patients from the 96 who were assigned to the non-HELP group by the computer. More importantly, no attempt was made to blind the outcome evaluators. This is particularly important in assessing disability (as opposed to death), where measurement is more prone to bias. Thus, a possibility exists that the results are influenced by bias in the selection and/or the measurement processes of the study.

2. Statistical significance does not equal clinical importance. It only tells us that the observed differences in the outcome are unlikely to be due to “chance alone.” This may be a useful first step in evaluating the importance of the observed differences, but it is important to examine the clinical importance of the observed differences. We should keep in mind that there may be differences between groups that are “statistically significant” but “clinically meaningless.” 27

The treatment resulted in a 3.6- to 6.3-point difference in the Barthel Activities of Daily Living Scale score and a 1.8- to 2.9-point difference in the Mini-Mental State Examination (MMSE). There is no evidence to suggest that these represent clinically important differences. According to the Barthel Index scale, the minimum change that can be recorded is 5 points, and this represents just one level of change in only one of the items. In view of this, most clinicians would not consider a 6-point difference as clinically important. Similarly, in the MMSE, a 2- to 3-point difference may not mean improvement in even one item for several of the items. Therefore, it is doubtful that this will be considered clinically important.

To summarize, the study demonstrates a statistically significant but clinically insignificant difference. This is not to say that the scales are meaningless but to emphasize that their use requires careful consideration of their properties. One good example of its proper use is the multicenter United Kingdom trial of nimodipine in acute stroke, 28 in which the Barthel Index score of 60 or more was used to define “independence,” which was their primary outcome. This cutoff score was obviously irrelevant in the study by Walzl et al, 25 because they included only cases with a score of 84 or more. One wonders what the authors expected to achieve in patients with a score of 84 or more, but a cutoff to meet their expectation could have been chosen. In the jargon of measurement theory, the scales have well-established “discriminative” but less validated “evaluative” properties. 4 Some authors consider simple methods of assessing outcome as equally valid 28 and reprimand the use of stroke scales. 6 Even though this position seems extreme, it serves as a useful reminder to select outcome measures that are (1) clinically relevant and meaningful; and (2) reliable, valid, and sensitive for the purpose of the study.

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References

Association of Abdominal Aortic Aneurysm and Carotid Artery Stenosis

We read with interest the article by Karanjia et al 1 that identified the association of aortic aneurysms with carotid artery disease. We have also identified this association in a previously published article that to our knowledge is the only other article to do so. 2 The authors identified aortic aneurysms in 20% of patients with carotid stenosis greater than 30% as measured by duplex ultrasound. The criteria that the authors used, however, defines an aortic aneurysm as any focal dilation of the vessel greater than 2.5 cm. Although a measurement of this diameter may be considered aneurysmal if a saccular dilatation is identified, it does not appear evident from the article. The subcommittee on reporting standards for arterial aneurysms has defined an aneurysm as a permanent
Experimental stroke treatment with high-dose methylprednisolone.
S Pomeranz and P Safar

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The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/25/7/1526.2.citation

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