Correspondence

The Diagnosis of Brain Death

To the Editor: At the beginning of his article on brain death (April 19 issue),[1] Dr. Wijdicks states, "Physicians, health care workers, members of the clergy, and laypeople throughout the world have accepted fully that a person is dead when his or her brain is dead." This statement is dogma, not fact. Many societies throughout the world and some cultures represented in American society do not accept this view. As he later implies, the introduction of brain death as a construct was a political decision first promoted in 1968 by an ad hoc committee at Harvard Medical School, prompted by a growing need for organs for transplantation.

Dr. Wijdicks also states, "After the clinical criteria of brain death have been met, the physician should inform the next of kin, who can be approached about organ donation." He adds, "If the legal next of kin declines to donate organs, it is good medical judgment to discontinue mechanical ventilation." Although decision making at the end of life should involve family members, the physician must first ascertain whether advance directives such as a living will or power of attorney for health care have been completed. If someone other than a family member has been named, then this agent is responsible for making such decisions.

ROBERT E. CRANSTON, M.D.
Carle Clinic Association
Urbana, IL 61801

1. Wijdicks EFM. The diagnosis of brain death. N Engl J Med 2001;344:1215-21.

To the Editor: In describing the apnea test, Dr. Wijdicks states, "The mechanical ventilator must be disconnected . . . because the ventilator's sensors may give false readings." Whether the patient breathes during the apnea test should be assessed by looking at the patient, not the ventilator. Apneic oxygenation can be performed in many ways, including by continuous flow of oxygen through a ventilator with a rate set at zero.[1,2] This is how the initial studies of apneic oxygenation were performed.[3] Patients with lung injury may be better oxygenated if they are provided with continuous positive airway pressure, which is most easily and safely delivered through a ventilator. The oxygenation technique Wijdicks advocates, with an oxygen catheter "at the carina (delivering oxygen at a rate of 6 liters per minute)," could result in a pneumothorax, especially in a small child.[4]

MARK A. ROCKOFF, M.D.
JOHN E. THOMPSON, R.R.T.
Children's Hospital
Boston, MA 02115-5737
mark.rockoff@tch.harvard.edu

1. Outwater KM, Rockoff MA. Apnea testing to confirm brain death in children. Crit Care Med 1984;12:357-8.
2. Ad Hoc Committee on Brain Death. Determination of brain death. J Pediatr 1987;110:15-9.
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To the Editor: There is no substantial evidence in support of Dr. Wijdick's claim that one criterion for the diagnosis of brain death is a pupil diameter between 4 and 6 mm. According to one report, the mean pupil diameter in seven brain-dead subjects was 6.7 mm.[1] We recently measured the pupil diameter in seven other brain-dead subjects, using calibrated infrared pupillometry (which is accurate to 0.1 mm); the mean (±SD) diameter was 5.5±1.0 mm. In one subject the pupil diameter was 3.9 mm, and in another it was 7.4 mm. Small (miotic)[2] as well as large[3] pupils in brain-dead subjects have also been observed by other investigators. The important pupillary sign in the diagnosis of brain death is the absence of the light reflex. The pupil is usually close to midposition, but its size is not relevant to the diagnosis of brain death.

We also disagree with the statement that the pupillary response to light remains intact under the influence of anesthetic agents. This may be true at low concentrations

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that permit other midbrain reflexes. However, higher concentrations prevent movement and coughing in response to noxious stimuli, effects that might raise the question of brain death. At high concentrations, anesthetic agents can even abolish all midbrain reflexes, including the pupillary light reflex.[4]

MERLIN D. LARSON, M.D.
ANDREW T. GRAY, M.D., PH.D.
University of California, San Francisco
San Francisco, CA 94143-0648
larsonm@anesthesia.ucsf.edu

1. Larson MD, Muhiudeen I. Pupillometric analysis of the 'absent light reflex.' Arch Neurol 1995;52:369-72.
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4. Gray AT, Krejci ST, Larson MD. Neuromuscular blocking drugs do not alter the pupillary light reflex of anesthetized humans. Arch Neurol 1997; 54:579-84.

To the Editor: Wijdicks fails to recognize the deep problems that exist with the concept of brain death. These problems begin with the title of his article, "The Diagnosis of Brain Death." It is difficult — indeed, impossible — to have diagnostic standards for a condition that has never been adequately defined. For example, although most states define brain death as the absence of all brain function,[1] no competent neurologist would argue that all cases in which brain death is diagnosed conform to this definition.[2] The typical reply to this criticism is to claim that surviving neurologic functions, such as the secretion of antidiuretic hormone from the pituitary, are not "significant."[2] But if it is a question of significance, why do we place great emphasis on the pupillary light and corneal reflexes (neurologic functions of minimal physiologic significance) and ignore the neurologic regulation of salt and water homeostasis (neurologic functions of critical physiologic significance)? Elsewhere, one of us has described many other problems with the concept.[3]

Although everyone would agree that society derives great benefit from a system that allows patients with devastating and unremediable brain injury to make gifts of their organs, we should not trivialize the complexities of justifying this practice on ethical and legal grounds. Capron concludes his accompanying editorial by admonishing physicians to "strive to be clear about the conceptual foundations of the definition [of brain death] they are implementing."[1] Those who choose to follow this advice should be prepared to find that these conceptual foundations are not as sturdy as the superficial reassurances in these articles would suggest.

ROBERT D. TRUOG, M.D.
WALTER M. ROBINSON, M.D.
Harvard Medical School
Boston, MA 02115
robert.truog@tch.harvard.edu

1. Capron AM. Brain death — well settled yet still unresolved. N Engl J Med 2001;344:1244-6.
2. Bernat JL. How much of the brain must die in brain death? J Clin Ethics 1992;3:21-6.
3. Truog RD. Is it time to abandon brain death? Hastings Cent Rep 1997; 27(1):29-37.

To the Editor: Capron confuses science and medicine with law and religion when he seeks to defend brain death as the legal measure of death in America. He adopts the view that brain death is a medical measure of death, thus "providing criteria for diagnosing a condition" of death. On the basis of this approach, he criticizes laws that allow "reasonable accommodation" of alternative standards for death, such as the statute in New Jersey.[1]

A determination of death is a legal determination that a collection of living cells is no longer entitled to the rights granted to human beings, rather than a scientific or medical determination that all biologic life has ended.

Reasonable people agree that human tissue loses its status as a person before there is complete cellular lysis, but cannot agree on whether "humanness" legally disappears when brain function ceases, cardiopulmonary function ceases, or some other criterion is met. The question is, at its core, not a medical question but a moral or religious one.

To a religious person, death is the departure of the soul from the body. To a secular person, death is the point at which human rights no longer apply. Medicine cannot provide answers to either of these questions.

Accommodation of personal beliefs in ethical and religious matters, when such an accommodation can be made at little cost, is the hallmark of a proper society. New Jersey's law on determining death is the ideal one.

MICHAEL J. BROYDE, J.D.
Emory University School of Law
Atlanta, GA 30322
mbroyde@law.emory.edu

1. Declaration of death. L. 1991, ch. 90; NJSA 26:6A-5.

Dr. Wijdicks replies:

To the Editor: In answer to Cranston: the Uniform Determination of Death Act has been accepted by 31 states and the District of Columbia, and 13 states have used it to codify their statutes on brain death.[1] Furthermore, a study of criteria in 78 countries showed that there is judicial recognition of brain death in more than two thirds of the countries, with actual statutes in 86 percent (unpublished data).

This does not mean the world is devoid of vocal critics who support a different criterion. In his eloquent review,[2] Truog expresses the view that brain death is out of date and should be uncoupled from its unique link to transplantation. He advances the argument that a patient in a vegetative state may be withdrawn from life support for the purposes of transplantation. I do not believe that physicians and the public are prepared for such a drastic step.

It is unclear why Truog and Robinson believe that physiologic regulation of salt and water balance is ignored. The pituitary gland is supplied through extracerebral circulation, and salt and water homeostasis may be preserved initially in patients who do not have an acute mass severing the stalk. But in many others, progressive deterioration occurs because of profound polyuria and pulmonary edema, recurrent cardiac arrhythmias, intravascular coagulation, the need for increasing doses of dopamine, and possibly thyroid failure.[3] This collapse distinguishes brain death from other comatose states. Although it is unusual, the spinal cord may reestablish a brittle homeostasis, but one should doubt a

clinical diagnosis of brain death in a patient whose condition remains stable.[4] Brain death may not necessarily indicate that every single hemispheric neuron has died, but it does indicate that the important ones in the brain stem have.

In response to Rockoff and Thompson: there have been no comparative studies of the performance of the apnea test. Disconnecting the ventilator with the use of adequate precautions and direct observation of possible breathing cycles is simple and safe. With a high flow of oxygen (more than 10 to 15 liters per minute), placement of the catheter at the carina has been linked to pneumothorax in only a few cases, and the causality is doubtful.[5] I am unaware of a study suggesting an increased risk of pneumothorax in children. Pneumothorax is more often due to prior cardiopulmonary resuscitation and traumatic lung injury. My concern is that inadequate delivery of oxygen may damage organs suitable for recovery.

The additional data that Larson and Gray provide on the diameter of the pupil confirm the empirical fact that the pupil is typically in midposition. Nevertheless, the main issue here is that in patients with persistent maximal dilatation of the pupils or pinpoint pupils, whether or not they are light-fixed, poison or drug intoxication should be considered.

EELCO F.M. WIJDICKS, M.D.
Mayo Clinic
Rochester, MN 55905

1. Weyrauchs S. Acceptance of whole brain criteria for determination of brain death: a comparative analysis of the United States and Japan. UCLA Pacific Basin Law J 1999;17:91-123.
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The editorialist replies:

To the Editor: Broyde seems both to misunderstand my editorial and to be applying ill-defined criteria in prescribing what would make a good law. To begin with, he confuses the "reasonable accommodation" requirement of the New York regulation[1] (which in practice means making minor adjustments in the timing and circumstances of declarations of death in the light of some families' religious customs) with the provisions of the New Jersey statute that effectively require physicians to use "traditional cardio-respiratory criteria" rather than "modern neurological criteria" when they have reason to believe that using the latter would violate the person's religious beliefs.[2] Does Broyde think these are equally appropriate "accommodations to personal beliefs"? Would a statute that said death should be declared when the soul departs (which he tells us is the definition used by "a religious person") be equally appropriate?

In my editorial, I cited these statutes not so much to criticize them as to show that lack of clarity about the relation of "brain death" (a term I did criticize) to cardiopulmonary standards can lead to the impression that determining death is a matter of individual preference. Does Broyde seriously believe that "anything goes" is a defensible basis for public policy?

When deciding that a human body "is no longer entitled to the rights granted to human beings" — which Broyde at another point offers as a basis for a legal standard, though the Constitution actually protects "persons" — society looks to medicine for criteria and tests that can be applied reliably in determining that specified standards are met. The standards are selected with scientific guidance on the basis of their relation to essential characteristics; they represent a social choice about which characteristics to count, but (at least in the case of defensible legal standards) they are not arbitrary.

Truog and Robinson suggest — and Truog has repeatedly argued — that other criteria, which are not present in the prevailing protocols, ought to be considered. As I argued in my editorial, other experts on the subject remain unconvinced. Should the importance of such additional tests (or the irrelevance of existing ones) be established as accepted medical practice, the Uniform Determination of Death Act not only does not prevent but also affirmatively allows their use. Truog and Robinson's argument is not with me but with their colleagues in neurology and related fields.

ALEXANDER MORGAN CAPRON, LL.B.
University of Southern California
Los Angeles, CA 90089-0071

1. Determination of death. 10 NYCRR § 400.16.
2. Declaration of death. L. 1991, ch. 90; NJSA 26:6A-5.

Cutaneous Reactions to STI571

To the Editor: The remarkable effects of the tyrosine kinase inhibitor STI571 in chronic myeloid leukemia and acute lymphoblastic leukemia reported by Druker et al. (April 5 issue)[1,2] are frequently associated with adverse cutaneous reactions. The rash was described in only two patients — as "exfoliative dermatitis" in one and as a "persistent and progressive rash" in the other.[1,2] We recently observed a severe adverse cutaneous reaction in a patient with chronic myeloid leukemia who was treated with STI571; it was an acute generalized exanthematous pustulosis, a well-characterized cutaneous reaction to drugs.[3,4] Interestingly, the scarlatiniform erythema with nonfollicular pustules was confined to flexural areas; such a pattern is often seen in skin reactions to mercury.[3] Mercury interferes with some tyrosine kinases.[3] As shown in Table 1, which was compiled from

TABLE 1. INCIDENCE OF ADVERSE CUTANEOUS REACTIONS ACCORDING TO THE DAILY DOSE OF STI571.*

SEVERITY OF RASH	DAILY DOSE OF STI571			
	25–140 mg (N=14)	200–300 mg (N=31)	350–500 mg (N=37)	600–1000 mg (N=61)
	% of patients			
Mild or moderate	7	13	16	21
Severe or life-threatening	0	0	0	5

*Data are from Druker et al.,[1,2] Brouard et al.,[3] and Joensuu et al.[5]

published reports,[1-3,5] the incidence of cutaneous reactions to STI571 appears to be dose-dependent. This might indicate that they are related to the pharmacologic effect of the drug rather than to hypersensitivity.

MICHEL BROUARD, M.D., PH.D.
JEAN-HILAIRE SAURAT, M.D.
University Hospital
CH-1211 Geneva, Switzerland
mcvpb@hotmail.com

1. Druker BJ, Talpaz M, Resta DJ, et al. Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. N Engl J Med 2001;344:1031-7.
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3. Brouard M, Prins C, Mach-Pascual S, Saurat JH. Acute generalized exanthematous pustulosis associated with STI571 in a patient with chronic myeloid leukemia. Dermatology (in press).
4. Roujeau JC, Bioulac-Sage P, Bourseau C, et al. Acute generalized exanthematous pustulosis: analysis of 63 cases. Arch Dermatol 1991;127:1333-8.
5. Joensuu H, Roberts PJ, Sarlomo-Rikala M, et al. Effect of the tyrosine kinase inhibitor STI571 in a patient with a metastatic gastrointestinal stromal tumor. N Engl J Med 2001;344:1052-6.

Heparin-Induced Thrombocytopenia

To the Editor: The article on temporal aspects of heparin-induced thrombocytopenia (April 26 issue)[1] lacks some information that would be helpful. In particular, there is no mention of the type of heparin used in the initial treatment. In addition, the authors do not note how many patients, when treated again, were treated with the same or a different preparation of heparin.

It has been stated that the incidence of heparin-induced thrombocytopenia is lower in patients treated with low-molecular-weight heparin than in those treated with formulations of unfractionated heparin. It has also been stated that patients who have heparin-induced thrombocytopenia when given unfractionated heparin may not have this complication when given low-molecular-weight heparin. It is important to know whether Warkentin and Kelton confirmed this hypothesis in their study.

CHARLES A. BOMZER, M.D.
Oncology of Wisconsin
Glendale, WI 53212

1. Warkentin TE, Kelton JG. Temporal aspects of heparin-induced thrombocytopenia. N Engl J Med 2001;344:1286-92.

To the Editor: Warkentin and Kelton describe a subgroup of patients in whom heparin-induced thrombocytopenia developed rapidly; the median time to a fall in the platelet count in this subgroup was 10.5 hours. Most of these patients (53 of 73) had been treated with heparin between 1 and 10 days before the current course of heparin and subsequent thrombocytopenia. We argue that one cannot rule out the possibility that in many of these patients, typical-onset heparin-induced thrombocytopenia may have been developing in response to the previous heparin treatment, with a delay of four or more days. We note the report by Barratt et al.[1] of a case in which heparin-induced thrombocytopenia with a platelet count of 53,000 per cubic millimeter and multiple pulmonary emboli developed four days after the cessation of prophylactic enoxaparin.

Reclassifying these 53 patients from the rapid-onset group to the typical-onset group would most likely render nonsignificant the correlation of rapid-onset heparin-induced thrombocytopenia with previous heparin treatment within 100 days.

KEVIN C. FUNG, M.B., B.S.
SUCHITRA CHANDAR, M.B., B.S.
DAVID BRIEGER, M.B., B.S., PH.D.
Concord Repatriation General Hospital
Concord, NSW 2139, Australia
kckfung@idx.com.au

1. Barratt SM, Ruff SJ, Edwards RC. Heparin-induced thrombocytopenia presenting after the cessation of low molecular weight heparin prophylaxis with enoxaparin. Med J Aust 2000;172:449.

The authors reply:

To the Editor: Bomzer asks about the type of heparin (unfractionated as compared with low-molecular-weight heparin) used in our study, particularly with regard to subsequent courses of treatment with heparin. Only 12 of our 243 patients (5 percent) received low-molecular-weight heparin in association with their episode of heparin-induced thrombocytopenia. In four of these patients, typical-onset thrombocytopenia developed during treatment with low-molecular-weight heparin; in five patients who had received unfractionated heparin during the previous week, rapid-onset thrombocytopenia developed during subsequent treatment with low-molecular-weight heparin; and in three patients who had received treatment with low-molecular-weight heparin within the preceding week, rapid-onset heparin-induced thrombocytopenia developed during subsequent treatment with unfractionated heparin. These observations indicate that the temporal features of heparin-induced thrombocytopenia are similar for the two types of heparin received. Our study was not designed to assess the relative risk of thrombocytopenia for each of the two types of heparin.

With regard to the seven patients (listed in Table 3 of our article) who underwent heparin treatment after they had recovered from a previous episode of serologically confirmed thrombocytopenia due to the use of unfractionated heparin and when heparin-dependent antibodies were no longer detectable: all these patients were subsequently treated with unfractionated heparin. Subsequent courses of treatment should probably be restricted to patients who require heparin for cardiac or vascular surgery; in these situations, the advantage of unfractionated heparin is that it can be reversed postoperatively with protamine.

Fung and colleagues argue that the 53 patients with rapid-onset heparin-induced thrombocytopenia who had received heparin within the preceding 10 days may in some cases have actually had typical-onset heparin-induced thrombocytopenia caused by the preceding heparin treatment. The classification of rapid-onset heparin-induced thrombocytopenia was made because the platelet count fell abruptly (and often dramatically) with the subsequent heparin use. Even if all 53 patients are reclassified as having typical-

onset heparin-induced thrombocytopenia, and even if all 24 (of the 53) patients known to have had a "definite" or "possible" history of heparin treatment are assumed to have had such treatment within the preceding 100 days, we still would have observed a strong association between rapid-onset heparin-induced thrombocytopenia and use of heparin within the preceding 100 days (in 20 of 20 patients, as compared with 40 of 71 patients who had typical-onset heparin-induced thrombocytopenia and are known or are assumed to have received heparin during that 100-day period; $P<0.001$). Thus, our study provides evidence that immune sensitization resulting from recent treatment with heparin explains rapid-onset heparin-induced thrombocytopenia on subsequent heparin treatment.

THEODORE E. WARKENTIN, M.D.
JOHN G. KELTON, M.D.
McMaster University
Hamilton, ON L8N 3Z5, Canada

Atrial Fibrillation

To the Editor: In his review article on atrial fibrillation (April 5 issue),[1] Falk suggests that patients admitted to the hospital with atrial fibrillation of less than 48 hours' duration should be treated differently from those with atrial fibrillation of more than 48 hours' duration. He suggests that all patients in whom spontaneous conversion to sinus rhythm does not occur should receive anticoagulation therapy with heparin; however, only those with atrial fibrillation of more than 48 hours' duration should undergo transesophageal-guided cardioversion to exclude the presence of atrial thrombi before cardioversion. Falk's suggestion perpetuates the myth that cardioversion of atrial fibrillation of less than 48 hours' duration is safe without echocardiographic guidance.

The past assumption that 48 hours is insufficient time for thrombi to form has been shown to be incorrect; thrombi occur within a few hours of the development of atrial fibrillation in some patients and are found in 14 percent of patients presenting with acute arrhythmia.[2] In our view, the safest way to deal with acute atrial fibrillation is to administer anticoagulation therapy with heparin at presentation. If the patient's fibrillation has not spontaneously reverted and cardioversion during that hospitalization is required, he or she should undergo transesophageal echocardiography before either chemical or electrical cardioversion.

If transesophageal echocardiography is not readily available, the alternative strategy is to give oral anticoagulants for three weeks and then readmit the patient for elective cardioversion, continuing the anticoagulants for a further three to four weeks after the procedure.

HOSSAN EL GENDI, M.R.C.P.
BALVINDER WASAN, M.R.C.P.
JAMIL MAYET, M.D.
St. Mary's Hospital
London W2 1NY, United Kingdom
j.mayet@ic.ac.uk

1. Falk RH. Atrial fibrillation. N Engl J Med 2001;344:1067-78.
2. Stoddard MF, Dawkins PR, Prince CR, Ammash NM. Left atrial appendage thrombus is not uncommon in patients with acute atrial fibrillation and a recent embolic event: a transesophageal echocardiographic study. J Am Coll Cardiol 1995;25:452-9.

To the Editor: Falk's article was an excellent review of atrial fibrillation. It covered the many issues and options that arise in the management of this common arrhythmia. I would like to add a summary, which I have found useful in treating patients with atrial fibrillation and in teaching both house staff and practicing clinicians. I have termed this summary of the management of atrial fibrillation "the five C's of atrial fibrillation": (1) cause: investigate the cause or triggers of the episode of atrial fibrillation; (2) coagulation: address the need for anticoagulation or antiplatelet therapy; (3) control: control the ventricular rate as necessary; (4) conversion: consider conversion to sinus rhythm, if this is appropriate and desirable; and (5) cure: consider options for long-term maintenance of sinus rhythm — again, if this is an appropriate and desirable strategy for the individual patient.

Although each item may not be applied to every patient, I have found that this is a simple and easily remembered framework on which to approach atrial fibrillation, both in patient care and teaching. I hope that others may find it useful.

DAVID M. GILLIGAN, M.D.
Veterans Affairs Medical Center
Richmond, VA 23233
davidmgilligan@yahoo.com

Dr. Falk replies:

To the Editor: El Gendi et al. state that I suggested that "only those with atrial fibrillation of more than 48 hours' duration should undergo transesophageal-guided cardioversion to exclude the presence of atrial thrombi," and they imply that there is a need to exclude the presence of atrial thrombi in patients with atrial fibrillation of short duration. They base their objection on a study that included patients who had recently had strokes and that was conducted at a time when monoplane probes for transesophageal imaging were used and the identification of thrombi was less precise than it is today. Unfortunately, they have misread my article and ignored important literature on this topic.

Figure 1 in my review addresses the issue of cardioversion in subjects with an arrhythmia of less than 48 hours' duration. It clearly indicates that this applies to those with "no clinically significant LV [left ventricular] dysfunction, mitral-valve disease, or previous embolism." These recommendations (which are supported by the consensus conference on antithrombotic therapy of the American College of Chest Physicians[1]) are based on published data.

In persistent atrial fibrillation, the risk of embolism can be stratified according to clinical criteria that correlate well with the prevalence of thrombi on echocardiographic examination.[2] Thus, it is likely that an absence of clinical risk factors in atrial fibrillation of recent onset indicates a low risk of embolism. However, the important questions are not about the prevalence of left atrial thrombi but about the embolic risk of "blind" restoration of sinus rhythm and whether anticoagulation with warfarin can offer a benefit.

Weigner et al. reported on a series of 357 patients with atrial fibrillation lasting 48 hours or less that converted to

sinus rhythm during hospitalization without transesophageal examination.[3] Two thirds of these patients had spontaneous conversion to sinus rhythm, and only three (0.8 percent) had a clinical embolus. All three events occurred in patients who had spontaneous conversion. This percentage is the same as the rate of embolism in the transesophageal-echocardiography group of the Assessment of Cardioversion Using Transesophageal Echocardiography Study in patients in whom thrombus was not present.[4] Given the low risk of embolism in atrial fibrillation of recent onset, the high likelihood of early spontaneous conversion, and the potential for major warfarin-related bleeding (1.5 percent in the warfarin arm of the Assessment of Cardioversion Using Transesophageal Echocardiography Study), the approach of El Gendi et al. is unsupported by evidence of a positive benefit–risk ratio.

I enjoyed Gilligan's mnemonic device for the approach to atrial fibrillation and would simply like to respond to his "five C's" with eight of my own: "Congratulations, colleague, on a concisely compiled, crystal-clear companion to cognition."

RODNEY H. FALK, M.D.
Boston Medical Center
Boston, MA 02118
rfalk@bu.edu

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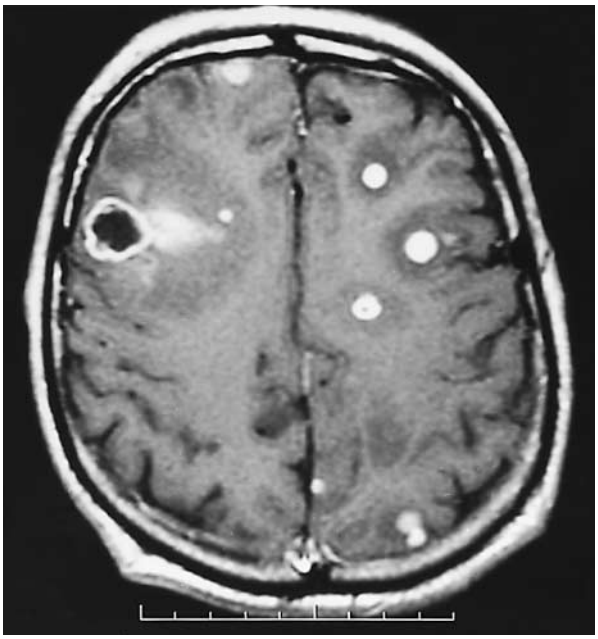
Treatment of Brain Metastases of Malignant Melanoma with Temozolomide

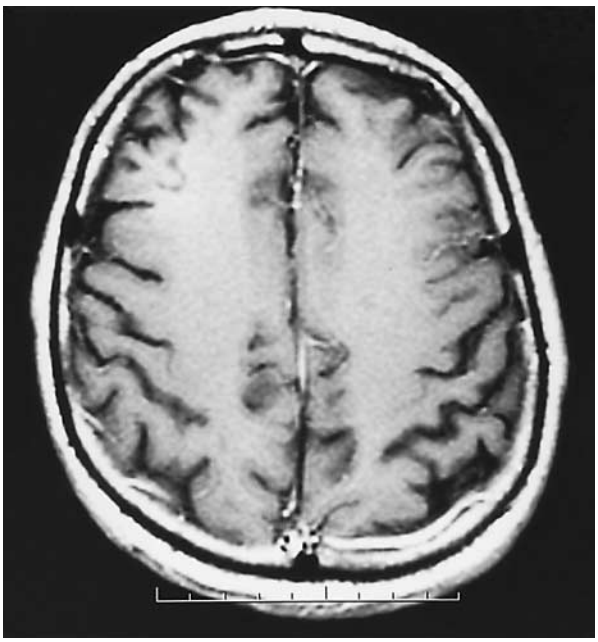
To the Editor: A 57-year-old man presented with an ulcerative, acral–lentiginous lesion on the sole of the left foot. Pathological examination showed a melanoma (Breslow depth, 2.2 mm; Clark level IV) without involvement of the surgical margins; the dissected ilioinguinal nodes showed micrometastases. A computed tomographic (CT) scan did not show any other lesion. The patient received interferon alfa, but two years later, plantar and ilioinguinal lesions recurred. They were removed twice in five months. Therapy with interferon alfa was stopped.

Two months later, a CT scan showed bilateral metastatic lesions in the lung. The patient was treated with dacarbazine, cisplatin, interferon alfa, and interleukin-2. After six cycles, a complete response was documented by total-body CT scanning, bilateral inguinal ultrasonography, and positron-emission tomography.

Two months later, confusion and epilepsy developed. A CT scan of the brain revealed multiple metastases (diameter, 0.5 to 1 cm), a finding confirmed by magnetic resonance imaging (Fig. 1A). The patient was treated with oral



A



B

Figure 1. Magnetic Resonance Images of the Brain.
There are multiple bilateral metastases before therapy with temozolomide (Panel A). After six cycles of temozolomide, the lesions detectable by magnetic resonance imaging have disappeared (Panel B).

temozolomide at a dose of 200 mg per square meter of body-surface area for five days every four weeks. After six cycles of the drug, magnetic resonance imaging showed that the brain lesions had disappeared (Fig. 1B). The patient is still receiving therapy with temozolomide. He is in good health, without signs or symptoms of relapse.

Temozolomide, a new oral alkylating agent, is as active as dacarbazine in malignant melanoma.[1] Temozolomide can cross the blood–brain barrier, and its concentration in the central nervous system is approximately 28 to 30 percent of its concentration in plasma.[2] Another report has suggested the efficacy of temozolomide plus radiotherapy for the treatment of brain metastases of malignant melanoma.[3] Our case shows that temozolomide alone can be effective in the treatment of such lesions.

GUIDO BIASCO, M.D.
MARIA A. PANTALEO, M.D.
SIMONA CASADEI, M.D.
University of Bologna
40138 Bologna, Italy
gbiasco@med.unibo.it

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Acquired Type I von Willebrand's Disease Associated with Highly Substituted Hydroxyethyl Starch

To the Editor: High-molecular-weight hydroxyethyl starches (hetastarches) can cause acquired type I von Willebrand's disease.[1] A case has also occurred after treatment with medium-molecular-weight hydroxyethyl starches (pentastarches).[2] We analyzed all patients with hemostatic disorders that occurred during treatment with pentastarch (Elohes and Hesteril, Fresenius, Paris; and Lomol, Dupont, Wilmington, Del.) and that were spontaneously reported to the 31 French regional drug-monitoring centers.

Nine cases of hemostatic disorders were reported between 1990 and 1997 (Table 1). All patients were treated with Elohes as hemodilution therapy (for vasospasm secondary to subarachnoid hemorrhage).

Of the nine patients, six had a diagnosis of acquired

TABLE 1. CHARACTERISTICS OF PATIENTS WITH A HEMOSTATIC DISORDER.

PATIENT NO.*	SEX/AGE (YR)	INITIAL CLINICAL MANIFESTATIONS	DAY OF OCCURRENCE AFTER INITIATION OF ELOHES TREATMENT	CUMULATIVE DOSE OF ELOHES	ACTIVATED PARTIAL-THROMBOPLASTIN TIME†	FACTOR VIIIc‡	LEVEL OF VON WILLEBRAND FACTOR ANTIGEN‡	RISTOCETIN COFACTOR ACTIVITY‡	FACTOR II	COMPLICATIONS	OUTCOME
				liters (ml/kg)		percent					
1	F/30	Hematoma, bleeding of scar	4	3.8 (76)	1.36	18	21	10	70		Recovered
2	F/11	Routine coagulation studies before neurosurgery	6	3.5 (87)	1.82	14	13	15	67		Recovered
3	F/37	Routine coagulation studies before neurosurgery	4	6 (88)	1.82	24	42	32	50	Cerebral hemorrhage	Recovered
4	F/42	Routine coagulation studies before neurosurgery	16	8	1.79	24	18	14	70	Cerebral hemorrhage	Died
5	F/27	Hematoma	11	11 (189)	1.52	43	40	31	64	Cerebral hemorrhage	Died
6	F/31	Epistaxis, bleeding at venous-puncture sites	18	10 (166)	1.8	28		64		Cerebral hemorrhage	Died
7	F/61	Hematoma	4	8	1.27						Recovered
8	M/40	Hematoma, bleeding at venous-puncture sites	6	12 (150)	1.43					Extradural hematoma	Recovered
9	M/39	Routine coagulation studies before neurosurgery	2	1 (11)	1.44						Recovered

*Patients 1 through 6 had acquired type 1 von Willebrand's disease; Patients 7, 8, and 9 had prolongation of the activated partial-thromboplastin time.

†The range of normal values is 0.85 to 1.25.

‡The range of normal values is 50 to 200 percent.

type I von Willebrand's disease. Before the abnormalities in coagulation were discovered, patients had received a mean dose of 121±52 ml of pentastarch per kilogram of body weight. The cumulative dose was higher in the three patients (Patients 1, 5, and 6) with hemorrhage (mean, 144 ml per kilogram) than in those without bleeding (mean, 87.5 ml per kilogram). Five patients received concentrates of von Willebrand factor (Patients 2, 3, 4, and 5) or desmopressin (Patient 6). The abnormalities resolved each time treatment with pentastarch was stopped. Of the nine patients with a hemostatic abnormality, four had cerebral hemorrhage (Patients 3, 4, 5, and 6), three of whom died (Patients 4, 5, and 6).

In three patients, the only reported abnormality was a prolonged activated partial-thromboplastin time (Patients 7, 8, and 9). In Patient 8, an extradural hematoma developed three days after pentastarch was withdrawn, even though the activated partial-thromboplastin time returned to normal. Acquired type I von Willebrand's disease was suspected in these three patients but not proved, since factor VIIIc and von Willebrand factor antigen levels were not measured.

In these patients, pentastarch probably induced acquired type I von Willebrand's disease, because blood-coagulation results were normal before treatment with pentastarch was initiated, and all abnormalities disappeared in patients who survived after pentastarch was withdrawn.

Accumulation of starch probably led to quantitative defects of the complex of factor VIII and von Willebrand factor by accelerated elimination from the circulation of complexes attached to starch molecules.[3] Because Elohes is highly substituted and has a higher C2/C6 ratio, it is difficult to break down and therefore is eliminated more slowly and has a longer-lasting effect on plasma volume than other pentastarches. The accumulation of Elohes after repeated administration can explain why its adverse effects on coagulation resemble those of hetastarch.[4] However, pentastarches other than Elohes affect the coagulation system much less, because their effect on plasma volume is transient.[5]

As a result of this study, the following guidelines for the use of Elohes were defined in France. The infusion should be limited to 33 ml per kilogram per day, and the cumulative dose to 80 ml per kilogram. Treatment should be given for no more than three days. Elohes is contraindicated in patients with coagulation disorders. Patients should be monitored with blood tests (activated partial-thromboplastin time and, if necessary, factor VIIIc and von Willebrand factor levels).

ANNIE-PIERRE JONVILLE-BÉRA, M.D.
ELISABETH AUTRET-LECA, M.D.
YVES GRUEL, M.D.
University Hospital of Tours
37044 Tours, France
jonville-bera@chu-tours.fr

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