Ethnicity and Equity: Missing the Point

To the Editor:

We read with interest the recent editorial by Fustinoni and Biller on ethnicity and stroke.1 We feel that ethnicity is a critical aspect of understanding stroke outcomes, particularly within the Pacific rim, and are concerned by what appears a dismissive and cursory approach to the subject.

Despite the variation in definitions of “ethnicity” and “stroke,” ethnicity has consistently been shown to “a significant influence” for stroke. Ethnic differences in stroke incidence and stroke related mortality have been well documented in the United States, Europe, and New Zealand.2–4 Differences in risk factor prevalence and management,5,6 utilization of services,7 and functional and motor impairments8 have also been described to a lesser extent.

We agree with the suggestion of Fustinoni and Biller that lower socioeconomic status and associated risk factors may explain some of the stroke burden carried by ethnic minority populations. However, within each social class, premature stroke mortality still remains substantially greater for black men than white men in the United States9 and for Maori than non-Maori in New Zealand.10

Despite the increased stroke incidence rates, increased stroke severity and poor functional outcomes, mortality rates, and discharge destinations are the same for both black and white populations in Europe,3 and our recent work found that such outcomes are better for non-Europeans than Europeans in New Zealand. This challenges the fallacy that ethnic minorities are an unhealthy burden and that “whites” are the “gold standard.” We propose that the family unit plays a pivotal part in this important stroke outcome and that more attention should be directed toward supporting their role in stroke care.

Finally, we believe that as an editorial on ethnicity and stroke, the article by Fustinoni and Biller missed the main point. Although genetic research may explain some of the differences reported, current literature suggests that equity of stroke care does not exist for ethnic minorities. Accessibility, quality of service, and equity cannot be separated when delivering effective stroke care. There is little information about access to and the quality of stroke care services for any ethnic minority group. Perhaps rather than attempting to locate a responsible gene(s), such a refocus of research demands more attention in order to guide practical action. Some may find ethnicity and stroke research repetitious, but it is a fundamental tool for assessing need and monitoring the impact of health policy.

A sense of control over one’s health and a sense of hope are important determinants of health status.11 We believe that these are best achieved when there is partnership between researchers, health providers from ethnic minority groups, and the communities themselves on ethnic-specific research. In doing so we aim to encourage participation of all ethnic groups in stroke research and identify barriers to stroke care. Obtaining this information is just one step in the development of a framework to improve stroke outcomes. The humanitarian and economic rewards for reducing ethnic disparities are great,12 but further quality research is needed for these rewards to materialize.

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Response

We thank Drs Harwood, McNaughton, McPherson, and Weatherall for their interest in our editorial.1 We agree that there may well be patterns of disease that distinguish different ethnic groups. We do not agree that these differences may be determined “despite the variation in definitions of ethnicity.” If groups that are to be matched are not properly defined on the basis of comparable features, results will be flawed. If various but incorrect criteria are applied repeatedly, results may appear “consistent” but in fact only reflect a marred methodology. All the more so with a variable that is defined socially rather than scientifically. For instance, one of the studies cited by Harwood compares stroke incidence between white, black (defined by skin color) and Hispanic (defined by language) residents of an urban community in Manhattan.2 Another reports stroke incidence among Maori, Pacific Islands people (defined by place of birth), and “Europeans” in Auckland.3 Not surprisingly, Europeans is not defined as a group, it is just included. Of course, how does one classify a European? By birth, descent, language, or merely “appearance”? One strongly suspects that “Europeans” in Auckland would probably be “whites” in the United States. Moreover, “persons of Indian or Chinese origin were included with Europeans because there were too few.”4 Can results obtained in this way be consistent? Harwood and colleagues point out that even if purportedly “ethnic” differences may be explained by socio-
economic factors, within each social class premature stroke mortality remains greater for blacks and Maoris than for whites and non-Maoris. This could perhaps reflect a real ethnic difference. It could also be the result of a different social and therapeutic attitude in the management of stroke toward blacks and Maoris. It is curious that in many published reports, ethnic minorities have usually fared worse, notwithstanding the fact that in some instances mortality, discharge destinations, and outcome have been similar or even better in minorities. In any case, results will continue to be controversial if ethnic groups are not properly defined and other possible variables not looked at.

We fully agree that accessibility, quality of service, and equity cannot be separated when delivering stroke care and that information in this respect is scarce regarding minorities. Nevertheless, as we showed, genetic research has provided some breakthroughs that have not entirely been expected, in some cases disproving false “ethnic” assumptions. This was the main point of our editorial.

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Fatal Hemorrhagic Transformation of Acute Cerebral Infarction After the Use of Abciximab

To the Editor:

The Abciximab in Ischemic Stroke Investigators reported the encouraging results of their randomized, double-blind, placebo-controlled, dose-escalation trial.1 Of 74 eligible and consenting patients presenting within 24 hours of onset of their ischemic stroke, 54 patients were treated with 4 escalating doses of intravenous abciximab and 20 patients with placebo. The scheduled post-study CT brain scan detected asymptomatic parenchymal hemorrhages in 7% of abciximab-treated patients and 5% of placebo-treated patients; another 11% of abciximab-treated patients had asymptomatic parenchymal hemorrhages on unscheduled brain imaging (CT or MRI) performed on days 2 through 35. Symptomatic hemorrhagic transformation was not seen, while asymptomatic parenchymal hemorrhages were associated with a higher baseline National Institute of Health Stroke Scale (NIHSS) score. We would raise the following issue for clarification by the authors and report our limited experience of using abciximab in Chinese stroke patients.

Concomitant use of antithrombotic medications during the time period of diagnosing parenchymal hemorrhage was listed in Table 3 of the article.2 The scheduled CT brain scan detected asymptomatic parenchymal hemorrhages in patients A, D, G, H, and I, who also received concomitant antithrombotic medications, such as systemic heparin, low-dose heparin, aspirin, and warfarin sodium. Nevertheless, the study protocol required that antplatelet agents or anticoagulants not be administered until the results of the scheduled CT brain scan became available (as stated in the subsection on Ancillary Care within Subjects and Methods).1 The investigators stated that they were not certain whether these agents were administered before or at the time of hemorrhage. While it is perceivable that some patients might be taking regular aspirin at the time of admission, the administration of systemic, low-dose, and low-molecular-weight heparin could only be in-hospital, and so their commencement time should be well documented in the study.

With a background similar to that indicated in the article by the Abciximab in Ischemic Stroke Investigators,1 we designed a pilot study to evaluate the safety issue of administering intravenous abciximab in Chinese patients within 6 hours of symptom onset. Our regimen was a 0.22-mg/kg intravenous bolus of abciximab followed by intravenous infusion at 9 μg/min for 12 hours. Concomitant use of oral antiplatelet agents was permitted. Of 2 consenting patients who received intravenous abciximab, the second patient had a fatal hemorrhagic transformation of his acute cerebral infarction.

This patient was a 65-year-old man with a history of hypertension, ischemic heart disease, peripheral vascular disease, hypercholesterolemia, mild bilateral carotid artery stenosis, and right vertebral artery occlusion. He had 2 previous episodes of nondisabling ischemic stroke and was taking aspirin and ticlopidine. He was admitted for percutaneous angioplasty to his stenotic left subclavian artery. On the morning of the day of the scheduled angioplasty, he developed right-sided weakness, with an NIHSS score of 8 and a Glasgow Coma Scale (GCS) score of 15. The clinical diagnosis was a recurrent lacunar infarction. The initial CT brain scan revealed old infarcts over the left middle cerebral artery territory, with no interval change when compared with the last CT brain scan performed 6 months before. Informed consent was obtained from the patient and his relatives, and intravenous abciximab was commenced at 5 hours after symptom onset. He was allowed to continue his oral medications, including enteric-coated aspirin (at 100 mg QD) and ticlopidine (which was reduced from 250 mg BID to 250 mg QD). Reassessment at 10 hours after onset showed an NIHSS of 6, but his relatives noted dramatic recovery at 14 hours after onset. Nevertheless, he deteriorated at 10 hours after commencement of intravenous infusion of abciximab (ie, at 15 hours after onset). He had dense right hemiplegia; his GCS score was 9. Repeat CT brain scan...
revealed massive hemorrhagic transformation involving both the presumed site of acute cerebral infarction and the old cerebral infarcts (Figure). Transfusion of platelet concentrates was given, and the neurosurgeon recommended conservative treatment. He became comatose and died 12 hours after onset of the sudden deterioration (ie, at 27 hours after onset, or at 22 hours after intravenous abciximab). Further recruitment of stroke patients into this safety study was stopped. After reading the encouraging results from the Abciximab in Ischemic Stroke Investigators, we will seek the approval of our Ethics Committee to modify our protocol and continue our safety study in Chinese patients with acute ischemic stroke. We will use a lower dose of intravenous abciximab for the 12-hour infusion and will avoid concomitant use of other antithrombotic medications such as aspirin.

Abciximab (ReoPro) was kindly provided by Eli Lilly Asia Inc.

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Response

I thank Drs Cheung and Ho for their letter and for the opportunity to clarify the information included in Table 3 of the dose escalation study of abciximab.1 Our data collection forms listed all ancillary agents given during the first 5 days after enrollment, and that information is included in Table 3. Obviously, this material spans the time of the mandated CT examination, performed at approximately 24 to 36 hours after entry. As Drs Cheung and Ho noted, the protocol stated that antiplatelet agents and anticoagulants could not be started until after the completion of the CT study. To ensure the accuracy of the information, we contacted the sites that enrolled the 5 patients in question (A, D, G, H, and I) to reconfirm that treatment with an anticoagulant or antiplatelet agent was not started before the scan was obtained. The sites report that no stroke-preventive medications had been started in these 5 cases before the CT was performed.

Abciximab is a potent antiplatelet agent, and some cases of symptomatic hemorrhagic transformation are possible. The report by Drs Cheung and Ho of a case of fatal intracranial hemorrhage following administration of abciximab is sobering. They point out that their patient had received ticlopidine and aspirin in conjunction with the abciximab. I recognize that our trial might have been very fortunate that we had no such serious bleeding event. The dose escalation study of abciximab enrolled patients with a wide spectrum of moderate-to-severe strokes, and many cases were treated more than 12 hours after stroke. Presumably, some of these patients should have been at very high risk for symptomatic hemorrhage. Still, the study made every effort to avoid situations that might have been associated with a high bleeding risk. Because the dose escalation study was primarily focusing on safety, we wanted to avoid any concomitant medications that might cause bleeding. The experience of Drs Cheung and Ho emphasizes the importance of determining the potential risks before testing the efficacy of any new therapy for stroke. Their experience also should prompt care about giving other medications that affect coagulation simultaneously with abciximab to patients with acute ischemic stroke.


Chlamydia pneumoniae Infection and PFO-Associated Ischemic Stroke

To the Editor:

Ischemic stroke in young adults is a topic that has received increasing attention in recent years and has been accompanied by descriptions of case series in which the relative frequencies of risk factors and presumed etiology are assessed.1 A number of epidemiological and pathogenic studies have been published on the association between Chlamydia pneumoniae infection and ischemic stroke. The results are, however, controversial. These studies show a high degree of heterogeneity in the selection of patients and controls and in the interpretation of serological results.2–3 Wimmer et al4 studied a series of stroke patients aged <50 years. They concluded that chronic C pneumoniae infection is associated with an increased risk of stroke and TIA but were unable to detect any correlation between antibody titers and etiologic stroke subtypes.

Our study was designed to evaluate the potential role of C pneumoniae infection in specific etiologic subtypes of stroke in young patients. In our consecutive series of 101 patients with ischemic stroke, aged <46 completed years, and 101 matched controls, we evaluated C pneumoniae IgG and IgM antibodies by means of the microimmunofluorescence method. When the study was planned, the detection of IgA was not yet available. There was a statistically significant difference between the 2 groups with regard to the frequency of active chronic C pneumoniae infection (IgG ≥1:512) (25.7% versus 7.8%, P<0.05). After adjustment for cerebrovascular risk factors, the OR for inactive chronic infection (IgG ≤1:256) was 1.3 (95% CI 0.6 to 3.2), whereas that for active chronic infection was 2.7 (95% CI 1.0 to 7.3).

Furthermore, we considered serological patterns for the following etiologic subtypes: (1) atherosclerosis, (2) cardioembolism (80% of patients had a “high-risk” patent foramen ovale [PFO; eg, width >2 mm] and larger amounts of intratral shunting, or PFO in association with atrial septal aneurysm),5 (3) nonatherosclerotic vasculopathy (arterial dissection, arteritis), (4) procoagulant conditions, and (5) undetermined cause. Although we did not find any significant difference between stroke etiologic subtypes, a positive trend toward an increased prevalence of active chronic C pneumoniae infection was found in the cohort of 35 patients with PFO (13 of 35; 7 of these 13 had IgG titers equal to 1:1024). In the remaining 66 stroke patients, only 5 had the higher IgG titers. Considering these data, what pathogenetic mechanisms might link active chronic C pneumoniae infection and PFO as a cause of stroke? Might C pneumoniae reinfection induce a transient procoagulant state and be an additional risk factor for symptomatic emboli, when a potential route for paradoxical emboli is patent? Because the lungs are the usual site of C pneumoniae infection, is the spreading of the pathogen from the lungs to the endothelium of the heart pathogenically plausible from an anatomic and physiopathological point of view?

Our preliminary study has certain limitations, such as the relatively small sample size, if compared with the 5 etiologic categories we considered, which may have limited the power of the statistical analysis performed to detect possible correlations. This correlations would require a larger study, perhaps including

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PCR and culture techniques to test whether C. pneumoniae infection, besides being associated with activation of the atherosclerotic plaque at later age, might indeed explain the occurrence of ischemic events associated with PFO in the young. Nevertheless, we wish to suggest the hypothesis of a possible role of C. pneumoniae infection in ischemic stroke for preventive purposes in the young, since the microorganism is susceptible to antibiotic therapy.

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Response
We thank Rasura et al for sharing with us their interesting data, which suggests a possible role of Chlamydia pneumoniae infection in ischemic strokes among young patients with patent foramen ovale. As the authors rightly point out, their cross-sectional study, as previous similar studies, does not prove a causative role of the agent but gives new insights into the mechanism(s) of association between C. pneumoniae infection and acute stroke and transient cerebral ischemia: the West Birmingham Stroke Project. Stroke. 1998:29:404–410.


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Response

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Letters to the Editor

To the Editor:

There's No Place Like Home . . . for Some

With great interest, we read the article by Mayo et al.\(^1\) which compares the effectiveness of early poststroke discharge and multidisciplinary home rehabilitation with other practices of poststroke rehabilitation. The authors suggest that “prompt discharge combined with home rehabilitation appeared to translate motor and functional gains . . . into a greater degree of higher-level function and satisfaction with community reintegration . . . .”

In reviewing the study data, we note that only 194 (12.6%) of the 1542 potential stroke subjects screened were included in the randomization. The vast majority of the stroke survivors seen in the emergency room were deemed ineligible or inappropriate for this level of care. Thus, it is difficult to generalize findings to the larger stroke population. Furthermore, the authors defined their “usual care” group as experiencing “a range of services, including . . . extended acute-care hospital stays; inpatient or outpatient rehabilitation; or home care via local community health clinics . . . .” Since only 52% in the control group received nursing visits and 50% received physical therapy visits, this implies that some patients received no rehabilitation care at all. By lumping subjects who received no or varying intensities of rehabilitation services together into one group, the potential of identifying superior outcomes for any individual level of care in this group is diluted. Therefore, it is difficult to conclude that the home care intervention is superior to any other venue of rehabilitation. A more appropriate conclusion would be that prompt discharge combined with home rehabilitation appeared to translate into a greater degree of high-level satisfaction and community integration for a select group of stroke survivors.

Another issue raised by the data are the functional levels of the groups prior to randomization. The average Barthel Scale scores of 82.7 in the “usual group” and 84.6 in the “home care group” indicate that the stroke survivors in this study had extremely mild disabilities. This compares to a mean admission Barthel score of 37 from an earlier study of 539 stroke survivors treated on 17 inpatient rehabilitation units.\(^2\) The mean discharge Barthel score of the inpatients was 66, which still is significantly lower than the average mean entry score of the stroke survivors in the home care protocol. Thus, the discharge planners and home care clinicians who cared for the inpatients faced even greater challenges.

Overall, the authors may not be addressing the correct question. Many studies have claimed superiority of acute rehabilitation,\(^3\) subacute rehabilitation,\(^4\) day hospital,\(^5\) and coordinated home care in rehabilitative stroke survivors. However, further research needs to address the optimal level of care for stroke survivors of differing functional severities. A number of authors have focused on the “middle band of stroke survivors” as the most appropriate for hospital-level rehabilitation.\(^6\) In contrast, stroke survivors with mild disabilities and supportive families can go directly home, and those with severe disabilities might be best served in skilled nursing or extended care facilities. Depending on the level of disability, one might triage care based on a clinical guideline, such as that proposed by the Agency for Health Care Research and Quality (formerly the Agency for Health Care Policy and Research).\(^7\)

With this in mind, the home care program may be a viable alternative for some patients, but it assumes that the family is capable of caring for the stroke survivor or that the stroke survivor is able to care for himself or herself. It may not be appropriate for those with complex strokes (eg, stroke survivors at risk for aspiration due to dysphagia or those who are incontinent of bowel and/or bladder, impulsive, or at risk of falling). A coordinated home care program might be more appropriate than more intensive settings for stroke survivors with mild disabilities whose goals focus more on community reintegration and instrumental rather than basic activities of daily living.

This article makes one point of importance to the rehabilitation process regardless of where it takes place. Outside of the randomization process, the authors note that the intervention empowered the subject and his or her family to take charge of decisions for rehabilitation services. If rehabilitation clinicians fail to involve stroke survivors and families in the decision-making process, and rather render them as passive observers, they are not doing their jobs.


To the Editor:

Three days before reading the article by Golledge et al.1 I recommended carotid stenting to a 74-year-old patient with critical asymptomatic left internal carotid artery stenosis. After reading the article, I was tempted to reconsider my recommendation, but a closer analysis reveals multiple flaws in the reasoning of Golledge et al.

The authors cite 14 endovascular studies published from 1992 through 1998 involving a total of 714 carotid arteries, of which
230 were treated with stenting. Three of the studies recruited fewer than 15 patients. The 20 studies on carotid endarterectomy (including the authors’ own article) were published from 1990 through 1999 and recruited 63 to 1997 patients. One cannot compare carotid endarterectomy, a technology that is several decades old, to carotid stenting, a technique that is only several years old. Carotid stenting has a very significant learning curve. To compare carotid endarterectomy in its infancy to carotid stenting in its infancy would be more valid.

I explained to my patient that he was being referred to a physician who had performed some 700 procedures (Dr Gary Roubin, personal communication, June 5, 2000). Vascular surgeons such as Dr Golledge may envision a “turf war” with the endovascular experts. I view stenting as a safer, less-invasive approach for my patients—provided that they are not part of the physician’s “learning curve.”

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Response
I read with interest the comments of Dr Jeret regarding our article published in Stroke this year. Dr Jeret correctly states that a number of the series of carotid angioplasty were small, while in general the carotid endarterectomy series were larger. Dr Jeret also points out correctly that carotid stenting is an evolving technique at present. It is also true to state that carotid endarterectomy has been demonstrated in enormous randomized controlled trials as the treatment of choice for patients with symptomatic severe carotid stenosis; unfortunately, such data is not available for carotid stenting. Dr Jeret states “I view stenting as a safer, less-invasive approach for my patients.” Where are the data for this? Surely, the only scientific way of proving the value of stenting is from randomized control trials. As stated in our article, only 1 published randomized trial presently exists. This study was stopped after only recruiting around 15 patients because of the severe complications with the stenting group.

Ideally, we would have liked to perform a meta-analysis comparing randomized studies of stenting with carotid endarterectomy; owing to the paucity of randomized trials, such a comparison was not possible. Due to the increasing numbers of reported series of carotid stenting, we felt that some sort of comparison was badly needed so we could correctly advise patients of the most appropriate treatment at present. Hence the analysis we presented in our article, which shows that in the present state of the art, carotid stenting would not be advised for most patients with symptomatic carotid artery disease. Surely if we are to introduce a new technique for the treatment of symptomatic carotid artery disease we have to ensure that it is safe to do so, in both the short and long terms. The present data would suggest that carotid stenting is not a safe option in the majority of hands and therefore should be introduced only as part of carefully controlled studies. I would disagree with Dr Jeret’s opinion and feel that the flaws in the reasoning come from Dr Jeret’s idea that the evidence presently available demonstrates that stenting is a safer option.

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The Time Concept in Ischemic Stroke: Misleading

To the Editor:
Wang and colleagues studied cerebral blood flow (CBF), the apparent diffusion coefficient (ADC), and brain tissue sodium concentration ([Na+]i) in the experimental animal after occlusion of the middle cerebral artery and of both common carotid arteries.1 They observed a steady increase in [Na+]i in the most severe ischemic areas with CBF ≤40 mL · 100 g−1 · min−1 and an ADC ≤520 μm²/s. They suggest the use of [Na+]i in addition to MR diffusion and perfusion imaging to exactly assess the time of stroke onset, which they regard as essential before initiating thrombolytic treatment.

The authors overlook the fact that the clinical onset of stroke in humans is not identical with the fall of CBF below thresholds that induce edema and irreversible damage. Otherwise, the reversibility of stroke symptoms would be impossible, and the penumbra concept would be invalid. The [Na+]i method may allow determination of the time point at which hypoperfusion has reached a critical level in certain areas of ischemic brain tissue. This time point is presumably not identical with the time of stroke onset. The authors did not show that [Na+]i steadily increases in areas with less-severe ischemia, which may, however, be responsible for functional impairment. This reflects the obvious weakness of the time concept in ischemic stroke: the clinical symptoms may represent a volume of ischemic brain tissue with functional impairment of viable tissue, already irreversibly damaged tissue, and in most instances a mixture of both. Ischemic functional impairment can last over hours without visible brain tissue damage. This explains why about one third of CT scans remained normal in large stroke studies during the first 6 hours of stroke onset.1,2

The proposed [Na+]i method, though impractical, appears to be useful in identifying the partition of ischemic tissue with developing edema after very severe ischemia. It is well established that [Na+]i highly correlates with tissue water content after arterial occlusion.5,6 There are more practical measures, however, to determine the water content of ischemic brain tissue under clinical conditions: x-ray attenuation directly correlates with the specific gravity of tissue.7 The linear decline of x-ray attenuation could be used to determine the time point of edema onset that requires a period of very severe ischemia.8 Moreover, the relatively simple CT method allows determination of the extent of edema within an arterial territory at risk. It has been shown that this extent is associated with the risk of secondary hemorrhage after treatment with tissue plasminogen activator (tPA).9 I do not agree with the authors that any study could prove that the risk of cerebral hemorrhage increases with time after tPA administration. It is more likely that the extent of very severe ischemia determines this risk.10 The slogan “Time is brain” is useful for discussion with laypersons but misleading. I think it is more correct to say that “perfusion is brain,” and time is an important cofactor. The ticking clock is not needed. It may keep away a promising treatment from patients who really need it.11 The clinical status of the patient tells us that the brain is at risk, and CT (and probably diffusion-weighted MRI) depicts the volume of tissue that is already damaged. Do we really need more information for the decision to treat a patient with thrombolytics, neuroprotective agents, or decompressive surgery?

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To the Editor:
Wang and colleagues studied cerebral blood flow (CBF), the apparent diffusion coefficient (ADC), and brain tissue sodium concentration ([Na+]i) in the experimental animal after occlusion of the middle cerebral artery and of both common carotid arteries.1 They observed a steady increase in [Na+]i in the most severe ischemic areas with CBF ≤40 mL · 100 g−1 · min−1 and an ADC ≤520 μm²/s. They suggest the use of [Na+]i in addition to MR diffusion and perfusion imaging to exactly assess the time of stroke onset, which they regard as essential before initiating thrombolytic treatment.

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**Response**

We appreciate the comments of Dr von Kummer concerning our recent publication.1 His comments concern several issues: (1) the direct application of experimental results to the clinical situation, (2) confusion about what we were actually doing in terms of using [Na+] (determining functional tissue versus determining unsalvageable tissue), (3) that there are more practical ways to measure time (using CT to determine water content), (4) that time after onset is not the best measure of pathological progression in ischemic stroke (perfusion plus time), and (5) that current techniques are satisfactory for stroke diagnosis. In addition to the obvious internal inconsistencies between points 3 and 4, they and the other issues do deserve serious consideration.

First, his comments concern human stroke, and while our experimental laboratory results might have bearing on this situation, this will only be after much additional work. The editorial comments2 concerning our work mentions that “considerable work remains to be done.” Hence, we cannot be determined unless this scheme is attempted in the “real” world of clinical stroke.

Second, an important point that Dr von Kummer seems to have missed is that we chose the most severely ischemic regions without regard to functional status or the extent of marginal ischemia for use in the sodium clock method, as shown in our Figure 2A.3 The choice of these regions was based on CBF and/or ADC thresholds of 40 mL·100 g−1·min−1 and 520 μm2/s, respectively. The ischemic threshold in the rat of 35 to 40 mL·100 g−1·min−1 corresponds to 10 to 15 mL·100 g−1·min−1 in nonhuman primates.4,5 For the sodium clock to work, just one region of severe ischemia and/or ADC decrease large enough to be imaged needs to be consistently present. If this region exists, then so does the pathological progression to irreversibility characterized by the eventual increase in blood-brain barrier permeability and increased intensity in contrast-enhanced CT.9,10. If this region of severe ischemia is present, the clock will tick, whether for the increase of [Na+] or the eventual loss of that tissue to encephalomalacia. This region corresponds to the proposed first side of the therapeutic window that “may already be closed when the patient first presents.” Thus, the basis of the method is to choose an area in which [Na+] is increasing. Perhaps in the future information could be extracted, using [Na+] or the rate of [Na+] increase, from other regions that might be recruited or salvaged, but for now, all we have shown is that in the most severely ischemic regions in experimental ischemia, the rate of increase is consistent and provides a “ticking clock.”

Part of Dr von Kummer’s objections could be based on the possibility that the most severe ischemia does not occur at the onset of clinical symptoms in human stroke, whereas in experimental stroke caused by arterial occlusion it definitely does. If this is true, the sodium clock will not start ticking until a certain threshold of perfusion is exceeded. In this regard, the [Na+] threshold proposed by Thulborn et al8 might be a more relevant concept that avoids the issue of timing; or, alternatively, time from the point of critical ischemia, not clinical symptoms, could be determined by the sodium clock.

Third, Dr von Kummer proposes using “the linear decline of x-ray attenuation . . . to determine the time point of edema onset,” even though he states that “‘time is brain’ is a comment for laymen.” Although this method to determine time after onset has been presented,7 it has not to our knowledge been prospectively validated or related to any other variable. The experimental data supporting this CT measure of edema is briefly presented as an unpublished observation, in what seems to be ex vivo tissue,2 and several studies seem to challenge the presumption that CT observation of edema is useful in early acute stroke. A study comparing CT and pathological examination of 13 human brains concludes that low-density areas can be caused by factors other than high fluid content and can be obscured by minerals, fat, or blood.4 A more recent study9 indicates that “there is a considerable lack of agreement, even among experienced clinicians, in recognizing and quantifying early CT changes” in the first few hours after stroke onset. These difficulties might be related to the small increase in water content of 2.5% from normal in the most severely ischemic regions, 4 hours after onset, with correspondingly small CT density changes of about 6.5 Hounsfield units.10 It is useful to note in this discussion that low-attenuation changes on CT scans are not unequivocally an indication of permanent ischemic injury.11 This method of measuring water content with CT might be complicated by the same factors present in a study by von Kummer et al12 that finds in “8 patients examined by CT within 180 minutes of the stroke, no low density could be identified, even in retrospect with the knowledge of the findings on follow-up.” Further adding to the questionable effectiveness of CT at detection of edema in early stroke is the acknowledgment that the large body of data supporting its usefulness was obtained in a cohort with 86% of the population studied 3 hours after onset.13 In this cohort, before 2 hours “the increase in tissue water is too small to cause a visible decrease in x-ray attenuation.”13 However, this hyperacute period is the crucial time for thrombolysis.

Fourth, we agree that the critical factor in determining the permanence of neurological injury is the relationship between perfusion and time. We also agree that the concept of a sodium clock is a preliminary proposition that requires substantiation. The relationship between accrual of “time” on the sodium clock to “real-time” versus neurological injury has to be determined. However, although the value of the sodium clock as a prognosticator is also undetermined, it may very well prove to be a more useful indicator of reversible versus permanent neurological injury than other methods currently used.

This point addresses the much broader issue of whether time is the appropriate variable to consider, and Dr von Kummer uses our manuscript as a touchstone to reiterate a point that he has made before. We are aware of Dr von Kummer’s excellent and original work in this regard and acknowledge that he presents a reasonable hypoth-
esis that there are other more sensitive ways to segregate appropriate patients for thrombolysis. However, as of now, it is still a hypothesis.

Dr von Kummer states that the authors “regard [the time of stroke onset] essential before initiating thrombolytic treatment.” Actually, in the United States, this is the standard of care, independent of what the authors, or Dr von Kummer, regard as ideal. The time window of 3 hours has been supported by several recent studies. Indeed, time might not be the perfect arbitrator of the effectiveness of tPA and the occurrence of hemorrhage. We certainly agree that there may very well be individual differences in the pattern of evolution of the ischemic process that interact with vulnerability to thrombolysis. In fact, in published studies, we discuss the relevant clinical conditions that alter the evolution of ischemia. For the foreseeable future, though, we feel it is a compelling goal to develop methods that extend the opportunity of thrombolysis to as many patients as possible, in particular to those in whom the onset is not known. We feel the methods described here are sufficiently promising that the extensive effort required to test them prospectively in humans is warranted.

The current standard of stroke care in the United States is based on onset time. Although this might be a first faltering step in the evolution of truly rational stroke care, it certainly represents an improvement over the period when time after onset was more or less ignored in stroke therapy. This anti-time argument should really be directed at the design of trials for thrombolytic agents. It is important to think of the future, not the present or past.

Dr von Kummer ascribes to our work that “the risk of cerebral hemorrhage increases with time after tPA administration.” However, we merely cited the results of Clark et al, who clearly document that hemorrhage becomes important in limiting the benefit of intravenous tPA between 3 to 5 hours after onset, whereas before 3 hours, the benefits of tPA outweigh the damage from hemorrhage.

We disagree with the statement that “the ticking clock is not needed. It may keep away a promising treatment from patients who really need it.” If the [Na+] increase is taken from the region of maximal ischemia, this region could be at risk for hemorrhage after thrombolysis and recirculation, in contrast to a more highly perfused region where the blood-brain barrier is intact. Alternatively, if this method of determining onset time were used in all possible candidates for thrombolytic therapy, it is possible that some strokes would be found to have occurred earlier than the patients were aware, that a region with severely ischemic tissue had been there longer than the clinical symptoms indicated.

Fifth, we do think that we need “more information for the decision to treat,” including perhaps the sodium clock. It is hard to imagine not trying to explore new techniques just because the present methods, such as CT or diffusion-weighted MRI (DWI), seem satisfactory. Although the proposed method for [Na+] determination in humans using MRI is currently impractical for wide application to ischemic stroke, so was the use CT in 1972 and DWI in 1989. If a method proves useful, then it will be used, as has happened with CT, MRI, and DWI.
Association Between Physiological Homeostasis and Early Recovery After Stroke

To the Editor:

Stroke patients who are managed in an organized (stroke unit) setting are more likely to make a good recovery than those who receive conventional care in general wards, an effect that has been attributed to the coordinated rehabilitation input. However, recent descriptive information from 2 Norwegian trials now indicates that some of the benefits of stroke unit care may also be due to acute medical interventions. In particular, these units employed early mobilization and the routine use of intravenous saline, plus selective use of antipyretic and antibiotic medication, oxygen, and insulin. We therefore wished to test the hypothesis that stroke patients who manage to maintain key physiological variables (osmolarity, temperature, oxygen saturation, blood glucose) within a narrow physiological range are more likely to enjoy an early recovery and better functional outcome.

We carried out a case-control study, recruiting consecutive individuals admitted to a large, urban teaching hospital with a clinical diagnosis of stroke in the previous 24 hours that was confirmed on CT scan. Patients were assessed on admission, day 3, and day 7 after stroke with the Scandinavian Stroke Scale, Barthel Index, and modified Rankin scale. Physiological variables were recorded up to 4 times daily as part of routine clinical care.

We compared the characteristics of patients who showed no major deviation from normal physiological values during the first 3 days (defined as a peak calculated serum osmolarity <300 mOsm/kg, peak temperature ≤37.5°C, peak blood glucose ≤10 mmol/L, minimum oxygen saturation ≥93%) compared with those who showed abnormalities of at least 1 of those variables. We controlled for the key predictors of stroke outcome by using a frequency-matching schedule, matching for age, prestroke disability (Rankin scale score) and initial stroke severity (Scandinavian Stroke Scale score). Matching of cases and controls was conducted blinded to the outcome data.

During a 3-month period, 102 eligible patients were admitted, of whom 35 showed no major physiological homeostatic upset in the first 3 days after stroke; we were able to match 28 of those

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Group A (Normal Physiological Observations)</th>
<th>Group B (Abnormal Physiological Observations)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>28</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>67 (63, 73)</td>
<td>69 (61, 74)</td>
<td>*</td>
</tr>
<tr>
<td>Sex (male:female)</td>
<td>19:9</td>
<td>15:13</td>
<td>NS</td>
</tr>
<tr>
<td>Independent before stroke</td>
<td>26</td>
<td>25</td>
<td>*</td>
</tr>
<tr>
<td>Stroke severity (baseline SSS)</td>
<td>43 (38, 49)</td>
<td>41 (31, 52)</td>
<td>*</td>
</tr>
<tr>
<td>Living alone</td>
<td>12</td>
<td>13</td>
<td>NS</td>
</tr>
<tr>
<td>Stroke subtype</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total anterior circulation infarct</td>
<td>5</td>
<td>6</td>
<td>NS</td>
</tr>
<tr>
<td>Partial anterior circulation infarct</td>
<td>12</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Lacunar infarct</td>
<td>7</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Posterior circulation infarct</td>
<td>3</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Primary intracerebral hemorrhage</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Admission delay (hours from symptom onset to hospital admission)</td>
<td>4.0 (2.2, 7)</td>
<td>4.5 (1.5, 9.5)</td>
<td>NS</td>
</tr>
<tr>
<td>Physiological features (days 0–3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak blood glucose, mmol/L</td>
<td>6.1 (5.5, 6.9)</td>
<td>6.9 (5.8, 10.1)</td>
<td>*</td>
</tr>
<tr>
<td>Peak serum osmolarity, mOsm/kg</td>
<td>288 (284, 293)</td>
<td>296 (287, 302)</td>
<td>*</td>
</tr>
<tr>
<td>Peak temperature, °C</td>
<td>36.7 (36.4, 37.0)</td>
<td>37.3 (36.8, 37.8)</td>
<td>*</td>
</tr>
<tr>
<td>Minimum oxygen saturation (%)</td>
<td>95 (94, 97)</td>
<td>93 (92, 95)</td>
<td>*</td>
</tr>
<tr>
<td>Outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSS score (day 3)</td>
<td>54 (44, 56)</td>
<td>45 (37, 51)</td>
<td>0.04</td>
</tr>
<tr>
<td>Change in SSS score (day 3–day 0)</td>
<td>+6 (5, 10)</td>
<td>+2 (–4, 6)</td>
<td>0.02</td>
</tr>
<tr>
<td>Neurological improvement (improving &gt;3 points on SSS)</td>
<td>22</td>
<td>9</td>
<td>0.001</td>
</tr>
<tr>
<td>Barthel Index (day 3)</td>
<td>17 (14, 18)</td>
<td>14 (5, 17)</td>
<td>0.03</td>
</tr>
<tr>
<td>Independent (Rankin 0–2) on day 7</td>
<td>17</td>
<td>10</td>
<td>0.03</td>
</tr>
<tr>
<td>Discharge home after acute care</td>
<td>20</td>
<td>13</td>
<td>0.10</td>
</tr>
</tbody>
</table>

Data are presented as the median (interquartile range) or the number in each category. Statistical analysis used the Mann-Whitney U test, χ² test, or Mantel-Haenszel odds ratio. SSS indicates Scandinavian Stroke Scale.

*Data used in matching are shown for reference only.
patients (group A) with 28 who showed 1 or more physiological abnormalities (group B). The main results are outlined in the Table. The 2 patient groups were well balanced for age, gender, prestroke independence, initial stroke severity and stroke subtype, and the prevalence of comorbidities. Patients who maintained physiological homeostasis (group A) showed improved outcomes across a range of measures.

These results lend support to the concept that some of the neurological impairment occurring in the acute phase of stroke is reversible and may be exacerbated by physiological abnormalities.\(^6\) In particular, hyperglycaemia may be neurotoxic through the promotion of lactic acidosis,\(^6\) dehydration and hypotension may impair cerebral perfusion to ischemic brain tissue,\(^6\) and pyrexia appears to be neurotoxic.\(^7\) The recent descriptions of some stroke unit practices\(^2,3\) suggest that intervening to maintain key physiological variables within narrow limits (in particular, avoiding extremes of blood glucose concentration, pyrexia, dehydration, and oxygen desaturation) may assist neurological recovery after stroke. We believe that further clinical trials of physiological control in acute stroke are justifiable and could focus on hydration, pyrexia control, blood glucose control, and prevention of hypoxia.

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Response

It is of great interest for us that Langhorne and coworkers have been able to achieve similar results. We think this is an important area for more research because control of such physiological variables may be the most important neuroprotective options in acute stroke patients. However, in traditional acute care or intensive care, control of physiological variables has very often been associated with intensive monitoring while the patient has been immobilized in bed.\(^7\) It is worth noting that in our trial early mobilization was even more important for a better outcome than control of physiological variables.\(^1\) Hence, control of these physiological variables should probably occur simultaneously with an early mobilization and start of rehabilitation. That advanced monitoring is not necessarily beneficial was shown for cardiological patients several years ago.\(^8\) If prolonged bedrest occurs, the beneficial effect may disappear. In our stroke unit we now perform studies to look at the effects of our very early mobilization on physiological variables. Our hypothesis is that early mobilization may not only reduce bed-associated complications and enhance recovery but may also contribute to more optimal control of some of the physiological variables.

Until more data are accumulated, we will continue the approach to acute stroke care that we developed during our stroke unit trial.\(^1\) Our approach can be summarized in the following way: Acute stroke patients need acute medical care in order to control physiological variables, and they need acute mobilization/training to reduce complications and enhance recovery. One reason that stroke units which combine acute care and acute rehabilitation are very beneficial might be that such units are able to offer both acute care and acute rehabilitation and that they are able to offer these options simultaneously. We think the results in the letter from Langhorne and coworkers support our approach, but we agree that more research is needed in this important field to achieve more knowledge and to improve acute care of stroke.

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The Time Concept in Ischemic Stroke: Misleading
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