Hyperhomocysteinemia, MTHFR 677C→T Polymorphism, and Stroke

To the Editor:

We welcome the report from Madonna and co-workers examining the role of prothrombotic and homocysteine (Hcy) pathway polymorphisms in risk of ischemic stroke in young adults.1 We wish to comment on several issues raised by their article relating to the design of studies of genetic risk factors for complex phenotypes such as ischemic stroke, which we believe to be important when interpreting their findings. As the report points out, genetic predisposition to a complex human phenotype such as stroke is unlikely to be mediated by a large influence of 1 or 2 genes. Many observers agree that it is likely to result from a combination of relatively small individual effects of several genes, each predisposing to stroke via their influence on intermediate phenotypic traits, such as hypertension or hyperlipidemia.2–4 This assumption has several implications for the design of epidemiological studies examining candidate genetic risk factors for stroke.

First, given the small anticipated effect size associated with any single candidate polymorphism, the group sample sizes required to robustly demonstrate an association will be very large. This is important to avoid a potentially erroneous conclusion that no association exists (type 2 error). This point is particularly relevant in the case of the MTHFR 677C→T polymorphism. Most prospective and retrospective studies to date have indicated that mildly elevated plasma Hcy is independently associated with ischemic stroke, and that the MTHFR TT genotype is associated with elevated Hcy. Paradoxically, most studies have not demonstrated an association between ischemic stroke and TT genotype.3 One potential explanation for this apparent inconsistency is that the majority of studies lacked sufficient power to detect an association. Given a background rate of 17% in the general population, as reported in the article by Madonna et al have been reported to cause cerebrovascular disease primarily by predisposing to large- and small-vessel atherosclerosis.5–7 In studies of this nature, underrepresentation of subjects with large- and small-vessel stroke may further dilute the ability to detect an association of stroke with Hcy pathway polymorphisms, such as MTHFR TT genotype.

Finally, it is important to control for potential modification of genetic influences by environmental factors, such as vitamin status in studies of Hcy pathway genes.2–4 Unfortunately, this information was not provided in the report. It is particularly relevant to studies of the MTHFR 677C→T substitution, as data consistently indicate that the adverse effect of the substitution on plasma Hcy are abolished by adequate folate intake, suggesting that the TT genotype may be relatively more important in populations with low folate intake. This is relevant when interpreting their results in the US context, as recent data indicate that folate levels have increased in the US population since folate fortification of cereals in 1998, with accompanying reductions in plasma Hcy.8

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Response:

We thank Dr Kelly et al for their letter that emphasizes major aspects concerning the design of our study as well as the role of some genetic predisposing factors. As acknowledged by Kelly et al, we interpret our data to support the concept that, rather than single genes, the combination of several genes, each causing a small effect per se, is important to lead to complex human phenotypes such as stroke. Nevertheless, our data emphasize that, similar to factors such as cigarette smoking, hypertension, diabetes, and hyperlipidemia, hyperhomocysteinemia is more common in cases than in controls and is important to help identify subjects with a history of early-onset ischemic stroke.
From studies on other conditions associated with the risk of ischemic events, hypercholesterolemia rather than genetic defects leading to hypercholesterolemia are associated with the clinical setting. In keeping with this, candidate genes thought to play a role in arterial thrombosis (including ischemic stroke) correlate with quantitative/qualitative changes in the levels of the protein and poorly with ischemic events. This is also true in the present report: rather than with the ischemic event, MTHFR TT mutation correlates with serum levels of homocysteine. As Dr Kelly et al are aware, there is a variety of combinations of genetic/environmental factors leading to hyperhomocysteinemia. Despite this, appropriate interventions (folate) correct hyperhomocysteinemia in subjects with as much as in those without homozygosity for the MTHFR TT mutation. This does not imply that it is not worth looking for the association of this polymorphism with the event in larger sample sizes; it only suggests that the impact that these findings may have for the identification of subjects at risk is likely to be rather limited.

The point of stratification of the sample(s) according to the type of event (atherothrombotic, cardioembolic) is well taken. Several groups believe that rather than in atherosclerosis, homocysteine is involved in platelet activation and thrombosis. Nor have we found conclusive clinical data that at low concentrations, homocysteine is atherogenic while it is thrombogenic at higher concentrations. Thus we are not entirely sure that stratifying the sample(s) according to the type of event will help clarify the role of the MTHFR TT mutation in early-onset ischemic stroke.

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**Helicobacter pylori, CagA-Positive Strains, and Ischemic Stroke**

To the Editor:

In their interesting study, Heuschmann et al showed the chronic *Helicobacter pylori* infection to be associated with a higher risk of stroke caused by small-artery occlusion, a subtype of ischemic stroke also sharing pathomechanisms with atherosclerotic disease. A similar trend was demonstrated for stroke caused by large-artery atherosclerosis, although this trend was not statistically significant. We would like to make some comments on it. Several studies have shown that the clinical outcome of *H pylori* infection is strictly related to the genetic polymorphism of both the bacterium and the host. In fact, recent findings have demonstrated *H pylori* infection to be only weakly associated with ischemic heart disease in multivariate analysis. On the other hand, the more cytotoxic *H pylori* strains, bearing the cytotoxin-associated gene A (CagA), were highly prevalent in patients with ischemic heart disease. On the basis of these observations, it could be interesting to investigate the prevalence of CagA-positive strains of the bacterium in patients with ischemic stroke. Various pathogenetic mechanisms have been postulated to explain the association between infection by the cytotoxic *H pylori* strains and the atherosclerotic process. Because atherosclerosis is a chronic inflammatory disease, the stronger persistent low-grade immunoinflammatory burden evoked by the infection by CagA-positive strains could play a role in this association. Moreover, a cross-mimicry between CagA protein and antigens of the endothelial wall of cerebral arteries has been demonstrated and has been postulated to promote the atherosclerotic process by inducing endothelial damage. More recently, authors hypothesized that CagA-positive strains of *H pylori*, predisposing to gastric atrophy, may induce vitamin malabsorption and therefore hyperhomocysteinemia, a well-documented risk factor for ischemic heart disease. However, not all patients infected by *H pylori* and its CagA-positive strains are affected by atherosclerosis-related diseases. The most convincing explanation for this observation could be found in the complex interaction between bacterium and host. In conclusion, the presence of particular factors, such as infection by CagA-positive strains, in subjects with a genetic susceptibility to develop ischemic stroke may explain the different clinical outcome of the infection in different patients.

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**Response**

We appreciate the comments of Dr Gabrielli and colleagues and their interest in our article on chronic *Helicobacter pylori* and *Chlamydia pneumoniae* infection in acute ischemic stroke. We agree that chronic *H pylori* infection in general seems only to have a weakly positive association with coronary artery disease, but this association could be caused by confounding and/or biases. Gabrielli and colleagues hypothesized that infection with more virulent *H pylori* strains, eg, strains bearing cytotoxin-associated gene A (CagA), might increase the relative risk of coronary artery disease, based on the findings of a retrospective case-control study on 88 subjects. However, a recently published prospective study failed in reproducing these results. Although there have been dozens of studies seroepidemiologically linking coronary artery disease and *H pylori* infection, until now 3 studies have investigated the potential association between ischemic stroke and chronic *H pylori* infection. All of these studies found similar results, as follows: Grau et al reported elevated antibodies to *H pylori* in ischemic stroke by athero-
thrombotic mechanism (adjusted odds ratio [OR] 3.5, 95% CI 1.1 to 11.4). Markus and Mendall demonstrated a positive association between chronic *H pylori* infection and stroke caused by large-vessel and lacunar subtype (adjusted OR 2.2, 95% CI 1.1 to 4.2, and adjusted OR 2.5, 95% CI 1.2 to 5.3, respectively), and in our analysis a higher risk of stroke caused by small-artery occlusion was found for *H pylori*-seropositive participants (adjusted OR 3.3, 95% CI 1.2 to 9.6). One possible explanation for the different findings on the causative role of chronic *H pylori* infection between ischemic stroke and coronary artery disease might be the fact that risk factors for stroke differs from risk factors for coronary artery disease. Although many studies assume that risk factors for coronary artery disease are very similar—or even identical—to those for ischemic stroke, in contrast to coronary artery disease, ischemic stroke is a heterogeneous mixture of different etiologic subtypes caused by atherosclerotic as well as nonatherosclerotic mechanisms. A recently published report could demonstrate that different etiologic subtypes are associated not only with different risk factors but also with differences in age at onset, recurrence rates, and outcome. Thus, we agree that it would be of great interest to investigate a potential association between CagA-positive strains of *H pylori* and the risk of ischemic stroke. Future seroepidemiological studies about the role of *H pylori* infection in stroke will have to regard carefully the impact of chronic infection within the different etiologic subtypes. Ischemic stroke etiology should be classified according to a standardized classification scheme, such as the TOAST classification, to allow valid comparisons between the results of different investigations. Power calculations have to consider the number of patients in each etiologic subtype that are necessary to detect a potential association between chronic infection and different subtypes of ischemic stroke.

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**Influenza Virus Infection, Infectious Burden, and Atherosclerosis**

To the Editor:

We read with great interest the study by Philippa Lavallée et al. in a recent issue of *Stroke*. The authors found in a case-control study of 450 subjects that the risk of stroke was significantly reduced in the subjects vaccinated against influenza during the last 5 years. The authors conclude that influenza vaccination may protect against brain infarction by reducing infections.

A possible relationship between influenza and atherosclerosis, in particular myocardial infarction, was first suggested after epidemics of influenza struck Europe and the United States in the early 1900s. Increasing evidence exists indicating that inflammation and possibly infections play an important role in atherogenesis. The hypothesis of infectious agents that may play an important role in the atherogenesis is supported by the results of several epidemiologic studies, suggesting a possible atherogenic potential from particular pathogens, like *Helicobacter pylori*, cytomegalovirus (CMV), herpes simplex virus (HSV), and *Chlamydia pneumoniae*. However, existing epidemiologic data about the association of some of these pathogens and atherosclerosis are conflicting, and although attractive, the microbial pathogenesis theory for atherosclerosis remains unproven. Clinical data about the association of influenza virus seropositivity (in unvaccinated subjects) and atherosclerosis are lacking. We tested the possible association between influenza type A and B infection and presence of atherosclerosis of coronary arteries (defined as >50% diameter stenosis of at least 1 coronary artery assessed angiographically) in a study of 218 consecutive patients (not previously vaccinated against influenza) undergoing coronary angiography.

Blood of all subjects was tested for serum IgG antibodies to influenza A and B and for seromarkers of 4 other pathogens (*C pneumoniae*, hepatitis A virus [HAV], *H pylori*, and CMV). Of the 218 patients (54.6% men, mean age 64.6 years), 95 (43.6%) had anti-influenza A IgG antibodies and 141 (64.7%) had anti-influenza B IgG antibodies. Coronary artery disease (CAD) prevalence was 69.5% in anti-influenza A seropositive patients and 61% in anti-influenza A seronegative patients (*P* = 0.25). CAD was found in 66% of anti-influenza B seropositive subjects and 62.3% of anti-influenza B seronegative patients (*P* = 0.69). This analysis demonstrates that influenza (A and B) seropositivity represents no predictor of risk for CAD. Moreover, seropositivity for each other pathogen (tested in our study) was not associated with CAD. In contrast, the number of infectious pathogens to which an individual has been exposed ("infectious burden") correlated with prevalence of CAD. Four or more of the 6 seromarkers tested for particular infections were positive in 48.8% of patients with CAD and in 31.2% of patients in patients without CAD (*P* = 0.02). Five or 6 seromarkers were positive in 21.3% of patients with CAD and in 9% of patients without CAD (*P* = 0.03).

Therefore, we support the interpretation of the results by Philippa Lavallée et al. that infections subsequent to influenza may play a role in promoting the complications of atherosclerotic disease (in particular, brain and myocardial infarction) and may also induce hypercoagulation, rather than influenza virus infection playing a causal role in atherogenesis. However, some triggers like additional exposure to other pathogens or nonspecific stimulation of the immune system could influence the susceptibility to the atherogenic effects of infection with a particular pathogen agent.
To the Editor:

mortality were Glasgow Coma Score, age and hemorrhage (ICH). Factors independently associated with 30-day mortality in patients following a spontaneous intracerebral hemorrhage (ICH) were demonstrated accurate in the population from which it was developed. However, in order for a scale such as the ICH Score to be useful, it must demonstrate validity in other patient populations. Additionally, in studies of acute neurologic catastrophes such as stroke or traumatic brain injury, functional outcome, and not just mortality, may be an important outcome measure as well.

Testing the ICH Score

Hemphill et al\(^1\) present an analysis of 161 patients carried out to determine a reliable grading score for the prediction of 30-day mortality in patients following a spontaneous intracerebral hemorrhage (ICH). Factors independently associated with 30-day mortality were Glasgow Coma Score, age >80 years, ICH volume, ICH of infratentorial position, and presence of intraventricular hemorrhage. A score based on these variables was assigned to each patient. All patients within their dataset with an ICH score of 0 survived, and all patients with a score of 5 (highest score assigned) died.

Hemphill et al restricted the testing of the scoring system to the data that produced it. We were interested in whether this scoring system could predict unfavorable outcome (severe disability, death, or vegetative state) at neurological discharge. From Figure 3 it is apparent that for all patients scoring above 2, the rate of unfavorable outcome approaches 100%. In fact, 38% of patients with a score of 0 and 70% with a score of 1 are not independent at neurological discharge.

It therefore appears that this ICH scoring system is generally applicable inasmuch as the mortality is low in patients with an ICH score of 0 or 1. Thirty-day mortality rises steeply with a score of 2 or above. Unfavorable outcomes, however, are common in patients with a low ICH score, and this rises to almost 100% with scores of 2 and above. We feel that some sort of system to predict those capable of making an independent recovery from their ICH would be more helpful and is not provided by this simple ICH grading score.

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Response:

The ICH Score is a clinical grading scale designed for risk stratification of patients after acute nontraumatic intracerebral hemorrhage (ICH).\(^1\) The outcome measure chosen for scale development was mortality at 30 days, which is a commonly used measure in other ICH prediction models. The ICH Score was demonstrated accurate in the population from which it was developed. However, in order for a scale such as the ICH Score to be useful, it must demonstrate validity in other patient populations. Additionally, in studies of acute neurologic catastrophes such as stroke or traumatic brain injury, functional outcome, and not just mortality, may be an important outcome measure as well.
Fernandes et al bring out these important points in their retrospective testing of the ICH Score on their patient population. As demonstrated by their Figure 2, the ICH Score accurately risk stratifies patients with regard to mortality across the range of scores, even though the distribution of patients with various ICH Scores differs somewhat from the UCSF ICH Cohort from which the ICH Score was developed, and “neurosurgical discharge,” not the uniform time point of 30 days, is used for outcome assessment. However, they also attempt to use the ICH Score to stratify functional outcome at this same early time point of “neurosurgical discharge” and found that the ICH Score was weighted heavily toward poor outcome across the entire scale.

In both cohorts of ICH patients, early death and disability were too frequent to distinguish nondisability from other outcomes by hospital discharge or 30 days after ICH. Perhaps a longer duration of follow-up would provide more useful information about recovery and long-term functional outcome. Most acute stroke and traumatic brain injury studies, including the Surgical Trial in Intracerebral Hemorrhage (STITCH), use functional assessment at more clinically meaningful time points such as 3 to 6 months after the event.2–4 Furthermore, at least in the United States, functional status may not be the only determinant in the timing of hospital discharge. Early transfer to rehabilitation may occur in centers without comprehensive facilities, health insurers may demand transfer of patients from an initial acute care hospital to a covered facility regardless of the functional status of the patient at the time, and patients likely to die may be transferred to hospice. We believe, therefore, that an assessment of the utility of a scale such as the ICH Score in stratifying surviving patients with regard to long-term functional outcome should use a standardized outcome measure at a uniform time point that is clinically meaningful regarding ICH recovery and not prone to local variation in hospital discharge practices. Such a scale would likely have utility in stratifying patients for clinical research and clinical care in ICH.

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When Is a Stroke Actually “Stable”?  
To the Editor:

Lazar et al1 recently published an interesting study on the possibility of midazolam to transiently unmask focal deficits in patients with a good recovery after a stroke. The authors pointed to a direct γ-amino butyric acid (GABAγ-mediated inhibition of neural activity, thus suggesting a possible role for this neurochemical mechanism in poststroke recovery.

We would like to stress an additional effect of benzodiazepine (BDZ) on cerebral blood flow (CBF). It is known that BDZ causes a global reduction of CBF in normal subjects.2–4 A state of chronic hypoperfusion, which in turn could affect particularly the peri-infarct areas, has been demonstrated in stroke patients in the acute as well as in the chronic phase.5–7 These findings suggest the role of transient cerebral hypoperfusion in unmasking an otherwise clinically silent tissue with a reduced “perfusion reserve.”

Therefore, in addition to a direct GABAγ-mediated action, we suggest that a global reduction of CBF, linked to BDZ administration, should also be considered. This raises the possibility that a drug-induced critical hypoperfusion of peri-infarct tissue might contribute to the reemergence of previous symptoms.

Lazar et al1 brilliantly demonstrated that a stroke lesion is never “stable,” even in the later stages. If a contribution to the reappearance of the old symptoms might be also ascribed to CBF reduction, the latter factor should shed a new light on the complex interaction between drugs and poststroke recovery.

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Response

We thank Dr Di Piero and his colleagues for bringing to our attention the relevance of recent findings that benzodiazepines produce changes in cerebral blood flow. It is certainly possible that, in addition to direct GABAγ-mediated inhibition of compensatory mechanisms, midazolam-induced global hypoperfusion could be reducing the ability of perilesional brain regions to carry out new functions. Although there could be a lowered perfusional threshold in a chronically hypoperfused area adjacent to the infarct, an alternative explanation might be that there are fewer neurons in the compensatory zone that participate in the target function, making them vulnerable to lowered cerebral blood flow. Experimental observations support the notion that compensatory networks after stroke consist of a markedly smaller neural pool than the original system.1 Research using transcranial magnetic stimulation in patients after stroke reveals smaller motor evoked potentials in the affected limbs after stroke as compared with normal, suggesting fewer descending neurons responsible for the generation of movement in these limbs.2 More important, however, is that Di Piero and his colleagues assume that the perilesional area is the region solely responsible for the restitution of function. Investigations with positron-
emission tomography and functional MRI to study motor recovery have suggested the importance of the contralateral and ipsilateral cortex in studies of recovery after hemiparesis, even as soon as 24 hours after the stroke onset. The roles of the contralateral hemisphere and preserved ipsilateral regions have been similarly implicated in the restitution of language, with recent work indicating that poststroke patients with bilateral language networks have better functional recovery. The manner in which the contralesional hemisphere gains such control and may be vulnerable to targeted pharmacological challenge remains to be determined.

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Microbleeding on MRI as a Marker for Hemorrhage After Stroke Thrombolysis

To the Editor:

We noted with interest the article by Dr Kidwell et al, who describe an MRI application that detects microbleeds. Kidwell et al propose that this technique can identify patients who might be at high risk for hemorrhagic complications, if intravenous or intra-arterial thrombolysis is given. We agree that this application merits further study and have recently seen an example of asymptomatic hemorrhage after thrombolysis, in an intravenous tissue plasminogen activator (IV tPA)–treated patient. This 76-year-old female had no evidence of hemorrhage on pretreatment noncontrast CT. IV tPA was initiated 149 minutes after onset of symptoms, because of persisting right hemiplegia and global aphasia. MRI was performed 25 minutes after tPA infusion was initiated. Six microbleeds were seen on T2*- (susceptibility) weighted image using a 3-Tesla MRI scanner (Signa Medical Systems) as illustrated in Figure 1. The following day, CT brain scan was repeated, identifying an asymptomatic post-tPA hemorrhage. This was in the general area where a microbleed was visualized initially (Figure 2). This case example supports the claim by Kidwell et al of an association between microbleeding and tPA-related hemorrhage. Imaging at 3 Tesla has greater sensitivity to magnetic susceptibility and, therefore, may increase the sensitivity in identifying these lesions. We would also note that the identification of microbleeds could predict long-term complications of anticoagulation. Our patient with multiple microbleeds received long-term anticoagulation for chronic atrial fibrillation, which was presumed to be the cause of her stroke. This decision is a problematic one, especially when considering that warfarin-related intracerebral hemorrhage occurs in approximately 0.2% to 0.6% of treated patients. If an elderly population has a rate of microbleeding in the range of 5%, as previous studies have suggested, this MRI finding could also represent an important predictor of this serious long-term complication.

Larger-scale studies are needed to evaluate if the presence of microbleeds is useful in predicting patients who are at a higher risk for intracerebral hemorrhage from thrombolysis or long-term anticoagulation therapy.

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Letters to the Editor

Outcomes in Carotid Endarterectomy Performed by Vascular Surgeons or Neurosurgeons

To the Editor:

The article on New York State carotid endarterectomy (CE) outcomes by Hannan et al1 reports an admirably low adverse outcome rate across all cases studied but also shows, as their title suggests, a surprising difference in outcome favoring the patients of vascular surgeons versus neurosurgeons (adjusted odds ratio for adverse events in neurosurgeons relative to vascular surgeons, 3.17 [95% CI, 1.26 to 7.97]). The authors themselves point out several reasons why this result may be erroneous, such as a possibly higher rate of detecting postoperative strokes by neurosurgeons. Another important difference that might have influenced the result was that the proportion of asymptomatic patients was 67% for vascular surgeons and 53.3% for neurosurgeons; additionally, the adverse outcome rate for asymptomatic patients is lower in this and other series.2 Perhaps more importantly, the study sample was clearly not representative of all CE procedures done in New York State. The authors studied a voluntary registry, including only 7% of the surgeons in the state doing CE, among whom the adverse event rate was substantially lower than for the rest of the state.

Most importantly, the authors acknowledge that this difference between surgeons was not found in four other studies of CE outcomes. Given the increasing recognition among research methodologists that Bayesian reasoning is required to interpret statistically significant findings from new research in the context of preexisting research,3,4 we would propose that the finding of outcome differences across surgical specialties needs to be interpreted with great caution.

The study by Hannan et al1 uses elegant analytic methods and has shown that very low adverse outcome rates can be achieved with CE. However, we believe that the finding of a significant difference in outcomes between the two surgical specialties studied is not externally valid.

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Response

We would like to thank the authors for their comments on our article. We agree that another potential caveat is that the neurosurgeons had a lower percentage of asymptomatic patients, but we would like to emphasize that the presence of preoperative symptomatic stenosis was controlled for in the process of calculating risk-adjusted mortality rates for the surgeon specialties.

We agree that the study sample was not representative of the state as a whole, and that the findings are contrary to what was found in other studies. These facts were pointed out in the caveats to the study. Nevertheless, we believe that our findings are extremely interesting and worthy of further investigation because, unlike others, we were able to identify a strong relationship between risk-adjusted adverse outcomes and the use of various processes of care. Furthermore, the use of these processes of care was very strongly related to surgeon specialty, and this relationship was not investigated in other settings. Consequently, we believe that it remains to be seen whether these findings are reproducible in other settings.

Ultimately, we hope these data may suggest ways to improve outcomes for all patients undergoing carotid endarterectomy regardless of the specialty of the surgeon because the elements of care that we have identified as being associated with better results can be used by any qualified surgeon performing this procedure.

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