Isolated Central Nervous System Hemophagocytic Lymphohistiocytosis: Case Report

To the Editor:

We read with great interest the article by Shinoda et al. (8) reporting a case of isolated central nervous system (CNS) hemophagocytic lymphohistiocytosis (HLH). We would like to comment on this very interesting case. First, the initial T1-weighted magnetic resonance imaging (MRI) findings of an irregular ring-like enhanced lesion in the posterior right frontal lobe looked similar to those in our previously published case (6). However, in contrast to the case presented by Shinoda et al., our patient first developed systemic HLH at 1 year and 3-months of age and received immunochemotherapy. On the 37th week of therapy (age, 2 yr), monoplegia occurred at her left arm when a brain MRI scan revealed a large mass-like lesion at the right cerebral hemisphere as shown in *Figure C1*. We thought the MRI findings were not typical for CNS-HLH lesions, compared with the previously published common features (4, 7), thus the differential diagnosis from several other neurological disorders was required. In fact, the histopathological findings in our case were quite the same and compatible with those of Shinoda et al.'s case, except for positive Epstein-Barr early regions. As monoclonally proliferating Epstein-Barr virus-positive T-cell tumor manifested as CNS-HLH, she received whole brain irradiation (18 Gy) in association with systemic immunochemotherapy, with marked neurological improvement.

Unfortunately, Shinoda et al. did not show any evidence of immune dysfunction in their case. Although the authors assumed that secondary HLH was more likely, we suspect familial hemophagocytic lymphohistiocytosis (FHL) based on their patient's poor outcome. In general, the first symptoms of FHL are intractable fever, hepatosplenomegaly, and pancytopenia. Most FHL patients subsequently develop the CNS manifestations due to the infiltration of tissues by activated lymphocytes and macrophages. However, as the authors pointed out, there were some reports of isolated CNS cases discussed in their study. In the majority of cases of FHL, there is a close association between absent (or reduced) natural killer cell activity and CNS-HLH (5).

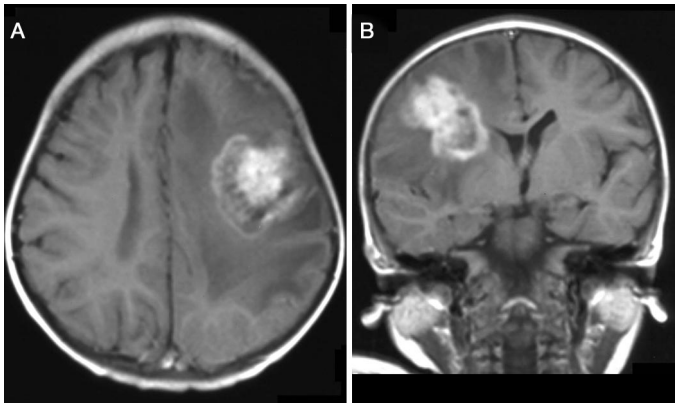

FIGURE C1. *Sagittal (A) and coronal (B) gadolinium enhanced T1-weighted MRI scans showing a large mass-like lesion with peri-tumor edema, noted at the right cerebral hemisphere.*

More recently, Feldmann et al. (3) reported two FHL patients with an atypical CNS-HLH and leading to an early death. Functional and molecular analyses revealed the novel missense mutation in the perforin gene (FHL2) in the calcium-binding domain in patients who showed impaired in vitro cytotoxic activity. Their report emphasizes the importance of early diagnosis of the atypical form of FHL as CNS involvement. If the case described by Shinoda et al. was also caused by similar pathogenetic mechanisms, determination of perforin gene mutation seems essential. In addition, it is worth searching for Munc13-4 (FHL3) gene mutations (2, 9), in which CNS disease is also high.

Finally, regarding the therapeutic measures, hematopoietic stem cell transplantation (HSCT) is essential to obtain a cure in FHL. Shinoda et al.'s patient took an aggressive clinical course and died without receiving HSCT, which may also strongly suggest FHL. By contrast, our patient, who was molecularly determined not to have FHL, has survived in response to continuation of immunochemotherapy and CD34+ peripheral blood stem cell transplantation from HLA-haploidentical father (although the graft was rejected and early autologous reconstitution occurred). Currently, she is off therapy and is doing well at 9 years of age. According to the report by Anna Carin et al. (1), 15 of the 25 (60%) patients with CNS-HLH at diagnosis have been long-term survivors after HSCT. In conclusion, early diagnosis with use of molecular methods for FHL gene mutations and early introduction of HSCT is essential to improve the prognosis of HLH patients with CNS disease.

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1. Anna Carin H, Janka G, Egeler M, Gadner H, Imashuku S, Ladisch S, Locatelli F, Montgomery SM, Webb D, Winiarski J, Filipovich AH, Henter JI: Hematopoietic stem cell transplantation in hemophagocytic lymphohistiocytosis. **Br J Haematol** (in press).
2. Feldmann J, Callebaut I, Raposo G, Certain S, Bacq D, Dumont C, Lambert N, Ouachee-Chardin M, Chedeville G, Tamary H, Minard-Colin V, Vilmer E, Blanche S, Le Deist F, Fischer A, de Saint Basile G: Munc13-4 is essential for cytolytic granules fusion and is mutated in a form of familial hemophagocytic lymphohistiocytosis (FHL3). **Cell** 115:461–473, 2003.
3. Feldmann J, Menasche G, Callebaut I, Minard-Colin V, Bader-Meunier B, Le Clainche L, Fischer A, Le Deist F, Tardieu M, de Saint Basile G: Severe and progressive encephalitis as a presenting manifestation of a novel missense perforin mutation and impaired cytolytic activity. **Blood** 105:2658–2663, 2005.
4. Haddad E, Sulis M-L, Jabado N, Blanche S, Fischer A, Tardieu M: Frequency and severity of central nervous system lesions in hemophagocytic lymphohistiocytosis. **Blood** 89:794–800, 1997.

5. Imashuku S, Hyakuna N, Funabiki T, Ikuta K, Sako M, Iwai A, Fukushima T, Kataoka S, Yabe M, Muramatsu K, Kohdera U, Nakadate H, Kitazawa K, Toyoda Y, Ishii E: Low natural killer activity and central nervous system disease as a high-risk prognostic indicator in young patients with hemophagocytic lymphohistiocytosis. **Cancer** 94:3023–3031, 2002.
6. Iwai A, Iwai, T, Suzuya H, Endo S, Nakagawa Y, Watanabe T, Kawano Y, Imashuku S: Development of a clonal and Epstein-Barr virus(EBV)-positive CNS tumor at recurrence in a case of hemophagocytic lymphohistiocytosis. **Int J Pediatr Hematol Oncol** 6:183–188, 1999.
7. Kollias SS, Ball WS, Tzika AA, Harris RE: Familial erythrophagocytic lymphohistiocytosis: Neuroradiologic evaluation with pathologic correlation. Radiology 192:743–754, 1994.
8. Shinoda J, Murase S, Takenaka K, Sakai N: Isolated Central Nervous System Hemophagocytic Lymphohistiocytosis: Case Report. **Neurosurgery** 56:187, 2005.
9. Yamamoto K, Ishii E, Sako M, Ohga S, Furuno K, Suzuki N, Ueda I, Imayoshi M, Yamamoto S, Morimoto A, Takada H, Hara T, Imashuku S, Sasazuki T, Yasukawa M: Identification of novel MUNC13-4 mutations in familial haemophagocytic lymphohistiocytosis and functional analysis of MUNC13-4-deficient cytotoxic T lymphocytes. **J Med Genet** 41:763–767, 2004.

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Scales and Scores

To the Editor:

Since its inception in 1977, articles in *Neurosurgery* and in other peer-reviewed neuroscience journals have increasingly contained detailed outcome analyses in discussions of therapeutic outcomes. Authors have used myriad scales and scoring systems to quantify the presentation of data. Subspecialization in the neurosurgical community has resulted in the publication of many articles devoted to procedures that require particular expertise. An example is the use of deep brain stimulation in Parkinson's disease. Although surgeons who perform this operation are surely conversant with the Unified Parkinson's Disease Rating Scale, a substantial number of our colleagues are not. It would greatly assist the average reader if the editors encouraged authors to append to their papers the details of a scale or score mentioned in the text. A minimum requirement should be a readily accessible annotated reference.

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Deep Brain Stimulation in Gilles de la Tourette's Syndrome

To the Editor:

The application of deep brain stimulation (DBS) in movement disorders such as Parkinson's disease (PD), essential tremor (ET), and dystonia is currently widespread. Long-term results of DBS of the subthalamic nucleus (STN) in PD, the ventral intermediate nucleus (VIM) of the thalamus in ET (5), and the globus pallidus internus (GPi) in dystonia (5) have shown that this technique is safe and has long-lasting beneficial effects on motor disability. Moreover, the advantages of this technique are widely acknowledged when compared with ablative surgery. In Gilles de la Tourette Syndrome (GTS), a disorder in which motor and vocal tics form the core symptoms, hardly any DBS experience has been acquired. GTS encompasses a neuropsychiatric disorder, in which, in most cases, symptoms wane before or at onset of adolescence (3). However, some patients develop severe and incapacitating tics and other comorbid conditions that are treatment refractory. In the past, these patients have been candidates for ablative procedures in different parts of the brain, such as the prefrontal lobe, cingulum, thalamus, and zona incerta (8). The results were often unsatisfactory or major side effects, such as hemiplegia or dystonia, occurred (8).

In 1999, DBS was introduced by our group as a new therapeutic approach for intractable GTS (10). To date, three patients who underwent bilateral thalamic stimulation with promising results have been described by Visser-Vandewalle et al. (11).

After these single case studies, the Dutch-Flemish Tourette Surgery Study Group has established guidelines for DBS in GTS. These guidelines are used for a prospective randomized double-blind cross-over study in order to evaluate the efficacy of bilateral thalamic stimulation in a larger group of patients experiencing intractable GTS. This study began on February 14, 2005.

These guidelines include conditions that collaborative centers should fulfill, as well as inclusion and exclusion criteria for patients to enter the study. Based on the pilot study, experiences in the first patients operated (11) and in line with the collaborative effort realized with regard to DBS in obsessive compulsive disorder (5), specific terms have been formulated.

General requirements to be met by the study center

First, it is of paramount importance that the execution of DBS be restricted to neurosurgical units experienced in DBS treatment of movement disorders, with established collaborations with neurological and psychiatric departments specializing in the diagnosis and treatment of GTS. Secondly, because DBS in GTS encompasses an invasive surgical technique in an experimental phase, the patients should be studied in a high-quality scientific setting using a blinded study design to ensure that sound answers can be given on short- and long-term treatment effect and prognostic factors involved in DBS. Third, an ethics committee (e.g., Institutional Review Board) of the participating institute should have given approval of all aspects of the study protocol. Only those patients who are fully capable of deciding on participation are included. Patient consent should be monitored throughout the DBS process and patients can drop out of the procedure whenever they choose.

Requirements with regard to patient selection

The GTS patients considered for DBS should comprise only very severe cases; they should be patients who have already fruitlessly received standard therapies. This has a number of implications for patient selection.

Inclusion of patients

The patient has a definite Tourette's syndrome, established by two independent clinicians. The diagnosis is being established according to the Diagnostic and Statistical Manual of Mental Disorders-IV criteria (2) and with the aid of the Diagnostic Confidence Index (7). According to Diagnostic Confidence Index standards, the patient should be rated as a definite case of GTS. Current as well as past tic status is being evaluated.

The patient has severe and incapacitating tics as his primary problem. The treatment of these tics, not of other comorbid behaviors such as obsessive-compulsive disorder, self-injurious behaviors, or attention deficit hyperactivity disorder are the main focus of the therapy. Psychiatric and neurological side effects are carefully monitored perioperatively, immediately postoperatively, and at long-term follow-up examinations. To assess tic severity, videotaped tic countings (1) and the Yale Tic Severity Scale (4) are being used. Patients with Yale Tic Severity Scale scores on subscale A-E $>$ 20 (scale scores, 0-40), and Yale Tic Severity Scale score on subscale F $>$ 5 (scale scores, 0-10) are included.

The patient is treatment refractory. This means that the patient either has not or very partially responded to three different medication regimes, each in adequate doses during at least 12 weeks, or has proven not to tolerate medication due to side-effects after serious attempts at taking medication have been made. With regard to the types of medication tried, three different groups can be distinguished that should be tried: 1) "classic" Dopamine-2 antagonists (e.g., haloperidol, pimozide) or clonidine, 2) modern antipsychotic medication (e.g., risperidone, olanzapine, tiapride, sulpiride), and 3) experimental drugs (e.g., quetiapine, aripiperazole, pergolide). Finally, a trial of at least 12 sessions of behavioral therapy for tics should have been attempted and failed. Behavioral therapy techniques should entail either self-control procedures (habit reversal) (6) or exposure therapy to premonitory urges (9). The patient should also be over 25 years of age.

Exclusion of patients

Tic disorder other than Tourette's syndrome, as well as severe psychiatric co-morbid conditions (e.g., psychotic, dissociative, depressive disorders, substance use disorders), cognitive disorders, and mental deficiency. Patients also have common contraindications for surgery, such as severe cardiovascular, pulmonary, or hematological disorders. Structural abnormalities are visible on MRI scans.

Requirements with regard to operation conditions

Surgeons should have substantial experience in DBS treatment of movement disorders to enhance efficacy and minimize complications. Compared with patients suffering from PD or ET, GTS patients require special anesthesiological measures because of the tics that hinder the stereotactic procedure. We advise not to bring the patient under general anesthesia because negative side effects reported during test stimulation might lead to alteration of the position of the electrode perioperatively (11). Sedating the patient to obtain tic suppression with maintenance of the possibility to communicate with the patients is preferable.

Finally, the Dutch Flemish Study Group is taking steps to establish a collaborative working group on DBS in GTS. The aim of this collaborative group, essentially being in line with the obsessive-compulsive disorder-DBS collaborative group, is to equalize protocol strategy and outcome measures, and to compare data in the future. The collaborative effort taken with respect to this type of treatment requires time, effort, mutual confidence, and respect, all of which are necessary to find high-quality scientific answers to the question of whether DBS is of additional aid in the treatment of treatment-refractory GTS patients.

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1. Chappell PB, McSwiggan-Hardin MT, Scahill L, Rubenstein M, Walker DE, Cohen DJ, Leckman JF: Videotape tic counts in the assessment of Tourette's syndrome: Stability, reliability, and validity. **J Am Acad Child Adolesc Psychiatry** 33:386–393, 1994.
2. *Diagnostic and Statistical Manual of Mental Disorders IV Task Force: Tic Disorders*. Washington DC, American Psychiatric Association, 1994, pp 100–105.
3. Leckman JF: Tourette's syndrome. **Lancet** 360:1577–1586, 2002.
4. Leckman JF, Riddle MA, Hardin MT: The Yale global tic severity scale: Initial testing of a clinician-rated scale of tic-severity. **J Am Acad Child Adolesc Psychiatry** 28:566–573, 1989.
5. Nuttin B, Gybels J, Cosyns P, Gabriels L, Meyerson B, Andréewitch S, Rasmussen S, Greenberg B, Friehs G, Rezai A, Montgomery E, Malone D, Fins J: Deep Brain Stimulation for Psychiatric Disorders. **Neurosurgery** 51:519, 2002.
6. Peterson AL, Azrin NA: Behavioral and pharmacological treatment for Tourette's syndrome: A review. **Appl Prev Psychol** 2:231–242, 1993.
7. Robertson, MM: The Tourette syndrome diagnostic confidence index: Development and clinical associations. **Neurology** 53:2108–2112, 1999.
8. Temel Y, Visser-Vandewalle V: Surgery in Tourette syndrome. **Mov Disord** 19:3–14, 2004.

9. Verdellen CW, Keijsers GP, Cath DC, Hoogduin CA: Exposure with response prevention versus habit reversal in Tourettes's syndrome: A controlled study. **Behav Res Ther** 42:501–511, 2004.
10. Vandewalle V, van der Linden C, Groenewegen HJ, Caemaert J: Stereotactic treatment of Gilles de la Tourette syndrome by high frequency stimulation of thalamus. **Lancet** 353:724, 1999.
11. Visser-Vandewalle V, Temel Y, Boon P, Vreeling F, Colle H, Hoogland G, Groenewegen HJ, van der Linden C: Chronic bilateral thalamic stimulation: A new therapeutic approach in intractable Tourette syndrome. **J Neurosurg** 99:1094–1100, 2003.

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Occult Hydrocephalus in Children with Cerebral Palsy

To the Editor:

We read with interest Albright et al.'s article entitled "Occult Hydrocephalus in Children with Cerebral Palsy" (2). Based on the observation that children with cerebral palsy (CP) have a higher rate of cerebrospinal fluid (CSF) leaks after baclofen pump implantation, the authors postulated that the increased incidence was due to elevated CSF pressure in this patient population. To test this hypothesis, 24 patients with CP and asymptomatic ventriculomegaly underwent lumbar puncture with opening pressure measurement before placement of a baclofen pump. Opening pressures in these patients ranged from 22 to 41 cm H_2O (mean H_2O, 27.3 cm). There was no correlation between ventricular size and opening pressure.

Opening pressures of 18 and 20 cm H_2O are often taken as the upper limits of normal in children and adults, respectively (6). These values are based on data published in the 1960s, and at least one more recent, dedicated study indicates that there is a significant amount of variability in opening pressures of pediatric patients. Ellis (4) reported on a series of 33 pediatric patients undergoing lumbar puncture in the flexed lateral decubitus position. Opening pressures in these patients ranged from 10 to 33 cm H_2O (mean, 19.0 $\pm$ 4.4), and the normal range, as determined statistically (Wilk-Shapiro test for normal distribution), was 10 to 28 cm H_2O.

Although the mean opening pressure reported by Albright et al. falls within the upper limits of this normal range, eight of the 24 patients in the Albright et al. series exceeded Ellis's normal range. In their discussion, Albright et al. noted that a potential shortcoming of their study was the use of isoflurane or sevoflurane for sedation in 22 of 24 patients. As the authors accurately point out, these agents have been to shown increase intracranial pressure by 2 $\pm$ 2.2 and 5 $\pm$ 4.6 mmHg, respectively (7). With this in mind, only 2 to 4 patients in their series had opening pressure in excess of Ellis's normal range.

Another issue is related to the interpretation of ventriculomegaly in the series by Albright et al. Sixty-eight to 100% of children with cerebral palsy demonstrate abnormalities on brain magnetic resonance imaging (MRI) or computed tomographic scans (1, 3). Periventricular leukomalacia (PVL) is the most common MRI abnormality, present in 67.8% of MRI scans in pre-term infants later diagnosed with CP (3). Furthermore, PVL may be even more prevalent among patients with spastic CP and may be related to the development of this CP subtype (8). Radiographically, PVL is characterized by reduction of the periventricular white matter, thinning of the posterior body of the corpus callosum, and ventriculomegaly with irregular walls of the lateral ventricles (5). In our view, the computed tomographic scan shown in the article is entirely consistent with PVL, and an MRI scan on the same patient would likely show signs of PVL.

We have performed more than 1300 selective dorsal rhizotomies (SDR) on children and young adults with spastic cerebral palsy since 1987. Before 1998, all patients under consideration for SDR underwent brain MRI scans as part of their preoperative evaluation. The overwhelming majority of the patients exhibited PVL and ventriculomegaly. To our knowledge, none of them developed symptoms of hydrocephalus. In addition, only one of our more than 1300 SDR patients developed an overt CSF leak requiring revision of the dural closure. This patient was an adult on whom we had to remove a baclofen pump at the time of SDR. As Albright et al caution, the report presents preliminary data, and further studies will be needed to determine the true incidence of intracranial hypertension in this population. Given our experience, however, we feel that the report should not be taken as a basis for CSF diversionary shunts in children with CP and asymptomatic ventriculomegaly or in those who develop CSF leaks following implantation of a baclofen pump.

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1. Accardo J, Kammann H, Hoon AH Jr: Neuroimaging in cerebral palsy. **J Pediatr** 145:S19–S27, 2004.
2. Albright AL, Ferson S, Carlos S: Occult hydrocephalus in children with cerebral palsy. **Neurosurgery** 56:93–97, 2005.
3. Ashwal S, Russman BS, Blasco PA, Miller G, Sandler A, Shevell M, Stevenson R: Practice parameter: Diagnostic assessment of the child with cerebral palsy. Report of the quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. **Neurology** 62:851–863, 2004.
4. Ellis R 3rd: Lumbar cerebrospinal fluid opening pressure measured in a flexed lateral decubitus position in children. **Pediatrics** 93:622–623, 1994.
5. Flodmark O, Roland EH, Hill A, Whitfield MF: Periventricular leukomalacia: Radiologic diagnosis. **Radiology** 162:119–124, 1987.
6. Meberg A, Broch H: Etiology of cerebral palsy. **J Perinat Med** 32:434–439, 2004.
7. Sponheim S, Skraastad O, Helseth E, Due-Tonnesen B, Aamodt G, Breivik H: Effects of 0.5 and 1.0 MAC isoflurane, sevoflurane and desflurane on intracranial and cerebral perfusion pressures in children. **Acta Anaesthesiol Scand** 47:932–938, 2003.
8. Volpe JJ: Neurobiology of periventricular leukomalacia in the premature infant. **Pediatr Res** 50:553–562, 2001.

In Reply:

Limbrick and Park refer to the 1994 study of Ellis (1), who reported opening pressures of 10 to 33cm H_2O, with a mean of

19.0 cm and a "normal" range of 10 to 28 cm. Ellis' study has three minor flaws and one major flaw. First, children were sedated with midazolam, which may increase intracranial pressure, especially when baseline intracranial pressure is less than 18 torr (3). Secondly, the children were tested in the flexed lateral position, which may increase cerebrospinal fluid (CSF) pressure by causing abdominal venous compression. Third, many of the children were undergoing a lumbar puncture to inject prophylactic chemotherapy and, thus, may not have had normal pressures. But, most importantly, Ellis did not measure opening pressure. Instead, he estimated it based on the number of drops that came through a 22 gauge needle in either 21 seconds (1.5 inch needle) or 39 seconds (3.5 inch needle). The title of his original description of the technique is "A simple method of estimating CSF pressure during lumbar puncture" (2). Based on these methodological concerns, Ellis' data should not be accepted as normal values.

Limbrick and Park correctly note that periventricular leukomalacia is often associated with ventriculomegaly. They do not know, however, how often ventriculomegaly is associated with pressures that are higher than normal. We suspect that some of their patients who were undergoing selective dorsal rhizotomies for spastic diplegia would have had ventriculoperitoneal shunts before the rhizotomy. Their comment that 1 out of 1300 children undergoing selective dorsal rhizotomies developed a postoperative CSF leak is remarkable, but probably irrelevant to the cases we discussed for two reasons. First, children needing intrathecal baclofen represent a completely different patient population than the young children with spastic diplegia who undergo selective dorsal rhizotomies; intrathecal baclofen children have hypertonicity in all their extremities, not just their legs, and often have either dystonic cerebral palsy or mixed dystonic/spastic cerebral palsy. Secondly, children undergoing rhizotomies do not have a catheter inserted into the thecal sac, a catheter around which CSF may leak, especially if intracranial pressure is high, until dura seals around the catheter.

The rate of CSF leak is higher in children with cerebral palsy undergoing pumps than in adults. We hypothesized that increased CSF pressure might be a factor in the increased frequency of leaks. Our finding of increased lumbar opening pressures is consistent with the hypothesis. Although the data are preliminary, if a child's opening pressure is substantially above normal, we think a shunt should be considered prophylactically before a pump and intrathecal catheter are inserted. The admonition to avoid shunts in children with high pressures or in those who develop CSF leaks is an opinion based on a limited experience with the prevention and treatment of CSF leaks in intrathecal baclofen patients.

Perhaps the most important point of our article, however, is that the data from our study raise the possibility that many children with cerebral palsy and asymptomatic ventriculomegaly have occult hydrocephalus, with increased pressure that could cause damage if left untreated for 10 to 20 years. That possibility is being evaluated with 24-hour intracranial pressure monitoring and a prospective clinical trial is anticipated.

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1. Ellis R 3rd: Lumbar cerebrospinal fluid opening pressure measured in a flexed lateral decubitus position in children. **Pediatrics** 93:622–623, 1994.
2. Ellis R 3rd, Strauss LC, Wiley JM, Killmond TM, Ellis RW Jr: A simple method of estimating cerebrospinal fluid pressure during lumbar puncture. **Pediatrics** 89:895–897, 1992.
3. Papazian L, Albanese J, Thirion X, Perrin G, Durbec O, Martin C: Effect of bolus doses of midazolam on intracranial pressure and cerebral perfusion pressure in patients with severe head injury. **Brit J Anaesth** 71:267–271, 1993.

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Perfusion-weighted Magnetic Resonance Imaging in Patients with Vasospasm: A Useful New Tool in the Management of Patients with Subarachnoid Hemorrhage

To the Editor:

We congratulate Hertel et al. (2) for their work and make some comments. We use magnetic resonance imaging (MRI), including perfusion-weighted and diffusion-weighted imaging (PWI/DWI), in patients with subarachnoid hemorrhage and agree that MRI, including PWI/DWI, is a very powerful and promising tool in the management of patients with subarachnoid hemorrhage.

As shown recently by our clinical research group, combining PWI with DWI yields even more information about cerebral tissue in vasospasm and allows the diagnosis of tissue at risk, i.e., "symptomatic vasospasm" (1). Our data support the conclusion drawn by the Hertel et al. that PWI can indeed detect tissue at risk before definitive infarction occurs. This is also true for intubated and ventilated patients who cannot be followed neurologically, but who are often poor grade patients with an especially high risk for development of vasospasm and cerebral infarcts. Therefore, we currently include such high risk patients in our protocol because MRI is able to detect "symptomatic vasospasm" in patients not amenable for neurological surveillance.

The authors claim that MRI in subarachnoid hemorrhage may detect tissue at risk similar to that found in the stroke literature and may influence the decision as to whether the patient should receive angiography for endovascular treatment of vasospasm. MRI bears the potential for an early change of therapy and the prevention of a permanent neurological deficit, and it may be used for monitoring and evaluation of therapy to help to reach a decision as to whether the patient should be treated with endovascular therapy.

Based on our initial experience, all these claims may prove true and we currently have a protocol that encompasses all

those proposals. This leads to a change of therapy. Based on PWI/DWI, we are able to use balloon-angioplasty more often and in a more focused manner, i.e., only when there is possibly salvageable tissue at risk.

We would also like to refer to J. Max Findlay's comment that it would be interesting to see whether a perfusion-weighted deficit could be promptly corrected with arterial dilation. We documented our first case with reversal of such a deficit and continue to monitor the effects of transluminal balloon angioplasty by MRI (1).

Very intriguing in this respect is the observation of Hertel et al. that PWI changes did not normalize in all their patients within 4-week window of time, a finding that emphasizes the normalization of PWI changes by transluminal balloon angioplasty. This method can detect changes over time, and PWI/DWI can be used for monitoring therapy.

To further improve the described technique, one should try to not only to qualitatively describe PWI changes, but to also try to quantify them to get results according to the stroke literature (3) and to define thresholds for hemodynamic infarction of tissue at risk in severe cerebral vasospasm after subarachnoid hemorrhage.

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1. Beck J, Raabe A, Lanfermann H, Seifert V, and Weidauer S: Tissue at risk concept for endovascular treatment of severe vasospasm after aneurysmal subarachnoid haemorrhage. **J Neurol Neurosurg Psychiatry** 75:1779–1781, 2004.
2. Hertel F, Walter C, Bettag M, and Morsdorf M: Perfusion-weighted magnetic resonance imaging in patients with vasospasm: A useful new tool in the management of patients with subarachnoid hemorrhage. **Neurosurgery** 56:28–35, 2005.
3. Neumann-Haefelin T, Wittsack HJ, Wenserski F, Siebler M, Seitz RJ, Modder U, Freund HJ: Diffusion- and perfusion-weighted MRI. The DWI/PWI mismatch region in acute stroke. **Stroke** 30:1591–1597, 1999.

In Reply:

We thank Beck et al. for their comment and their confirmation of our thesis (1) that perfusion-weighted magnetic resonance imaging (pwMRI) can detect tissue at risk in patients with subarachnoid hemorrhage and, therefore, may gain influence on the management of those patients. We also agree that a special protocol containing pwMRI, as well as diffusion-weighted MRI, may be extremely helpful for the individual risk determination and therapy control. Both groups could show that MRI techniques are much more sensitive in the detection of tissue at risk than transcranial Doppler.

However, MRI may be time consuming and online registration is not possible. On the other hand, pwMRI can show the locations of the highest risks for infarction and, therefore, may lead to the most helpful implantation sites for invasive monitoring tools, such as probes for the measurement of cerebral tissue oxygenation or cerebral blood flow. According to R. Loch Macdonald's comment (1), we also fully agree that a comparison of MRI with perfusion sensitive computed tomography is required. There may also exist some disadvantages for MRI owing to the intensive care unit management of the patients, as Gabriele Schackert's (1) comment mentioned. Therefore, in our opinion, a prospective (multicenter, if possible) trial is necessary for the exact determination of the values of those techniques within the next future.

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1. Hertel F, Walter C, Bettag M, and Morsdorf M: Perfusion-weighted magnetic resonance imaging in patients with vasospasm: A useful new tool in the management of patients with subarachnoid hemorrhage. **Neurosurgery** 56:28–35, 2005.

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Herophilus of Chalcedon: A Pioneer in Neuroscience

To the Editor:

I read "Herophilus of Chalcedon: A Pioneer in Neuroscience" by Acar et. al. (1) with interest. I would like to clarify a commonly misunderstood term (Torcular Herophili) mentioned in the article, which has infiltrated all fields associated with neuroanatomy. The term torcular is an incorrect version of the original Greek word $\sigma\omega\lambda\eta\nu$ (a canal or gutter) used by Herophilus. The original term was meant to describe the concavity on the internal aspect of the occipital bone that houses the confluence of sinuses. However, over time, this term has been used incorrectly as an interchangeable name for the confluence of sinuses. It is true that these two entities are intimately related, but they clearly represent different anatomical structures, i.e., one bone and one vascular. Just as other venous sinuses erode the inner table of the cranium, such as the transverse sinus sulcus, the confluence of sinuses erodes the occipital bone, thus producing the "torcular" (2, 3). The original Greek term has been mistranslated as "wine press," thus propagating the idea that this area is where the major venous sinuses (wine) meet (press) in the midline.

R. Shane Tubbs
Birmingham, Alabama

1. Acar F, Naderi S, Guvencer M, Ture U, Arda MN: Herophilus of Chalcedon: A Pioneer in Neuroscience. **Neurosurgery** 56:861–867, 2005.
2. Grant JC: *A Method of Anatomy Descriptive and Deductive*. Baltimore, Williams and Wilkins, 1940, ed 2, pp 581.
3. Holden L: *Holden's Anatomy. A manual of dissection of the human body*, in Langton J (ed): Philadelphia, P. Blakiston, Son & Co., 1885, ed 5, pp 32.

In Reply:

We read with interest the letter to the editor written by Dr. Tubbs. A similar letter was published by Tubbs et al. on the same subject in 2002 (3). On the basis of the ancient Greek language, the author states that "Torcular Herophili" described the bony concavity on the occipital bone where confluence of sinuses is located.

Torculum and Torcular are two Latin words derived from ancient Greek. These two words were widely used in Latin agriculture (2). Torculum is a press for making wine and olive (2). Within the cranium, the veins (actually venous sinuses), come together at the back of the cranium in a structure called the confluence of the sinuses. This cavity has four large veins radiating from it, resembling, supposedly, the spigots that pour dark purple juice out of the four sides of the ancient wine press used to squeeze grapes with a handled screw on the top (4).

"Torcular Herophili" is accepted by the medical literature in describing the confluence of sinuses. This agreement has two aspects: 1) the word "torcular," or "wine press," fits the physical outlook of confluence and 2) the term was first published by an ancient master of medicine, Claudius Galen in original Latin, not in Greek: "at the crown of the head the folds of the membrane (sinus transversus) that conduct the blood come together into a common space like cistern, and for this very reason it was Herophilus' custom to call it 'wine vat' (torcular Herophili). From this point, as from some acropolis, they (sinuses) send forth canals to all the parts lying below them. . ." (1). There are no ancient publications reporting "Torcula" as the occipital bone concavity.

Based on this perspective, we still think "Torcular Herophili" accurately describes the confluence of sinuses. To propose misunderstanding of the term would be a speculation.

Feridun Acar
Denizli, Turkey

1. Furley DJ, Wilkie JS: *De usu pulsuum*. Princeton, Princeton University Press, 1984.
2. Smith W: *A Dictionary of Greek and Roman Antiqities*. John Murray, London, 1875, pp 1137–1138.
3. Tubbs RS, Oakes WJ: Letter to the editor. **Neuroanatomy** 1:14, 2002.
4. www.uomhs.edu/anatomy/anatomicalword1999.htm. Accessed May 5, 2005.

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Serum Biomarkers for Experimental Acute Spinal Cord Injury: Rapid Elevation of Neuron-specific Enolase and S-100β

To the Editor:

We read with great interest the article by Loy et al. (1), describing significant increases in serum levels of neuron-specific enolase (NSE) and S-100β 6 hours after a graded contusive spinal cord injury (SCI) in rats. These values decreased by 24 hours after the injury, but still remained elevated above sham levels. From these findings, the authors conclude that NSE and S-100β serum levels may be useful experimental tools for assessing damage to the spinal cord after acute SCI.

They further state that, in a clinical setting, no test exists to predict functional outcome of patients with acute SCI reliably, and that all diagnostic tools available in this regard have proved ineffective. However, despite these considerations, the authors unfortunately failed to add to the solution of this problem. Owing to the design of the study, they did not correlate the levels of NSE and S-100β with the outcome of their animals and, thus, omitted to obtain possibly unveiling results referring thereto, at least in an experimental set-up. Insofar as the observation of increased serum levels after acute SCI is of great importance, it is of limited significance because their potential role as prognostic markers for the prediction of functional outcome has not been investigated.

Serum levels of S-100β have already been evaluated with regard to subacute damage to the spinal cord. In this context, our results obtained in patients with paresis owing to subacute spinal cord compression of infectious (2) and metastatic (3) origin seem to be worth mentioning. In both groups of patients, we found a significant correlation between the individual time course of S-100β serum levels and outcome in terms of motor function. All patients with a favorable outcome (i.e., retrieval or maintenance of walking capacity) had serum levels of S-100β that were either normal all the time or that were raised preoperatively, but normalized within 3 days. Thereby, normalization of initially increased S-100β values invariably preceded recovery of neurological function. On the other hand, all patients with unfavorable outcome (i.e., permanent loss of the ability to walk) had increased levels throughout that showed either a further increase or only a slow decrease within approximately 2 weeks. These results were statistically significant suggesting that, analogous to cerebral disorders, S-100β might be a promising serum marker with prognostic significance in the event of subacute spinal cord compression.

Identical results were found in four patients who sustained isolated acute traumatic lesions of the spinal cord (Marquardt et al., unpublished data).

To rule out intracranial injuries, all patients were additionally examined by cranial magnetic resonance imaging. This is of utmost importance to assess only changes of S-100β serum concentrations that are exclusively caused by the medullary lesion, but that are not induced by concomitant cerebral lesions. Thus the number of examined patients was rather small because natural injuries that are purely confined to the spinal cord are seldom. And this, as the authors have pointed out, might hamper the clinical applicability of serum markers to acute SCI.

Nevertheless, the work of these authors should be acknowledged. Because the focus of investigation had been on cerebral lesions so far, their work will undoubtedly stimulate further

studies to evaluate the predictive potential of serum markers in lesions of the spinal cord.

Gerhard Marquardt
Matthias Setzer
Volker Seifert
Frankfurt, Germany

1. Loy DN, Sroufe AE, Pelt JL, Burke DA, Cao QL, Talbott JF, Whittemore SR: Serum biomarkers for experimental acute spinal cord injury: Rapid elevation of neuron-specific enolase and S-100β. **Neurosurgery** 56:391–397, 2005.
2. Marquardt G, Setzer M, Seifert V: Protein S-100β for individual prediction of functional outcome in spinal epidural empyema. **Spine** 29:59–62, 2004.
3. Marquardt G, Setzer M, Seifert V: S-100β as serum marker for prediction of functional outcome in malignant spinal cord compression. **Acta Neurochir** 146:449–452, 2004.

In Reply:

We appreciate the constructive comments from Drs. Marquardt, Setzer, and Seifert. We agree that functional data from basic science studies of spinal cord injury (SCI) are essential for meaningful comparisons with clinical studies. The design of our experiments necessitated the killing of animals at 6 and 24 hours after injury when functional assessments are of little value in experimental models or in human patients. Therefore, standardized rat models of experimental SCI with well characterized locomotor and electrophysiological outcomes were used. Graded contusive injuries are routinely produced with highly reproducible hind limb locomotor scores measured on the 21-point Basso-Beattie-Bresnahan (BBB) scale (1). These data have been described previously in detail (2). Briefly, a 150 kdyn injury is moderate in severity, resulting in coordination deficits without loss of weight support, at 1 week post-injury (BBB score, 10.1 $\pm$ 1.8). These animals recover with only mild residual coordination deficits (BBB score, 15 $\pm$ 1.9) at 4 weeks. Alternatively, 200 kdyn injuries are severe and result in complete loss of weight support (BBB score, 7.4 $\pm$ 1.8) at 1 week post-injury followed by recovery of severely impaired weight supported locomotion (BBB score, 11.4 $\pm$ 1.1) at 4 weeks.

Our data demonstrate significant elevations in serum levels of an astroglial biomarker, S-100β, 6 hours after severe 200 kdyn injuries (3). S-100β levels were not significantly elevated in animals with favorable expected functional outcomes. These findings are similar to those of corresponding authors who demonstrated a significant correlation between serum S-100β levels and return of ambulation after surgical decompression in patients with spinal cord compression resulting from epidural abscess or metastatic disease (4, 5). Increased postoperative levels in serum concentrations of S-100β were associated with unfavorable outcomes. Our data further demonstrate significant elevations of the biomarker neuron-specific enolase (NSE) at both 6 and 24 hours post-injury. No significant differences in serum levels of NSE were observed between 150 and 200 kdyn injuries.

These studies indicate that S-100β and NSE may be helpful experimental tools for assessing damage in acute SCI. The corresponding authors have taken the first steps to apply these methods in SCI patients and we look forward to future reports. The objective of ongoing SCI biomarker research is to identify additional proteins that can better stratify patients based on expected functional outcomes in the acute phase where currently available clinical tests are unreliable.

David N. Loy
Scott R. Whittemore
Louisville, Kentucky

1. Basso DM, Beattie MS, Bresnahan JC: A sensitive and reliable locomotor rating scale for open field testing in rats. **J Neurotrauma** 12:1–21, 1995.
2. Cao Q, Zhang YP, Iannotti C, DeVries WH, Xu XM, Shields CB, Whittemore SR: Functional and electrophysiological changes after graded traumatic spinal cord injury in adult rat. **Exp Neurol** 191 [Suppl 1]:S3–S16, 2005.
3. Loy DN, Sroufe AE, Pelt JL, Burke DA, Cao QL, Talbott JF, Whittemore SR: Serum biomarkers for experimental acute spinal cord injury: Rapid elevation of neuron-specific enolase and S-100β. **Neurosurgery** 56:391–397, 2005.
4. Marquardt G, Setzer M, Seifert V: S-100β as serum marker for prediction of functional outcome in malignant spinal cord compression. **Acta Neurochir (Wein)** 146:449–452, 2004.
5. Marquardt G, Setzer M, Seifert V: Protein S-100β for individual prediction of functional outcome in spinal epidural empyema. **Spine** 29:59–62, 2004.

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Nonoperative Management of Vertical C2 Body Fractures

To the Editor:

The authors (3) describe fractures of the vertebral body C2. Their incidence, morphological appearance according to the author's classification, which differentiates vertical, coronally, and sagittally oriented, as well as transverse, axially oriented fractures, and the successful conservative treatment is described. Fusion at the fracture site in 18 patients was documented after an average of 7 and 5 months.

Unfortunately, the authors do not comment on whether dynamic x-rays or magnetic resonance imaging were performed to rule out any discoligamentous injury at the C2-C3 level. The authors cite Rainov et al. (7), who treated an atypical traumatic spondylolisthesis at C2-C3 with anterior fusion and C2 bilateral dorsal isthmic screw fixation. The report of these authors, and those of many others (8), emphasizes the need for further investigation of the intersegmental space at C2-C3 in 'alleged' stable fractures of the vertebral body C2. Concerning this, we want to remember that many of the so-called 'benign' fractures of the vertebral body C2 present masked, discoligamentous unstable, atypical traumatic spondylolisthesis, which cannot be safely treated in a conservative manner to achieve primary stability or a favorable outcome. Furthermore, those cases in which the posterior intact wall of the fractured axis remains completely or partially fixed to that of C3, anterior lithosis of the anterior C2-fragment on the ruptured disc can cause impingement of C1-C2 of the spinal cord owing to the incomplete fracture of the C2 ring.

The authors state that C2 body fractures seem to have a favorable prognosis. In their well written report there is no comment

on which of their C2 fractures affected main parts of the superior articular facets C2. As we know, the latter one can lead to a higher incidence of symptomatic, atlantoaxial incongruency, which was also observed in the cited papers of Fujimura et al. (2) and Korres et al. (6). Actually, Jeanneret and Magerl (4) were the first to notice that there might be a minor outcome in those traumatic spondylolisthesis C2-C3 affecting the articular facets. We could confirm these observations (5). Finally, there are a reasonable number of fractures of the vertebral body C2, as demonstrated by de Mourgues et al. (1), which are not benign in nature and tend to re-dislocate with conservative treatment owing to instability between the fragments or to discoligamentous instability at the C2-C3 level, as mentioned above.

We want to emphasize that vertical, sagittal, axial, or oblique fractures of the axis are part of a potential discoligamentous injury at C2-C3. The probability of any instability has to be worked up with dynamic x-rays or magnetic resonance imaging. To call these fractures benign injuries with favorable outcomes, one has to offer functional long-term outcomes, which are still lacking in the current literature (8).

Heiko Koller
Stuttgart, Germany
Anton Kathrein
Innsbruck, Germany

1. de Mourgues G, Fischer LP, Bejui J, Carret JP, Gonon GP, Subasi H, Amoa J, Herzberg G, Massardier J: Fracture of the odontoid process [in French]. **Rev Chir Orthop Reparatrice Appar Mot** 67:783–790, 1981.
2. Fujimura Y, Nishi Y, Kobayashi K: Classification and treatment of axis body fractures. **J Orthop Trauma** 10:536–540, 1996.
3. German JW, Hart BL, Benzel EC: Nonoperative management of vertical C2 body fractures. **Neurosurgery** 56:516–521, 2005.
4. Jeanneret B, Magerl M: Klinische analyse der spätresultate nach hangmanfrakturen. **Z Orthop** 123:721, 1985.
5. Koller H, Kathrein A, Daniaux H, Blauth M: Recommendations for the treatment of unstable traumatic spondylolisthesis C2-3. Presented at Spine Week, Porto, Portugal, May 39–June 5, 2004.
6. Korres DS, Papagelopoulos PJ, Mavrogenis AF, Sapkas GS, Patsinevelos A, Kyriazopoulos P, Evangelopoulos D: Multiple fractures of the axis. **Orthopedics** 27:1096–1099, 2004.
7. Rainov NG, Heidecke V, Burkert W: Coronally oriented fractures of the axis body: Surgical treatment of a rare condition. **Minim Invasive Neurosurg** 41:93–96, 1998.
8. www.dynaprog.de/hangman. Accessed March 2005.

In Reply:

We thank Drs. Koller and Kathrein for their comments regarding our study on C2 body fractures (1). As mentioned in the discussion, our study is a small, retrospective review of the management of vertical C2 body fractures. Accordingly, it should be interpreted in the context of a small, retrospective review with the disadvantages that such a study affords.

We agree that there is certainly concern for C2-C3 disc and/or ligamentous injury in these patients. At our institution, all patients routinely underwent magnetic resonance imaging evaluation. If ligamentous injury was suspected, the patient was placed in a hard collar for 6 weeks. At that time, flexion-extension x-rays were obtained to assess ligamentous instability. All of the surviving patients received delayed flexion-extension x-rays of the cervical spine and no patient was noted to have a ligamentous injury. Again, the follow-up time is short and the readership should acknowledge this shortcoming.

We do not mean to imply that all patients with a vertical C2 body fracture should be managed non-operatively. As always in medicine, each patient should be assessed and treated on an individual basis.

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Blaine L. Hart
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Edward C. Benzel
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1. German JW, Hart BL, Benzel EC: Nonoperative management of vertical C2 body fractures. **Neurosurgery** 56:516–552, 2005.

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Toward an Expanded View of Radiosurgery

To the Editor:

A dozen years ago the American Association of Neurological Surgeons and the American Society for Therapeutic Radiology and Oncology independently commissioned task forces to develop quality standards for the rapidly evolving field of radiosurgery. The two task forces eventually produced a joint consensus statement, published simultaneously by editorial agreement in specialty journals representing radiation oncology and neurosurgery (3, 4). Since then, brain radiosurgery (implying single fraction) has become a common radiation procedure in North America, performed safely and effectively in both hospital and freestanding settings with a multidisciplinary team using any of several commercially available radiation delivery devices. The single fraction part is most important, and most radiosurgeons wholeheartedly agree with Pollock and Lunsford (5) that "radiosurgery" involves one fraction, rather than up to five fractions, as advocated by Adler et al. (1). Like Pollock and Lunsford, I eschew "radiosurgery" preceded by "fractionated" or "fractionated stereotactic." Even "body radiosurgery" or "stereotactic body radiosurgery" are more properly called "stereotactic body radiation therapy".

The list of possible "radiosurgery" nuances seems endless. To what end? Surely, the issues of definition raised by Pollock and Lunsford (5) and by Adler et al. (1) have little to do with whether the patient is treated in a hospital or in a freestanding facility. Likewise, it is hard to think that they should depend on a specific type of radiosurgery apparatus, because even the most experienced radiosurgeons are likely unable to determine which company's apparatus produced any particular set of (scrubbed) isodose curves. More importantly, but not surprisingly, outcome seems to depend far more on process of care than the exact

technology used (2, 6). Nevertheless, apparatus does need to be addressed, if only parenthetically, because the rapid strides made by radiation equipment manufacturers in the past decade are not widely appreciated beyond radiation oncology circles. Notions that radiotherapy apparatus is inherently inaccurate, imprecise, or nonstereotactic, or that such apparatus produces only homogeneous dose distributions, or that radiation oncologists always prefer homogeneous dose distributions, or that treatments are ineffective or toxic, are dated, categorical, and frankly incorrect.

Finally, the notion that some intermediate number of fractions, such as two through five, might be more safe or more effective than one or 30 remains an open clinical question. This question is certainly worthy of formal investigation, although it is difficult to see why such an investigation would require a redefinition of terminology, absent of a dramatic (and entirely unanticipated) demonstration of improvement in the therapeutic ratio. In any case, any notion that radiation treatments not somehow defined as "radiosurgery" are needlessly ineffective or toxic flies in the face of both a wealth of peer-reviewed clinical data and radiobiology principles. Radiosurgery damages cells by the same mechanisms that govern radiation damage after other radiation techniques. The underlying radiobiology principles are neither flawed because relative α and β ratios are imprecisely known; nor are they altered because the number of fractions might be one or 30.

Radiosurgery (implying brain, single fraction) represents a most important clinical advance, and all practicing radiosurgeons salute its creators, as well as the hundreds, if not thousands, of radiation oncologists, neurosurgeons, and physicists who have documented its clinical utility. Perhaps some future technology or technique, whether radiation or surgical or otherwise, will demonstrate major improvements in the therapeutic ratio. When that happens, we will salute its developers and join them in developing new descriptive nomenclature. In the meantime, I favor avoiding the widespread confusion, marketing, and coat tailing that goes along with the indiscriminate use of "radiosurgery."

David A. Larson
San Francisco, California

1. Adler JR Jr, Colombo F, Heilbrun MP, Winston K: Toward an expanded view of radiosurgery. **Neurosurgery** 55:1374–1376, 2004.
2. Andrews DW, Scott CB, Sperduto PW, Flanders AE, Gaspar LE, Schell MC, Werner-Wasik M, Demas W, Ryu J, Bahary J-P, Souhami L, Rotman M, Mehta MP, Curran WJ Jr: Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: Phase III results of the RTOG 9508 randomized trial. **Lancet** 363:1665–1672, 2004.
3. Larson DA, Bova F, Eisert D, Kline R, Loeffler J, Lutz W, Mehta M, Palta J, Schewe K, Schultz C, Shaw E, Wilson JF, Lunsford LD, Alexander E, Chapman P, Coffey R, Friedman W, Harsh G 4th, Maciunas R, Olivíer A, Steinberg G, Walsh J: Consensus statement on stereotactic radiosurgery quality improvement. **Int J Radiat Oncol Biol Phys** 28:527–530, 1993.
4. Lunsford LD, Alexander E, Chapman P, Coffey R, Friedman W, Harsh G 4th, Maciunas R, Olivíer A, Steinberg G, Walsh J, Larson DA Bova F, Eisert D, Kline R, Loeffler J, Lutz W, Mehta M, Palta J, Schewe K, Schultz C, Shaw E, Wilson JF: Consensus statement on stereotactic radiosurgery: Quality improvement. **Neurosurgery** 34:193–195, 1994.
5. Pollock BE, Lunsford LD: A call to define stereotactic radiosurgery. **Neurosurgery** 55:1371–1373, 2004.
6. Souhami L, Seiferheld W, Brachman D, Podgorsak EB, Werner-Wasik M, Lustig R, Schultz CJ, Sause W, Okunieff P, Buckner J, Zamorano L, Mehta MP, Curran WJ Jr: Randomized comparison of stereotactic radiosurgery followed by conventional radiotherapy with carmustine to conventional radiotherapy with carmustine for patients with glioblastoma multiforme: Report of Radiation Therapy Oncology Group 93-05 protocol. **Int J Radiat Oncol Biol Phys** 60:853–860, 2004.

In Reply:

We thank our good friend Dr. Larson for his response to our opinion piece entitled "Toward an expanded view of radiosurgery" (1). Needless to say, we respectfully disagree with his perspective. Although the clinical utility of the original concept for single session radiosurgery is appreciated by all of us, we differ in our choice of vocabulary for describing an emerging class of procedure that uses very precise irradiation and incorporates the principle of limited fractionation. Even if guilty of "coat tailing," we think the terminology we are advocating is generally less confusing and more unambiguously descriptive of the procedure in question than that being advocated by Dr. Larson.

For neurosurgeons too, the "process" to which Dr. Larson alludes is an important characteristic of radiosurgery. In particular, we see the intimate involvement of neurosurgeons throughout the course of radiosurgery as an important reason for its past and future success. The continued use of the word radiosurgery, even with limited fractionation, emphasizes a key role for the neurosurgeon's mindset. In addition the primary objective of a procedure that combines fractionation with radiosurgical principles strengthens the argument for our proposed terminology. The intent, just like single session treatment, is the ablation of a defined volume of tissue, which was also very much at the heart of Leksell's original invention of the word radiosurgery. Fractionation is simply a means to that end. However, because some radiosurgical practitioners, like Dr. Larson, seem troubled by "fractionated radiosurgery," we have recently chosen to compromise by using the description "staged or multi-session" radiosurgery in our publications, a term which also does a better job of emphasizing this procedure's long surgical lineage.

Although we do not completely agree on terminology, we absolutely agree with Dr. Larson that there is more work to be done before the definite value of multiple session treatment is established. Despite this reservation, it is important to note that several published studies already demonstrate some benefit from this approach and numerous other studies are nearing publication or in the later stages of completion.

If we interpret Dr. Larson's letter correctly, he seems to imply that modern radiation therapy equipment is every bit the equal of traditional stereotactic devices in terms of targeting accuracy, i.e., such instruments are not "inaccurate, imprecise or non-stereotactic" (although we remain a little uncertain as the exact meaning of the last term). It is true that such technology has, through the years, grown more precise, but we sincerely doubt that there are many knowledgeable

neurosurgeons who share Dr. Larson's conviction. Moreover, we are unaware that extremely accurate "stereotactic-like" targeting precision has been even credibly demonstrated in the radiation oncology or medical physics literature (as opposed to vendor's claims). Perhaps the measure of scientific evidence Dr. Larson so fervently seeks for demonstrating the efficacy of staged radiosurgery can, in the future, also be used to characterize the technical specifications of contemporary radiation therapy equipment and be disseminated here in the neurosurgical literature. Ultimately, throughout our professional careers, we have observed that radiation oncologists tend to obsess with biology, whereas surgeons obsess with tools and process. We acknowledge that such an obsession with spatial accuracy may be superfluous. Ultimately, it is only through further clinical investigation of the type being advocated by Dr. Larson that we can prove this assertion one way or another. Going forward, we truly hope that Dr. Larson will join the surgical community in investigating the virtue, if any, of these new therapeutic concepts.

John R. Adler
Peter M. Heilbrun
Stanford, California

1. Adler JR Jr, Colombo F, Heilbrun MP, Winston K: Toward an expanded view of radiosurgery. **Neurosurgery** 55:1374–1376, 2004.

In Reply:

I had the pleasure of serving as the neurosurgical leader of the original Task Force on Stereotactic Radiosurgery, and Dr. Larson was my counterpart on the American Society for Therapeutic Radiology and Oncology Task Force. Together, we published a consensus statement more than 10 years ago relative to radiosurgery, a field that, at the time, was variously thought to be fringe, unimportant, or potentially harmful to the microsurgery hegemony. Of course, much has changed in this interval, not the least of which is the million or so patients worldwide who have had radiosurgery performed using a variety of technologies. The term radiosurgery, as emphasized by Lars Leksell, the father of radiosurgery, in 1951 refers to a single procedure. The difference is the use of radiation methodologies to deliver the intracranial effect. As might be expected with the further development of imaging tools and precision radiation delivery technologies, and in a very competitive medical environment, various alternative strategies have developed. I do think that neurosurgeons who perform radiosurgery should avoid the 'F word'. Fractionation, whether one or 30, implies a radiation therapy technique rather than a surgical procedure. I, personally, think that radiosurgery, as a methodology, can be applied to intracranial, spinal, and body pathologies as warranted by the clinical condition, and hopefully guided by long-term future outcome studies. To do radiosurgery, the procedure should be done in a single stage, wheels in to wheels out, and involving all aspects of the procedure completed in a single day, including a stereotactic guidance technology, imaging, planning, and delivery of the effect. The great advantage of radiosurgery is its minimally invasive nature, the ability to gain the effect without even a skin incision.

Recently, the reformed American Association of Neurological Surgeons/Congress of Neurological Surgeons Task Force on Stereotactic Radiosurgery, of which I am a member, recommended that the term stereotactic radiosurgery be expanded to include those technologies which deliver the effect in one or up to five different procedures. Hopefully, this ecumenical viewpoint will help to resolve the angst reported by surgeons who use technologies that seem to warrant staging of the dose. I think that 'staging' is very instrument dependent. I agree with Dr. Larson that there is a tremendous absence of data to understand bio-equivalency of radiosurgery, staged radiosurgery, hypofractionated stereotactic radiation therapy, or conventional radiation therapy techniques even done with intensity-modulated radiation therapy planning. We are still growing and we are still learning.

I do not think that variations in technologies and delivery of dose should be guided by reimbursement enhancement. Sadly, I am aware of marketing efforts which seem to emphasize the potential for maximal professional reimbursement when the dose effect is delivered in multiple stages.

The technologies continue to grow, prosper and evolve. Our knowledge and understanding of terminology will hopefully do the same.

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The Art of Alleviating Pain in Greek Mythology

To the Editor:

We read with great interest the article by Türe et al. (4) in which the authors provide an excellent review of some of the most important Greek myths regarding the treatment of pain. In a most delightful way, Türe et al. provide a description of various methods to alleviate pain found in the rich classical work of the fascinating Greek mythology. They specifically refer to hypnosis, treatment of pain with music and drugs, and euthanasia. We would like to communicate with you a particular myth, in which anesthesia was used not to alleviate pre-existing pain, but prophylactically, to protect from pain, and enable the hero to withstand suffering and achieve his goal.

Jason, sent to exile by his uncle Pelias, returned to claim his right to the throne. To ascend to the throne, he was obliged to travel to Colhis, land of king Aeetes, and get the fleece of the golden ram. To enable him to withstand pain and overcome the dragon that guarded the ram, Medea, daughter of King Aeetes, who had fallen in love with Jason, prepared a magic emulsion for him, with the aid of Aphrodite. After applying the emulsion on his body's surface, Jason was protected from pain and, therefore, successfully took the golden ram from the dragon (1–3). Apollonios from Rhodes, in his *Argonautics*, described the origin of that miraculous emulsion: "The plant, from which it is produced, first grew in the canyon of Caucasus, from the blood that dripped off the beak of the eagle that ravished the liver of poor Prometheus.

Its double stem has on top a flower similar in color to the crocus of Cilicy. Its root resembles a piece of fresh sliced meat and contains a black liquid, similar to the one that seeps from the oaks in the mountains" (3).

The application of such an emulsion as a means of tolerating pain strongly reminds us of modern anesthetic creams used topically before surgery. This myth is an indication that the concept of anesthesia, not just in terms of alleviating pain, but also of preventing the genesis of the sensation of pain, existed in pre-classical Greece.

We congratulate the authors on their interesting and well-presented work. We totally agree with them that, in many of the Greek myths, one can find evidence of the historical significance of the treatment of pain. We hope that our current communication provided an additional dimension to the art of alleviating pain in Greek mythology.

Theofilos G. Machinis
Kostas N. Fountas
Macon, Georgia

1. Graves R: *The Greek Myths* [in Greek]. Greece, Plias-Rougas, 1988, pp 308–309.
2. Kacridis I: *Greek Mythology: Hercules-Panhellenic Campaigns* [in Greek]. Greece, Ecdotiki Athinon, 1986, pp 158.
3. Rispen J: *Hellenic Mythology* [in Greek]. Greece, Avlos Athens, pp 158–159.
4. Türe H, Türe U, Gogus FY, Valavanis A, Yaşargil MG: The art of alleviating pain in greek mythology. **Neurosurgery** 56:178–186, 2005.

In Reply:

"*our portion, all of misery, given by Zeus*
that we may live in song for men to come" (5)

We thank Drs. Machinis and Fountas for their comments to our article (7). The extensive body of Greek mythology covers many myths, and these are useful in orientating our instincts to finding new ways of thinking, interpreting, and searching clues of the contemporaneous philosophy. Machinis and Fountas have summarized, in a very beautiful way, the myth of Jason and Arganout and Medeia. These kinds of myths are the examples with which we can share these feelings. Medeia spread a cream onto the body of the Jason, with whom she was in love, to enable him to take the Golden Fleece from the dragon. The contents of the cream, as well as the true reasons for spreading the cream, are unknown because many of the available sources provide different knowledge deduced from rumors which spread from one language to others. There is also some information, according to which, the reason for the spreading of the cream by Medeia was to protect Jason and his sword from iron and fire (2, 3, 6), to protect Jason against the badness and to protect him while making him invincible (4), or to make him immortal for 1 day (1). In the sources cited by Machinis and Fountas, we are provided with a new perspective. But, because the examples we drew upon in our article are from different sources, there was not a place in our article to include the myth of Jason and Medeia. We are sure that the Greek mythology still has many things to tell us through researchers such as Drs. Machinis and Fountas. We thank them again for their contribution.

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1. Colette E, Laporte H: *Le Livre de la Mythologie Grecque et Romaine*. Paris, Editions Gallimard, 1987, p 194.
2. Cotterell A, Storm R: *The Ultimate Encyclopedia of Mythology*. China, Hermes House, 1999, p 24.
3. Grimal P: *The Dictionary of Classical Mythology*. Oxford, Blackwell Publishers, 1996, p 91.
4. Hamilton E: *Mythology*. New York, Mentor Books, 1955.
5. Homer: The Iliad. Translated by R. Fitzgerald. Oxford, Oxford University Press, 1974, Book VI, lines 357–358.
6. Parker J, Stanton J: *Mythology. Myths, Legends, & Fantasies*. New Jersey, Wellfleet Press, 2004, p 143.
7. Türe H, Türe U, Göğüş FY, Valavanis A, Yaşargil MG: The art of alleviating pain in Greek Mythology. **Neurosurgery** 56: 178–186, 2005.

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Cerebral Perfusion Pressure between 50 and 60 mmHg may be Beneficial in Head-injured Patients: A Computerized Secondary Insult Monitoring Study

To the Editor:

I read with interest the article by Elf et al. (5). I fear, however, that their contribution will add more confusion to the ongoing discussion regarding the optimal cerebral perfusion pressure (CPP) in patients with severe brain trauma.

The "Lund concept" referred to in their presentation, as well as in the subsequent comments, is a therapeutic protocol based on established physiological and biochemical principles aiming at a reduction of a critical increase in intracranial pressure (ICP) (1, 5, 7, 8, 12). The main part of the "Lund concept" is based on the biological properties of the blood-brain barrier (BBB). In addition to its other physiological functions, the BBB is the most important regulator of cerebral volume (6). Under normal conditions, the BBB is virtually impermeable for crystalloids (total osmotic pressure, approx. 5.700 mmHg) and the net transport of water across the capillaries is accordingly hardly influenced by variations in intracapillary hydrostatic and/or colloidal osmotic pressure (both of them amounting to about 20 mmHg). Under pathophysiological conditions, the BBB may have an increased permeability for crystalloids (sometimes also for large molecules) and the transport of water across the cerebral capillaries may then, like in all other tissues, be described as a Starling equilibrium: the net flux of water is determined by the differences in hydrostatic and colloidal osmotic pressure across the capillary wall (1, 6-8, 12). Accordingly, it is often important to keep intracapillary hydrostatic pressure at a low level in patients with severe brain lesions and high ICP. This goal is mainly achieved by a controlled reduction of CPP (3, 8, 12). For obvious reasons,

a too pronounced decrease in CPP may jeopardize cerebral energy metabolism. This risk is avoided by performing intracerebral microdialysis with bedside biochemical analysis (13).

By applying these physiological principles, it has been possible to decrease mortality to a very low level in several centers without increasing the number of patients surviving in a persistent vegetative state (3, 10, 11). However, by reducing mortality, an increasing number of patients may survive with cognitive defects and the demands for qualified rehabilitation services have increased (4).

The study by Elf et al. (5) describes a completely different and unexpected experience: they claim that a CPP of 60 mmHg constituted an important upper limit for favorable prognosis, despite the fact that few patients had a dangerous increase in ICP. From a physiological point of view it is difficult to understand why a CPP above this limit would have a negative influence on the eventual quality of life. The sole explanation of their observation is a reference to a clinical microdialysis study from our group (13). They claim that our study shows that the intracerebral lactate level increases in the biochemical "penumbra zone" compared with less injured areas at a CPP level above 70 mmHg. Unfortunately, this is a complete misconception of our publication. In our study, we have shown that the lactate level is higher in the "penumbra zone" irrespective of the CPP level (*Fig. C1*) and that, in most patients, the lactate/pyruvate ratio increases at a CPP below 50 mmHg (*Fig. 2*). The latter observation does not contradict the fact that some patients need a CPP above 60 mmHg to preserve adequate cerebral oxygenation.

In the absence of biochemical or physiological explanations of their highly unexpected finding, we might try to elucidate what caused the statistical significance presented. Another unexpected finding, closely related to their CPP experience, may give a clue: the authors also found that the

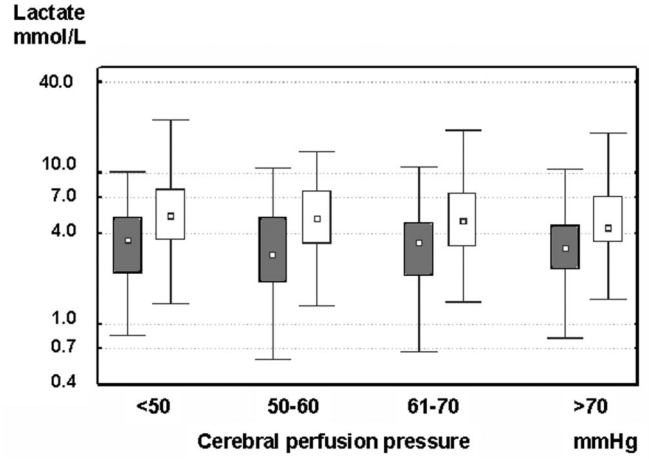

FIGURE C2. *Median level (central square) for lactate (n = 11,538; logarithmic scale) in the "better" and "worse" positions in relation to four ranges of CPP. The boxes (gray, better; open, "penumbra") represent the lower and the upper quartile and the whiskers represent range (from, [13]).*

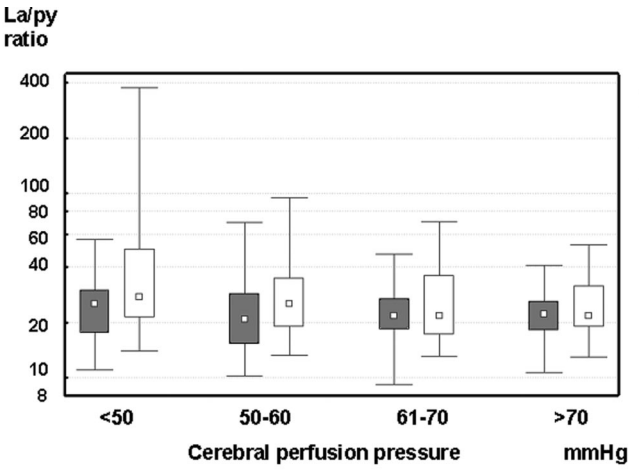

FIGURE C3. *Median level (central square) for the lactate/pyruvate ratio (n = 7704; logarithmic scale) in the "better" and "worse" positions in relation to four ranges of CPP. The boxes (gray, better; open, "penumbra") represent the lower and the upper quartile and the whiskers represent range (from, [13]).*

level of ICP was unrelated to clinical outcome. In patients with severe head injuries, it is well established that increased ICP is not only related to mortality (for obvious reasons), but also to the final clinical outcome (2). The absence of correlation between ICP and outcome in the study by Elf et al. (5) strongly indicates that, owing to the selection of their patient material and/or the layout of their study, the results are not representative of patients with severe traumatic brain lesions in general. The article by Elf et al. (5) is another example of the fact that a statistically significant correlation does not constitute a sufficient foundation of a scientific conclusion; there must also be a reasonable theoretical explanation (9).

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1. Asgeirsson B, Grände PO: Effects of arterial and venous pressure alterations on transcapillary fluid exchange during raised tissue pressure. **Intensive Care Med** 20:567–572, 1994.
2. Clifton GL, Miller ER, Choi SC, Levin HS: Fluid thresholds and outcome from severe brain injury. **Crit Care Med** 30:739–745, 2002.
3. Eker C, Asgeirsson B, Grände PO, Schalén W, Nordström CH: Improved outcome after severe head injury with a new therapy based on principles for brain volume regulation and improved microcirculation. **Crit Care Med** 26:1881–1886, 1998.
4. Eker C, Schalén W, Asgeirsson B, Grände PO, Ranstam J, Nordström CH: Reduced mortality after severe head injury will increase the demands for rehabilitation services. **Brain Injury** 14:605–619, 2000.
5. Elf K, Nilsson P, Ronne-Engström E, Howells T, Enblad P: Cerebral perfusion pressure between 50 and 60 mm Hg may be beneficial in head-injured patients: A computerized secondary insult monitoring study. **Neurosurgery** 56:962–971, 2005.
6. Fenstermacher JD: Volume regulation of the central nervous system, in Staub NC, Taylor AE (eds): *Edema*. New York, Raven Press, 1984, pp 383–404.

7. Grände PO, Asgeirsson B, Nordström CH: Physiological principles for volume regulation of a tissue enclosed in a rigid shell with application to the injured brain. **J Trauma** 42 [Suppl 5]:S23–S31, 1997.
8. Grände PO, Asgeirsson B, Nordström CH: Volume targeted therapy of increased intracranial pressure: The Lund concept unifies surgical and nonsurgical treatments. **Acta Anaesthesiol Scand** 46:929–941, 2002.
9. Leibovici L: Effects of remote, retroactive intercessory prayer on outcomes in patients with bloodstream infection: Randomized controlled trial. **BMJ** 323: 1450–1451, 2001.
10. Naredi S, Edén E, Zäll S, Stephensen H, Rydenhag B: A standardized neurosurgical/neurointensive therapy directed toward vasogenic edema after severe traumatic brain injury: Clinical results. **Intensive Care Med** 24:446–451, 1998.
11. Naredi S, Olivecrona M, Lindgren A, Östlund AL, Grände PO, Koskinen LO: An outcome study of severe traumatic head injury using the "Lund therapy" with low-dose prostacyclin. **Acta Anaesthesiol Scand** 45:401–405, 2001.
12. Nordström CH: Treatment of increased intracranial pressure: Physiological and biochemical principles underlying volume targeted therapy-the "Lund concept." **Neurocritical Care** 2:83–96, 2005.
13. Nordström CH, Reinstrup P, Xu W, Gärdenfors A, Ungerstedt U: Assessment of the lower limit for cerebral perfusion pressure in severe head injuries by bedside monitoring of regional energy metabolism. **Anesthesiology** 98:809–814, 2003.

In Reply:

Dr. Nordström fears that our article will add more confusion to the ongoing debate regarding the optimal cerebral perfusion pressure (CPP) in patients with traumatic brain injury. We agree that the association we reported between relatively low CPP levels and favorable outcome in our patients is surprising. At this point, we can only speculate about the physiological or metabolic factors contributing to this result. Nevertheless, the result is valid and has been rigorously tested. As described in our article (1), the effects of age and injury severity were controlled, as well as the parallel occurrence of intracranial pressure (ICP) and mean arterial pressure insults. We did not claim, however, that "a CPP of 60 mmHg constituted an important upper limit for favorable prognosis." The threshold of 60 mmHg was chosen because it is a widely used lower limit. The result obtained was the opposite of what might have been expected. Of course, this does not mean that a CPP over 60 is harmful; it simply means that patients with generally lower CPP did better overall. It is important to distinguish between a clinical and a statistical threshold.

When the possible pathophysiological explanations for our finding is discussed, it is important to consider that the primary injury often is heterogeneously distributed within the brain and that secondary brain injury may be regional and not always related to increased ICP. We suggested changes in the microenvironment as a general explanation. Nordström himself considers blood-brain barrier leakage as an important factor for the formation of brain edema. A lower blood pressure and CPP may prevent vasogenic brain edema in the case of regional blood-brain barrier disruption. In the study by Nordström et al. (4) we referred to, the lactate concentration was significantly higher in the worse position than in the better position for CPPs greater than 70 mmHg ($P = 0.0015$) and CPPs less than 50 mmHg, whereas no significant difference was reported in the ranges 50 to 60 and 61 to 70 mmHg. In that study, Nordström also referred to an experimental study showing that the contusion volumes were increased at low and high CPP levels (3). Low CPP levels with risk of ischemia were very rare in our patients.

Nordström argues that because we did not find a significant relationship between ICP insults and outcome our results are inconsistent with a large body of established research. However, as discussed in the article, our results are entirely consistent with a well-known study in which ICP was found to be a significant prognostic factor in preliminary univariate analyses, but was not significant when admission variables were controlled for (2). As we made clear in our discussion, this does not imply that ICP is not a critical clinical factor that should be treated aggressively. ICP may have not been found to be an independent prognostic factor in these studies precisely because it was aggressively treated. It is a well-known phenomenon that if an important prognostic factor is treated successfully, the prognostic information disappears.

Finally, we can, of course, agree with Dr. Nordström that a statistical association does not imply causality and that these results must be interpreted with care. Nevertheless, unexpected results should not be automatically rejected.

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1. Elf K, Nilsson P, Ronne-Engström E, Howells T, Enblad P: Cerebral perfusion pressure between 50 and 60 mm Hg may be beneficial in head-injured patients: A computerized secondary insult monitoring study. **Neurosurgery** 56:962–971, 2005.
2. Jones PA, Andrews PJ, Midgley S, Anderson SI, Piper IR, Tocher JL, Housley AM, Corrie JA, Slattery J, Dearden NM, Miller JD: Measuring the burden of secondary insults in head-injured patients during intensive care. **J Neurosurg Anesthesiol** 6:4–14, 1994.
3. Kroppenstedt SN, Kern M, Tomale UW, Schneider GH, Lanksch WR, Unterberg AW: Effect of cerebral perfusion pressure on contusion volume following impact injury. **J Neurosurg** 90:520–526, 1999.
4. Nordström C-H, Reinstrup P, Xu W, Gärdenfors A, Ungerstedt U: Assessment of the lower limit for cerebral perfusion pressure in severe head injuries by bedside monitoring of regional energy metabolism. **Anesthesiology** 98:809–814, 2003.

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