letters to the editor

Guidelines for the determination of death

To the Editor: We applaud the humane stance of the consultants' report to the President's Commission that brain death is equivalent to death and endorse the recognition of the fact that guidelines diagnosing brain death are necessary.

We do, however, have some points of criticism. Most of these relate to the Commission's proposed model statute for a "Uniform Determination of Death Act":

> "An individual who has sustained either (1) irreversible cessation of circulatory and respiratory functions, or (2) irreversible cessation of all functions of the entire brain, including the brainstem, is dead. A determination of death must be made in accordance with accepted medical standards."

(A) The formulation "entire brain, including the brainstem" is clumsy: the whole always subsumes all of its parts. We surmise that the words, "including the brainstem," had to be added to ensure that patients in a chronic vegetative state (ie, with severely damaged hemispheres but some residual brainstem function) were not diagnosed as brain dead. Our courts—unlike yours—have not as yet had to address this specific issue. The difficulty could be avoided if the emphasis was placed, as in the UK, on irreversible loss of brainstem function. This achieves the desired objective of not certifying as dead patients who are in a chronic vegetative state. It also proves prognostically critical, in the acute situation.

(B) To demonstrate "cessation of all functions of the entire brain" is—we feel—an impossible task. No currently available technique or combination of techniques can ever hope to assess "all functions of the entire brain." The commission's report explicitly states, it is true, that "all functions" are not meant to include "electrical and metabolic activity at the level of individual cells or even groups of cells." But in the clinical context of suspected brain death there is a great deal more than isolated "cellular activity" that, quite simply, cannot be evaluated. There is no way of adequately testing, for instance, such important brain functions as those of the thalamus, basal ganglia, or cerebellum.

The proposed model statute gives the impression of seeking to identify what some of us, on this side of the water, consider an inappropriate objective, namely the functional disintegration of all the main intracranial systems (what one might call "death of the whole of the brain"). The UK code, by contrast, seeks to document irreversible loss of critical functions (namely those of the brainstem). Such loss, in our opinion, implies death of the brain as a functional unit, or "death of the brain as a whole."

(C) The disclaimer in your new guidelines that "all functions of the entire brain" only means "those functions which are clinically ascertainable" is disingenuous. The introduction to the commission's report states wisely that "in language as well as content, any legislation ought to make personal sense to lay people." But the average layman does not know that many cerebral functions cannot be clinically ascertained. Legislation which spoke of "all citizens" in its preamble—and then went on in the text proper to explain that "all citizens" only meant those citizens easily seen to be working—would rightly provoke criticism.

(D) The suggestion that when brainstem reflexes "cannot be adequately assessed confirmatory tests are recommended" is, we feel, fraught with danger. One of the confirmatory tests your guidelines seem to have in mind is electroencephalography. But this does not assess brainstem function. Its advocacy (as a "confirmatory test" of loss of brainstem function) is a non sequitur. An isoelectric EEG may occasionally be encountered in the presence of retained brainstem reflexes.

When, for any reason, there is uncertainty as to the status of the brainstem reflexes, there is no doubt—in our opinion—as to what one should do: one should not seek to diagnose brain death. The loss of a few donor kidneys is a small price to pay for diagnostic certainty as to the presence of mortal brainstem injury.

(E) We are particularly worried by the statement in your new guidelines that "electrocerebral silence verifies irreversible loss of cortical functions, except in patients with drug intoxication or hypothermia." These are indeed important caveats. One should also be careful, however, in dealing with patients in whom circulation has been adequately restored following cardiac arrest. Such patients may, for a while, remain in apneic coma with absent brainstem reflexes and exhibit electrocerebral silence. They may then pass into a state (which may last several hours) in which spontaneous respiration and brainstem reflexes return while no cortical activity can be recorded in the EEG.[2] Some will survive. Such patients are not in shock (which your guidelines rightly stress may give rise to diagnostic difficulties). Dangers may also arise in patients with severe combined facial and thoracic injuries: the former may prevent the testing of certain brainstem reflexes, while the latter may lead (via an episode of asystole) to the aforementioned transiently isoelectric EEG.

Maintained apneic coma (strictly defined) and brainstem areflexia (properly tested), when encountered in the context of established irremediable structural brain disease, remain the surest and most easily assessable foundations for a diagnosis of death on neurologic grounds.

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Medicine and Biomedical and Behavioral Research, Neurology (NY) 1982;32:395-9.
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Editors Note: The above letter was sent to Dr. Joanne Lynn, Assistant Director of the President's Commission, who coordinated the drafting of the following response from four of the principal authors.

Reply from the Authors: The letter from Drs. Pallis and Prior about the "Guidelines for the Determination of Death"[1] is welcome for its approval of most of the guidelines and also for pointing toward some areas that may need further clarification and discussion.

Whether the statute should say "entire brain, including the brainstem," or should focus on brainstem alone seems to have no effect on the tests that the guidelines recommend for establishing that brain functions have irreversibly ceased. There are reasons to prefer a "whole brain conception"[2] but that is not a problem that the guidelines resolve.

The proposed statute (already law in 11 states) requires that physicians certify that "all functions of the entire brain" have irreversibly ceased. It then leaves to physicians the task of defining medical standards appropriate to that task. We do not see this task as being different from the British experience with criteria set forth by the Conference of Royal Colleges and Faculties in 1980, under which death is established when "all functions of the brain have permanently and irreversibly ceased."

The use of "functions" in the American proposal was deliberate; it builds on a legal tradition that differentiates "functions" from "activities." "Activities," in this usage, are biologic processes that are, usually because of the damage to the entire organ, no longer of any significance to the functioning of the organ as a whole. The guidelines are intended to identify those bodies for whom there has been, in Pallis and Prior's words, "functional disintegration of all the main intracranial systems." We do not agree with them that this is an inappropriate objective. Rather, the way the statute works in this country will be to leave to physicians the responsibility of defining what tests are relevant to determining that the brain's functions have irreversibly ceased. That is exactly what the guidelines sought to do. There is nothing disingenuous about this. The statute makes clear that a determination of death is to be based on measuring those functions that can be measured. What else, indeed, would one expect.

Pallis and Prior's critique of the confirmatory tests suggested for use when brainstem reflexes cannot be adequately tested is misleading. In the consultants' report, we have emphasized the need for good clinical judgment. Whether one should use EEG, angiography, evoked potentials, or other tests would depend on the circumstances. Those that utilize these tests need to appreciate their limitations.

Pallis and Prior's comments on hypoxic coma and electroencephalography do not contradict the guidelines, but rather expand on our treatment in useful ways. We believe that discussion of these issues and further research on resuscitation and diagnosis of brain damage is very important. Throughout, the medical profession needs to be attentive to updating the guidelines as warranted.

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Anticoagulation and embolic infarction

To the Editor: We read with interest the reports by Furlan et al[1] Koller[2], and the accompanying editorial by Yatsu and Mohr[3] in March *Neurology* on the immediate anticoagulation of embolic stroke. We are currently carrying out a multicenter, prospective, randomized trial of immediate anticoagulation in this setting in association with the above authors and offer several comments.

The table summarizes the available data on early recurrence of embolism after embolic brain infarction. In most studies, about half of all clinical embolism involves the brain. Aggregate data from these series[1,2,4-6] indicate a 10 to 15% risk of re-embolization to the brain within 2 weeks of initial stroke.

There are no published reports demonstrating CT evidence of hemorrhagic transformation of embolic brain infarction associated with acute anticoagulation (although briefly mentioned by Weisberg[7]). Figure 1 is the initial CT of a 36-year-old woman with mitral stenosis and atrial fibrillation who abruptly developed left hemiparesis 2 days following elective hysterectomy for which chronic anticoagulation had been temporarily discontinued. Coumadin was immediately restarted, but 8 days later hemiparesis abruptly worsened (figure 2) while the prothrombin time was within therapeutic range (17.0 sec/control 11.8 sec). However, we have seen another patient with spontaneous transformation of pale into hemorrhagic infarction (HI) documented by initial low density on CT changing into mottled high density on

Table. Risk of early re-embolization after embolic stroke*

Author	Embolic source	N	%
Systemic and cerebral			
Daly et al[4]	RHD	194	17%
Szekely[5]	RHD	72	10%
Darling et al[6]	RHD	89	19%
Darling et al[6]	MI	28	18%
Darling et al[6]	AF	59	20%
Cerebral only†			
Furlan et al[1]	Mixed		
Immediate anticoagulation		25	8%
Delayed/no anticoagulation		29	17%
Koller[2]	Mixed		
Immediate anticoagulation		15	0%
Delayed/no anticoagulation		29	14%

* % is the incidence of recurrent embolism within 2 weeks or less of initial embolism except for Szekely's[5] figure which is for 1 month.
† Nonrandomized studies. Koller's[2] report is retrospective.
RHD rheumatic heart disease.
MI acute myocardial infarction.
AF nonvalvular atrial fibrillation.

Figure 1. A low-density area is seen in the right hemisphere (left side of picture).

Figure 2. CT without contrast shows hemorrhagic infarction with dimmer areas of hematoma and midline shift.

day three without administration of anticoagulants or antiplatelet agents.

How often does hemorrhagic infarction (HI) occur after embolic stroke? Fisher's pathologic studies show some degree of HI in the majority of acute embolic stroke at postmortem.[8] We retrospectively found CT evidence of HI in 4 (3%) of 147 patients with a clinical diagnosis of embolic stroke who underwent initial CT prior to any anticoagulation. Our figure agrees with Furlan et al[1] (2%), emphasizing that HI detected by CT is uncommon in embolic stroke. Others have reported HI detected by CT in 10% of all ischemic stroke.[9,10] Spontaneous transformation of pale infarction into CT-detectable HI may occur after the initial hours or days, as described above. Atypical contrast enhancement on CT after high dose infusion may help identify patients who later develop hemorrhagic infarction.[11]

The risk of developing HI, either spontaneously or in association with anticoagulation, may well depend upon the size of infarction and source of embolus as well as patient factors (age, hypertension, etc.). Although we agree with Yatsu and Mohr that, for the time being, "the bandwagon for immediate and optimal anticoagulation of cardiogenic emboli to the brain can be boarded without reluctance in the absence of brain hemorrhage,"[3] we believe that further prospective studies to accurately define the relative risks are ethically justified and urgently needed.

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Reply from the Authors: We appreciate and agree with the observations made by Dr. Hart. The problem of anticoagulation after acute nonseptic embolic brain infarction revolves around the relative risks of hemorrhage and recurrent embolization in a not entirely homogeneous patient population. Some cardiac conditions (especially atrial fibrillation) are probably associated with a higher risk of recurrent embolization. Some patients will suffer hemorrhage whether or not they receive anticoagulants, and despite control of coagulation and blood pressure.

Since the natural course for the evolution of hemorrhage after embolic infarction is unclear, it is difficult to know when it is "safest" to start anticoagulation based solely on the presence or absence of blood in the brain. A clear distinction should be made between microscopic (petechial) hemorrhagic infarction, macroscopic hemorrhagic infarction, and frank intracerebral hemorrhage; each may have a different natural history. CT criteria for differentiating macroscopic hemorrhagic infarction from intracerebral hemorrhage sometimes consist of "eyeballing" and subjective impressions. We do not recommend anticoagulation if CT shows hemorrhage, but we safely treated one patient with macroscopic hemorrhagic infarction and a particularly unstable cardiac condition. Thus CT alone is not necessarily the best indicator of anticoagulation risk. Embolus composition, infarct size, enhancement patterns, type and dose of heparin, blood pressure, age, and other variables all enter into the risk equation.

We hope that data from the prospective, randomized trial in which we are participating will clarify some of these issues. Until then, when faced with such a patient, the available evidence supporting the efficacy and safety of immediate anticoagulation therapy is persuasive if not conclusive.

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Reply from the author: Dr. Hart addresses the most critical problem in the management of the embolic infarct—transformation into hemorrhagic infarction (HI).

The use of anticoagulants in reducing embolic cerebral infarction is widely accepted[1-3] and some studies[4,5] suggest that recurrence is also reduced by anticoagulation. Weighed against this benefit is the risk of HI. As Dr. Hart notes, the risk appears to be less than 5% which certainly seems outweighed by the 10 to 15% risk of reembolization.

What determines whether an embolic infarct becomes an HI? I agree with Dr. Hart that the answer is multifactorial. Experimental evidence suggests that inflammatory emboli are more likely to cause HI.[6] Anecdotal experience suggests that the larger the infarct, the more likely it is to convert to an HI. Even exogenous agents that damage the blood-brain-barrier, such as mannitol or other hyperosmotics, might also be suspect.[7,8] For this reason, the use of high-dose contrast infusion to identify patients at risk must be viewed with caution. Hayman et al[9] had a 20% incidence of HI, much higher than the previously cited studies, which raises the question of cause and effect.

A properly designed prospective study should help clarify these issues and deserves full support.

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An eye movement disorder in ALS

To the Editor: Jacobs et al[1] reported defective pursuit eye movements by electro-oculography in 61% (11/18) of patients with amyotrophic lateral sclerosis (ALS). Similarly, we found impaired visual scanning despite intact visual search in nine consecutive patients with ALS. All of the patients were right-handed (seven women, two men) with a mean of age of 58.3 years (range, 35 to 77 years); average duration of symptoms was 13.8 months. The first symptoms were bulbar in five cases and spinal in four. Twenty-seven healthy control subjects (mean age, 55.3, 14 women, 13 men) were also studied.

Two standard neuropsychological tests were used to assess ocular motor status: (1) the Geneva Lines test[2] which requires speeded scanning of tangled lines from left to right and vice versa and (2) a visual search task that requires voluntary saccades to left and right of a central region to locate a small sketch drawn in any of four visual quadrants.[3] Accuracy and speeded response times were recorded. No abnormal asymmetries were found in patients or controls and the directional scores were combined. On the Geneva Lines test 71.4% (5/7) of the ALS patients made one or more errors (maximum of eight in eight attempts) in contrast to 37.0% (10/27) of the controls (χ^2 = 1.45, ns). While the patient group

was less accurate than the control group, this was not significant. However, speed of eye movements was significantly slower for patients (12.6 sec) than controls (7.8 sec) ($t = -6.22$, $df = 32$, $p < 0.001$). In contrast performance on the visual search task did not differentiate the groups (patients = 6.0 sec; controls = 6.3 sec, ns).

Hence, we agree with Jacobs et al[1] that some ocular motor functions are impaired in ALS. These abnormalities can be detected by a neuropsychological test that takes no special equipment and requires only 5 minutes to administer.

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Valproic acid embryopathy?

To the Editor: Establishing a drug as a human teratogen is often an arduous task, particularly if the malformations do not form a unique pattern. Valproic acid has only recently been implicated as a possible teratogen.[1-3] The following case should bring the potential problem to the attention of neurologists.

A 15-year-old woman had recurrent episodes of inability to speak that were followed by generalized seizures in October 1979. Although she admitted to having used street drugs intravenously in the past, no recent drug abuse was reported. No other medical or family historical factors suggested a predisposition to the development of seizures or dysraphic states. Routine serum chemistries, CSF examination, and enhanced CT excluded were normal. EEG revealed bilateral frontal synchronous spiking, more over the left frontotemporal area than the right. After an unsuccessful trial of phenobarbital, valproate acid, 1000 my per day, completely stopped her seizures. EEG was normal in January 1980.

Because of headaches and depression she was given amitriptyline, 75 mg each night, for several months until depression and headaches subsided. Three months after discontinuing the amitriptyline and 1 month prior to conception, she again became depressed and ingested roughly 1500 mg of amitriptyline. No persistent medical problems followed although she remained semicomatose for 3 days. She resumed usage of valproic acid when she returned home.

On or about July 1, 1981, conception occurred. Valproic acid was taken regularly until the third month of gestation when a physician advised discontinuation of the medication because of the pregnancy. She continued to use it sporadically, however, when headaches occurred. The pregnancy was uneventful and only one seizure occurred during that time. In November 1981, her physician recommended an ultrasonographic examination because of possible twinning. This examination was reported to be normal.

In April 1982, she delivered a well-grown boy who had a large meningomyelocoele in the midlumbosacral region; an Arnold-Chiari malformation was diagnosed clinically and radiographically. No other dysmorphic features were present.

This is the fourth reported occurrence of congential malformations associated with valproic acid. In two of the four, this was the only anticonvulsant taken by the mother. Although the mother was advised to discontinue the anticonvulsant during the third month of gestation, the drug was taken conscientiously during the critical period of neural tube closure (posterior neuropore closure at approximately 28 days).[4] Our patient is the second in whom a meningomyelocoele was recorded, and valproic acid may cause neural tube defects in experimental animals.[5]

Although four case reports do not constitute proof of teratogenicity, the evidence suggests that valproic acid should be used with caution in women of child-bearing age.

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Correction

"Somatosensory evoked potentials in patients with supraclavicular brachial plexus injuries" by V.M. Synek and J.C. Cowen. In **Methods** 1,000 samples (not 100) were averaged. In the last paragraph of **Discussion** the sentence "There may be more deficit" should read "There may be motor deficit." Neurology (NY) 1982;32:1347-52.

Somatosensory evoked potentials in patients with supraclavicular brachial plexus injuries

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