Anticoagulation of embolic strokes

To the Editor: The review article by Yatsu et al¹ is thoughtful and timely. The suggestion to limit anticoagulation use in patients with mild neurologic deficit with expected useful functional recovery is well accepted.

I have the following questions for them. While they described conditions under which we should not anticoagulate, they did not specify when we should start anticoagulation in certain clinical settings. Most of us probably agree on immediate anticoagulation in patients with TIA who have large intraventricular thrombus. However, the timing of anticoagulation in the following patients is not that clear. The first group of patients are those with atrial fibrillation, seen within hours of onset with moderate neurologic deficit, negative CT, and normal or moderately enlarged cardiac size without thrombus. The second group of patients are similar to the above except that CT reveals small or moderate size of attenuation within hours. It is not very clear to me whether the authors would anticoagulate these two groups of patients (with good recovery potential and smaller risk of reembolization but possible hemorrhagic transformation with anticoagulation) immediately or wait for 3 to 5 days. (But why 3 to 5 days and not 7 to 10 days or 10 to 14 days to minimize hemorrhagic transformation?)

Yatsu et al suggested avoiding anticoagulation in the presence of contrast enhancement. Contrast CT is usually not recommended in stroke patients in our institution. Would they advise routine non-contrast and contrast CT in strokes of possible cardiac origin on the first day or only after 3 to 5 days? Since strokes of significant size usually develop contrast enhancement at 10 to 14 days, then, following their guideline, could we presume that these patients are vulnerable for hemorrhagic transformations (not just at 3 to 5 days) and, therefore, should one repeat contrasted CT during heparinization (and how often?) to identify and avoid potential disaster in time?

For atrial fibrillation patients with moderate-size cerebral infarctions and normal or slightly enlarged heart, some of us prescribed Coumadin (sodium warfarin) immediately, hoping the PT would be within therapeutic range in 5 to 10 days without the use of IV heparin and avoiding early potential cerebral complication. Is this approach acceptable?

Sun-Hoo Foo, MD, FRCP

New York, NY

Reply from the Authors: Dr. Foo identifies precisely that group of patients in whom management is most often unclear, ie, those with acute moderate neurologic deficit, negative or mildly abnormal CT, and probable but not definite source of embolism in the heart. We tried to emphasize in our editorial that, in all patients, treatment should be individualized based upon the clinician's assessment of the relative risk of recurrent embolism without anticoagulants versus the risk of hemorrhagic transformation associated with anticoagulation use. In the patient described by Dr. Foo, we would generally wait 48 to 72 hours and repeat the CT without contrast. If there was no blood present, we would start the patient on anticoagulation with heparin. This would be our recommendation whether the initial CT was negative or abnormal as long as no hemorrhage was seen. We have chosen a waiting period of 48 to 72 hours because hemorrhagic transformation usually can be detected within this time period, and waiting a longer time (ie, 10 to 14 days, as suggested by Dr. Foo) exposes the patient to prolonged risk of recurrent embolus. While it is true that hemorrhagic transformation may occur beyond this 72-hour period, we believe that most cases can be detected by 72 hours high-resolution CT or MRI if one has a high index of suspicion.

Further study is needed to make conclusive statements about the utility of contrast enhancement in predicting hemorrhagic transformation, though preliminary data suggest that this is the case. We do not recommend, however, contrast-enhanced CT routinely on admission or during the follow-up period. Further study of contrast-enhanced CT and MRI is needed to help predict and identify hemorrhagic transformation.

Finally, we do not recommend immediate Coumadin anticoagulation, since this medication cannot be readily reversed should hemorrhagic changes occur.

Frank M. Yatsu, MD

Houston, TX

Robert G. Hart, MD

San Antonio, TX

J.P. Mohr, MD

New York, NY

James C. Grotta, MD

Houston, TX

Reference

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Is smoking a risk factor in Alzheimer's disease?

To the Editor: Shalat et al¹ pointed out that there is a positive association of Alzheimer's disease (AD) and cigarette smoking. We disagreed with their report. Our study and data are as follows:

The investigated areas we examined were located in western Japan. Clinically diagnosed cases of AD in these areas were obtained for more than 3 years before inclusion in this study. The diagnosis of AD was made on the basis of a history of progressive dementia with gradual onset and after excluding other possible causes of dementia according to diagnostic criteria of the *Diagnostic and Statistical Manual of Mental Disorders-III*² and NIH-ADRDA.³ Assessment of these patients involved a careful medical history and physical examination, a comprehensive cognitive evaluation with the use of the Mini-Mental Status Examination and the Blessed Dementia score, ADL evaluation with the Barthel index, a psychosocial assessment of the patient's environment, routine laboratory tests, and computed tomography. An ischemic score by Hachinski et al⁴ was used to distinguish AD from multi-infarct dementia. Seventy-seven individuals (16 men, 61 women) met the above criteria. Information on cigarette smoking was obtained by family members residing at the same address. Results are shown in the table. There were 12 male smokers, but only one female smoker. Smokers were 16.9% (13 cases) and nonsmokers 83.1% (64 cases).

The results showed that AD patients were almost all nonsmokers. AD is an especially common disease in women. In Japan, women did not have the habit of smoking in those days. Although not evaluated by statistics, we believe our results show no association between AD and smoking.

Katsuya Urakami, MD

Yoshiki Adachi, MD

Kazuro Takahashi, MD

Yonago, Japan

Table. Frequency of smokers in AD

	Total no.	Smokers	Nonsmokers
Men	16	12	4
Women	61	1	60
Total	77	13 (16.9%)	64 (83.1%)

continued

Reply from the Authors: We appreciate the comments of Dr. Urakami and his associates on our study of AD¹ and find their observations of AD and smoking in western Japan most interesting. While we, as they, are skeptical of drawing any causal inference from the association reported in our study, we would disagree that the reported prevalence of smokers in their case series is inconsistent with smoking as a possible etiologic factor in AD.

They observed 16.9% of all their cases and <2% of women as having reported being smokers. As noted in their letter, Japanese women of this birth cohort have a generally low prevalence of smoking. This low prevalence of smoking in the women obscured the fact that 75% of the men were smokers. The truly pertinent question would be, what is the appropriate rate of smoking among men of this birth cohort, in general. It should be noted that the population of the study we reported on was all men.¹

Confounding by gender is a potential problem in the interpretation of etiologic factors that vary in background frequencies in men and women. While it is difficult to draw inference owing to the small number of men studied, the 75% prevalence of smoking among male AD patients observed by Dr. Urakami is virtually identical to our own experience, where 74 of 98 cases of AD were smokers (75.5%). Even though the predominance of women in Dr. Urakami's data set would tend to preclude smoking as playing a major role as an etiologic factor in AD, we believe that, given the state of knowledge on the causes of AD, it is imprudent to too rapidly exclude cigarette smoking as a possible risk factor.

Stuart L. Shalat, ScD
New Haven, CT

Benjamin Seltzer, MD
Bedford, MA

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Myasthenia in Chinese females (correction)

To the Editor: Unfortunately, in our paper published in *Neurology*,¹ the data used to plot one section of figure 2 (age of onset distribution for Chinese females with grade IIa disease) and to draw up the distribution of age of onset and sex in the table were incorrect; there was thus a discrepancy with figure 1.

The distribution of Chinese female patients with grade IIa disease should be shifted to the left by 10 years. When this is done, the correct data for the table are as follows:

Age of onset	Chinese		
	Total	M	F
0-10	65	33	32
10-20	66	18	48
20-30	49	18	31
30-40	30	11	19
40-50	28	13	15
50-60	11	6	5
60-70	6	4	2
70-80	3	3	0

The Caucasian data and values quoted in the text are correct.

While this error does not alter the basis for the conclusions of the paper, we are grateful for the opportunity to set the record straight.

H-C. Chiu, MD
A. Vincent, MBBS, MSc
J. Newsom-Davis, MD, FRCP
K-H. Hsieh, MD
T-p. Hung, MD
Oxford, England

Reference

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Phenobarbital for status epilepticus

To the Editor: We would like to point out what in our opinion are important flaws in the experimental design in the study of Shaner et al¹:

(1) The authors' decision to infuse phenytoin (DPH) at a maximum rate of 40 mg/min, unlike accepted protocols which recommend infusion at 50 mg/min if tolerated,^{2,3} prolongs artificially the response latency for this drug. For example, infusion of only 9 mg/kg of DPH to a person weighing 70 kg at 40 mg/min will take 3.1 min longer than if administered at 50 mg/min; the larger the dose the greater the time difference. We wonder what recalculation of the Wilcoxon rank test, adjusting for the time differences, would do to the questionable statistical significance of their results.

(2) Seven patients (p. 204) and/or five patients (p. 205) assigned to the phenobarbital (PB) protocol also received DPH at an unspecified time. Patients on both treatments should have been excluded from the final analysis to avoid biasing of results.

(3) The lack of standardization of diazepam (DZ) dosage, defensible medico-ethically, confounds the interpretation of the results and hinders objective intergroup comparisons.

(4) The times at which blood was drawn for determinations of serum concentration of DPH in relation to completion of the infusion were not specified; therefore, the values reported here cannot be interpreted pharmacokinetically. For example, if blood was obtained before completion of redistribution (3 to 4 hours, based on $t_{1/2\alpha}$ of 1.6 hr⁴), the reported values were falsely high. The same caveat applies to serum concentrations of the PB, which redistributes in 1 hour (based on $t_{1/2\alpha}$ of 0.18 hr⁵). This comment is prompted by the suspicion that some readers may conclude that PB is more efficacious than DPH since it was effective at "subtherapeutic" concentrations (mean, 18.3 mg/l), unlike the latter whose average concentration of 22 mg/l (unclear if applicable to all DZ/DPH patients and/or 7 patients in PB group) is slightly above the upper therapeutic range. Conversely, the data could suggest to other readers that status epilepticus was less severe in the PB than in the DPH group since it was controlled at subtherapeutic concentrations.

(5) The time elapsed between arrival of the patients to the emergency room and institution of therapy and approximate duration of convulsive activity before arrival to the emergency room were not reported. These two variables may render comparison of therapeutic efficacy of two treatment protocols invalid if status epilepticus affected one group for a considerably longer time than the other. Although this study was randomized, the size of the sample may have been inadequate to prevent skewing of results.

It is clear that the authors favored, for practical considerations, PB over DZ/DPH for treatment of convulsive status epilepticus, but their preference finds no support in the data. Furthermore, the results of the VA cooperative study indicate that DPH and carbamazepine are not only more efficacious than PB for treatment of partial and secondarily generalized seizures, but also have considerably less side effects.⁶ The results of this study raise two important questions: How

likely is it that PB, proven less efficacious for control of seizures than DPH, will be superior for treatment of convulsive status, an extreme expression of epilepsy? Should patients be kept, following recovery from status, on the third-best available drug for long-term treatment?

In brief, the experimental design of this study limits considerably the validity of any intergroup comparison. The only acceptable conclusion, in our opinion, is that PB may be efficacious for treatment of type A status epilepticus and, certainly, this is not a recent discovery.

Ivan Osorio, MD
Ronald C. Reed, PharmD
Cleveland, OH

Reply from the Authors: Drs. Osorio and Reed argue that the rate of DPH infusion may affect the response latency of status epilepticus. Although the calculations to determine the duration of infusion are simple, the precise relationship of infusion time to response latency is uncertain and not directly predictable. No studies document a linear relationship between infusion rate of DPH and response latency of status epilepticus. Therefore, recalculation of statistics based on arbitrary speculations would be of doubtful significance. Furthermore, while a maximum infusion rate of 50 mg/min is generally recommended, infusion rates as low as 11.8 mg/min have been necessary in some patients. In the study by Cranford et al.,² quoted by Drs. Osorio and Reed, the mean infusion rate was 43 mg/min in patients who manifested no side effects and 32 mg/min in patients who developed hypotension. The same study provides evidence that hypotension related to infusion rate occurs more frequently in patients over the age of 40. An associated reason for concern is that the parenteral forms of both DZ and DPH are supplied in a 40% propylene glycol solution, which has been implicated as a causative factor of hypotension. Since both these drugs were administered simultaneously, we felt the risk of side effects would be greater than reported for DPH alone, and we wished to avoid unnecessary risk to patients. In any case, any potential benefit from increasing the rate of infusion of DPH by a nominal 10 mg/min is not likely to affect our finding that fully 33% of the patients receiving DZ/DPH and only 11% of the patients receiving PB/DPH failed to achieve control after 25 minutes of therapy (see our figure 2).¹ These data would be unaffected even if the response latency for all patients in the DZ/DPH group were decreased by as much as 5 minutes.

Only seven of the 18 patients in the PB/DPH group received DPH. Infusion of DPH in five of these seven patients may have been unnecessary, since no seizures occurred after the PB infusion. We compared two treatment protocols rather than specific drugs. Therefore, the rationale supporting the recommendation to exclude these seven patients "to avoid biasing of results" is a bit mysterious.

We are also puzzled as to why Drs. Osorio and Reed raised the issue of medico-ethical considerations as a defense in determining the DZ dosage schedule. The dosage schedule we used for DZ is generally considered to be one of the more aggressive recommended regimens for this application. We therefore felt it was appropriate to use it for comparison.

Our report states explicitly (p. 205) that the study was not designed to examine rigorously pharmacokinetic relationships and mechanisms. The dose/level relationships for PB described in the report we believe to be valid as a first approximation because they conform closely to previous reports from well-controlled pharmacokinetic studies referenced in our report. In any case, the implications regarding the relatively low serum levels of PB that were measured and effective in controlling status epilepticus are interesting. Animal studies⁷ provide evidence that PB entry into the brain is facilitated during status epilepticus, thereby enhancing the efficacy of serum concentrations that would otherwise be considered subtherapeutic. This explanation for the reported effectiveness of low serum PB levels is more convincing than arguing that the experimental groups were not comparable, despite randomization and evidence that the groups were similar with respect to age, sex, criteria for entry into the study, etiology, and seizure type.

Finally, we are at a loss to understand the justification for comparing treatment regimens designed for maintenance therapy such as those used in the VA cooperative study with protocols designed for

treatment of status epilepticus. Use of PB as long-term maintenance therapy is neither recommended nor implied, but certainly remains an option.

To our knowledge, our paper represents the first controlled prospective comparison of these two protocols for the treatment of status epilepticus. The data describe the relative efficacy of the two protocols. We have provided evidence supported by statistical testing that there is no advantage of the DZ/DPH protocol over the PB/DPH protocol used in this study. In addition, the data suggest that the efficacy of PB/DPH is greater than DZ/DPH. The practical advantages of the PB/DPH protocol are clear.

Due to the paucity of control data, we cannot be certain that the rate of administration or total dose of PB were optimal. It is possible that the rate of administration and/or the total dose of the drug administered could be increased, resulting in a more prompt response without significant added risk. We hope that our study will serve to encourage further investigations rather than be viewed as an absolute recommendation for an ideal rate of administration and drug concentration for PB in the treatment of status epilepticus.

D. Malcolm Shaner, MD
Stephen A. McCurdy, MD, MPH
Mark O. Herring, MD
Andrew J. Gabor, MD
Sacramento, CA

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Model curriculum

To the Editor: Mancall and associates¹ recently outlined a proposal for the substance of a "Model Clinical Neuroscience Curriculum." First, the authors proposed that all medical students must "acquire a basic fund of information essential for establishing an accurate diagnosis and thereby undertaking rational therapy." Second, "the graduating student should be familiar with those disorders that are common, . . . treatable, . . . or illustrative." Third, "students must become acquainted with those disorders that require rapid intervention in an emergency setting." Based upon these principles, the contents of the model curriculum must include (1) the neurologic examination, (2) principles of topographic localization, (3) education in the cardinal manifestations of neurologic disorders, (4) the knowledge of specific neurologic disorders, and (5) familiarity in the use of laboratory analyses to diagnose neurologic disease.

We agree that the clinical neuroscience curriculum must include the material highlighted above. However, the authors mistitled their article, because clinical neuroscience is not clinical neurology. Clinical neuroscience, as included in the typical medical school curriculum, is a broadly defined discipline. It can be regarded as including study of learning and developmental disorders, psychopathology, the mental

status examination, pathophysiology of drug withdrawal states, the neurobiologic effects of all psychotropics (anticonvulsants, antidepressants, anxiolytics, neuroleptics, and sedative hypnotics), and the use of brain imaging strategies in neuropsychiatry. Much more could be listed.

As educators and researchers in clinical neuroscience and psychiatry, we find the misidentification of our discipline's content unfortunate. The discipline of psychiatry makes noteworthy contributions to both clinical and basic neuroscience. All that one must do to verify this is to read a selection of psychiatry journals. The *Archives of General Psychiatry*, *Biological Psychiatry*, *Neuropsychopharmacology*, and *Psychopharmacology Bulletin* are but four of those many journals that regularly contain articles belonging to the field of clinical neuroscience. Neurology is a part of clinical neuroscience, but not the whole of the subject. Neuroscience is a discipline that necessarily and as a matter of fact includes clinical pharmacology, immunology, internal medicine, neurosurgery, pediatrics, psychiatry, radiology, and other clinical sciences.

Steven C. Dilsaver, MD
Nicholas A. Votolato, BS
Jeffrey A. Coffman, MD
Columbus, OH

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Intracerebral hematoma

To the Editor: In support of Caplan's hypothesis¹ concerning the need to reevaluate the conventional belief that nearly all spontaneous intracerebral hematomas are caused by chronic hypertensive damage to penetrating and subcortical arteries and arterioles, I would like to offer supporting evidence based upon data derived from the case material at the Tulane Medical Center. Of 300 consecutive hypertensive patients who were studied with high resolution CT and had findings consistent with an acute intracerebral hemorrhage (ICH), there was CT evidence of an accompanying lacunar infarction in only 3% of cases. This low incidence is surprising because systemic arterial hypertension is the major risk factor for lacunes and ICH. One prior necropsy (pre-CT) study reported that 35% of patients with lacunes suffered ICH.² Of those patients with ICH and an accompanying lacune, all had been treated with antihypertensive medication for 7 to 14 years. These patients also had evidence of chronic hypertensive, vascular change as manifested by cardiographic evidence of left ventricular hypertrophy, chest radiographic evidence of cardiomegaly, and clinical funduscopic evidence of hypertensive retinopathy. The patients with ICH and accompanying lacunes had hematomas in characteristic locations for hypertensive hemorrhage, eg, putamen, thalamus, subcortical white matter. These hemorrhages were the smallest lesions of all the hematomas encountered in these specific locations. It is hypothesized that chronic hypertensive vascular disease causes arteriolar wall damage including lipohyalinosis, and this is responsible for the lacunar infarction. This arteriolar wall thickening due to chronic hypertensive vascular disease protects these hypertensive patients from the development of large parenchymal hemorrhages.

In the author's personal series of 100 consecutive patients with putaminal hemorrhage,³ long duration of systemic arterial hyperten-

sion and chronic hypertensive end-organ complications occurred most frequently in patients with smaller putaminal hemorrhages (confined to the basal ganglia and subcortical white matter). In hypertensive patients with larger putaminal hemorrhages (as manifested by cerebral hemispheric and thalamic extension in addition to involvement of the subcortical white matter), the incidence of long-duration (greater than 4 years) hypertension and chronic hypertensive vascular change was markedly lower. This would suggest that chronic hypertensive change with arteriolar wall thickening protects these patients from large putaminal hemorrhages. The larger putaminal hemorrhages occurred in patients with hypertension of shorter duration and without end-organ evidence of chronic hypertensive vascular disease. It may be hypothesized that the acute rise in blood pressure causes larger parenchymal hemorrhages in patients without chronic hypertensive vascular disease than in patients with chronic hypertensive vascular disease.

Leon Weisberg, MD
New Orleans, LA

Reply from the Author: I agree with Dr. Weisberg that the infrequent finding of prior lacunar infarction on CT in patients with spontaneous intracerebral hematomas (ICHs) is additional evidence against the hypothesis that chronic degenerative arteriolar disease causes most instances of ICH.

The finding that those patients with evidence of prior prolonged hypertension (lacunes on CT or end-organ changes) have smaller hemorrhages is more difficult to understand. I don't see how the degenerative changes could both lead to bleeding and yet protect from extensive bleeding. An alternate explanation is that the mechanism of bleeding in these chronic hypertension patients is different. Could they leak from a small microaneurysm, a process that might involve lesser pressure and be more restricted than vascular rupture from sudden increase in arterial pressure or flow? Perhaps the size of the vessels in the two processes is different? Unfortunately, there are no pathologic or other data that now confirm or deny these various hypotheses.

Louis R. Caplan, MD
Boston, MA

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Correction

In the article entitled "Monoclonal IgM with unique specificity to gangliosides GM₁ and GD_{1b} and to lacto-N-tetraose associated with human motor neuron disease," published in the May issue of *Neurology* (1988;38:763-768), an author's first name and surname were transposed. "K. Manoussos" should have appeared as "Manoussos Konstadoulakis" in the byline.

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Correction

Neurology 1988;38;1506-1506-b
DOI 10.1212/WNL.38.9.1506-b

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