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A hypothesis accounting for the inconsistent benefit of glucocorticoid therapy in closed head trauma

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Summary Because of disagreement between clinical studies, the American College of Neurological Surgeons (ACNS) most recent recommendation (1996) is that glucocorticoids should not be used in the treatment of closed head trauma (CHT). The current paper reviews clinical studies of glucocorticoids and CHT in order to examine what factors might have accounted for the inconsistent results leading to the ACNS's recommendation. A careful analysIs of these studies reveals that, contrary to the ACNS's sweeping conclusion, the available data support the use of glucocorticoids for patients with CHT, but only in specific cases. Glucocorticoids may be beneficial in the treatment of CHT uncomplicated by intracranial hemorrhage; in situations where intracranial hemorrhage accompanies CHT, glucocorticoid treatment appears detrimental. The second part of this paper examines possible mechanisms accounting for the differential effectiveness of glucocorticoids in CHT patients with and without intracranial hemorrhage. These mechanisms include vasospasm, free radical damage, blood-borne factors, and glutamate neurotoxicity. © 2001 Harcourt Publishers Ltd

INTRODUCTION

Interest in the use of glucocorticoids (GC) in neurosurgery began with Galicich and French's (1) observation that dexamethasone reduces brain edema and edema-related symptoms in brain tumor patients. A reduction in edema-related post-operative neurological complications was later described in patients after temporal lobectomy for intractable seizures (2). Following these initial observations in patients, a number of studies were performed to examine possible benefits of GCs in the treatment of patients with closed heat trauma (CHT).* These studies failed to consistently identify clinical benefit unlike the initial studies with patients with brain tumors and temporal lobectomy (reviewed in (4)). As the expected result, the current assessment of the American College of Neurological Surgeons (5) is that GCs should not be used in the routine treatment of CHT.

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It is the author's opinion that a close review of the available studies suggests a compromise position: namely, that GCs are an effective therapeutic modality in CHT that is uncomplicated by intracranial hemorrhage (ICH)[2] and that similar GC treatment in CHT with ICH is ineffective. This paper will first review the data on the use of GCs in CHT with and without ICH. This will be followed by a brief description of pathophysiological mechanisms that could account for the differential effectiveness of GC treatment in patients with CHT complicated and uncomplicated by ICH.

*The definition of closed head trauma excludes depressed cranial fractures and any dural penetration, but may include skull fractures and any type of ICH. Open head trauma, particularly penetrating trauma, has distinct pathology (e.g., tissue maceration, damage from shock waves), complications (e.g., development of infection, missile fragment migration), treatment (e.g., removal of pulped brain), and prognosis (94% mortality with gunshot wound to head) (3), and would ideally not be grouped with or compared against CHT.

[2]ICH includes subdural, epidural, intraparenchymal, and subarachnoid hemorrhage, which necessarily are radiologically identifiable. Most studies reviewed here report the incidence of only the first three types.

CLINICAL STUDIES

Extrapolating from their pioneering work with brain tumor patients, French and Galicich (*6*) described clinical improvement after dexamethasone treatment in 11 CHT patients, all of whom were (i) comatose for at least 24 h and (ii) lacked ICH. In their report, dexamethasone dispelled the comatose state in 5 of the 11 CHT patients within a day of beginning treatment. Several subsequent clinical studies employing control groups reinforced the usefulness of GC treatment in CHT (*7*, Randt and Wood in *8*,*9*). In reports from Gobiet and colleagues, head injured patients (*96*% of whom were CHT and 21% of whom exhibited ICH) treated with dexamethasone had a relative risk (RR) of death of 0.5 in comparison with untreated patients (*7*,10). The extent of injury upon admission was poorly defined in these reports and is estimated here to be equivalent to a Glasgow coma scale (GCS) less than 5. A small group of CHT patients ($n = 17$) examined by Randt and Wood (reported in (8) as a personal communication) failed to statistically show benefit of methylprednisone treatment despite a RR of survival after steroid treatment of 1.*9*, a conflict likely caused by population size. Here the patients were selected for inclusion in the study based on the absence of 'angiographic shift or significant clots' indicating that none of the cases involved ICH. In Saul et al. (*9*), treatment with methylprednisolone or dexamethasone appeared to promote complete recovery (defined as a score of 5 on the Glasgow outcome scale (GOS)) from CHT by *6* months after injury (RR = 1.8), but it did not reduce the mortality rate. In this study, the frequency of ICH was 10%. GCs proved particularly beneficial in a subgroup of patients who were clinically improving on a standard head trauma protocol that included surgical drainage of intracranial hematomas (RR of death = 0.4; RR of complete recovery = 1.3); conversely, patients not responding to the standard treatment protocol did worse with steroid treatment (RR of complete recovery = 0.2; RR of death = 1.3).

Not all of the controlled studies that followed French and Galicich (*6*) supported the use of GCs in CHT. Gutterman and Shenkin (11) found that dexamethasone or hydrocortisone actually decreased survival and the likelihood of a good outcome (defined as a score of 5 or 4 on the GOS) in a series of CHT patients exhibiting a decerebrate posture (RR of death = 1.*6*; RR of good outcome = 0.4). Gutterman and Shenkin reported a 54% ICH rate in their patient population, in accordance with the established association between decerebrate posturing and ICH (*60*–80% of cases (12)). An even worse outcome was reported in steroid-treated, decerebrate patients who required surgical drainage of an identified intracranial hematoma (RR of death = 1.8). However, this study is non-randomized and unblinded, and considering the pervading belief at the time of the study that GCs improved outcome in CHT, it is quite possible that the patients who received steroid were clinically in worse condition than those who did not receive steroid. Gudeman et al. (13) failed to improve clinical outcome in a group of 20 CHT patients after treatment with methylprednisone. Here, *60*% of patients exhibited some type of ICH. Outcomes from methylprednisone-treated patients were compared against a non-concurrent control group whose members were less severely injured (e.g., exhibited less brainstem reflex impairment, cranial nerve injury, and, importantly, ICH) than the steroid-treated patients. Cooper et al. (14) compared the effects of dexamethasone in *76* CHT patients with an initial GCS value <8 and, in comparison with no treatment, dexamethasone treatment was associated with greater mortality (RR = 1.4). Patients in this study were diagnosed with either focal or diffuse brain trauma; of the 33% that were considered focal brain trauma, it is expected that a majority involve ICH. Patient randomization in the study by Cooper et al. was probably inadequate since patients diagnosed with the focal brain trauma were more commonly assigned to receive steroid treatment. Cooper et al.'s own control data show that the diagnosis of focal brain injury carries greater morbidity and mortality than does that of diffuse (e.g., no intracranial mass) brain injury, a finding that has been supported elsewhere (15).

Two large studies performed in a controlled and blinded manner recently reexamined the issue of GC treatment in CHT. Gaab et al. (16) reported that an intense, albeit short, dexamethasone treatment (see Table 1) failed to reduce mortality or improve outcome assessed 10–14 months after injury. Grumme et al. (17), using the pure anti-inflammatory GC triamCinolone, reduced mortality of all CHT at the time of discharge from the hospital (RR of death = 0.7). At that early time of assessment, benefits of GC treatment were observed specifically in patients with subdural or epidural hemorrhage (RR of good outcome after subdural hemorrhage = 1.*6*; RR of good outcome after epidural hemorrhage = 1.3) and in patients with brain contusions (RR of good outcome = 1.*6*). Reexamination of the study group one year after discharge, however, failed to show a statistically better outcome after triamcinolone treatment in the general treatment population (RR of death = 0.*9*) or specifically in epidural or subdural hemorrhage patients, although a persistent benefit of triamcinolone treatment in patients with brain contusions was found at one year (RR of good outcome = 1.*7*, RR of death = 0.5). Both Gaab et al. and Grumme et al. were liberal with admission criteria, including patients with moderate to minor CHT (GCS >8); this is reflected in the low mortality rates of their control groups. However, the incidence of intracranial

Table 1 Human trials using glucocorticoids in the treatment of closed head trauma

Study	*n*[1]	Steroid	Steroid dosage /duration[2]	Admission criteria	Outcome measure	Good recovery (GOS 1 or 2)	Death	Hemorrhage rate		Placebo mortality	Subgroup specific outcomes
Randt and Wood, in Ransohoff, 1972	17	mePred	10 g/4 d	no intracranial hemorrhage	death within 163d	RR = 1.9[4]	RR = 0.7	0%	72%	(+) decerebrate	
Saul et al., 1981	50	mePred, Dex	28.1 g/11 d	GCS < 7; OHT; NOSBI	GOS @6mo	RR = 1.8[6]	RR = 0.9	10%	18%	(+) responders to standard tx. protocol	
Gobiet et al., 1976	34	Dex	10.8 g/8 d	GCS < 5, est.; OHT	death within 10 d	n/a	RR = 0.5	21%	46%		
Dearden et al., 1986	68	Dex	12.7 g/6 d	GCS < 8; NRA	GOS @ 6mo	RR = 0.9	RR = 1.4	n/a	34%	(–) ICP > 30 mmHg, (–) surgical pts.	
Cooper et al., 1979	49	Dex	20.6 g/7 d	GCS < 8	GOS @ 6mo	RR = 1.0	RR = 1.4	< 33%	48%		
Gutterman & Shenkin, 1970	23	Dex, Hdct	Dex 0.5–0.7 g qd hcort 0.6 g qd,undefined	decerebrate posture	GOS @ DC	RR = 0.4	RR = 1.6	54%	38%	(–) surgical patients	
Grumme et al., 1995	187	Triam	4.6 g/9 d	GCS < 8 in 65%	GOS @ discharge & l yr	RR = 1.1 @ DC RR = 1.0 @ 1yr	RR = 0.7 @DC RR = 0.9 @ 1 yr	41–54%	16%	(+) brain contusion	
Gudeman et al., 1979	20	mePred	23.5 g/3 d	GCS < 8 in 80 %	GOS @ 3 mo	RR = 0.9	RR = 1.1	60%	35%		
Gaab et al., 1994	147	Dex	57.5 g/2 d	GCS < 8 in 76%; stable @ GCS > 4 for 24 h	Gos@ 10–14 mo	RR = 1.0	RR = 0.9	>55%	15%		

Controlled studies examining glucocorticoid therapy on clinical outcome in human closed head trauma. Light gray, studies with intracranial hemorrhage rates <25%; dark gray, studies with intracranial hemorrhage rates > 25%. Dex = dexamethasone, mePred = methylprednisolone, Hdct = hydrocortisone, Triam = triamcinolone; NRA = does not specify rapid administration of steroid; OHT = open head trauma included; NOSBI = no other significant body injury; (+) = beneficial; (–) = detrimental.
[1]number of head-trauma patients treated with steroid; [2]total dose over treatment course of the most efficacious dose or, in the absence of effect, the highest dose; dose standardized to a hydrocortisone equivalent based on antiinflammatory properties; assumes 70 kg man; [3]based on age, pupil reactivity to light, and best motor response; [4]measured as survival; [5]or equivalent scale; [6]GOS = 1 only.

hemorrhage in these studies was comparatively high (>55% in Gaab et al.[3]; 41–54% in Grumme et al.[4]).

The findings of the aforementioned studies are summarized in Table 1. In reviewing the available information of GC treatment of CHT, several hypotheses that could explain the varied conclusions of the clinical studies are eliminated, including:

1. Differences in steroid dosage – Those studies that show a benefit of GC treatment employ a range of steroid doses (expressed in terms of hydrocortisone anti-inflammatory equivalents in Table 1) that is comparable to studies that show no benefit of treatment.
2. Differences in steroid bioactivity – Clinical improvement is reported with both dexamethasone and methylprednisone. This is important because methylprednisone activates aldosterone- and GC-specific nuclear receptors, whereas dexamethasone is effective at only the GC-specific receptor (18,19).
3. Promptness of steroid administration – Reanalysis of the data presented in one of the clinical trials of GC in CHT (20) supports improved outcomes in patients treated within 6 h of injury (21). In fact, all of the controlled clinical studies reviewed here had treatment protocols that required initial steroid administration within 6 h of admission.
4. Differences in patient populations – The patients examined in these studies are relatively uniform in terms of sex (range of male sex = 74–79%) and age (range of average age = 26–40).
5. Differences in non-steroid treatment protocols – The only means of comparing the overall quality of medical care is by comparing the mortality rates of the control groups. Except for the study by Saul et al. (9), who excluded deaths within 72 h of admission, mortality rates were comparable (average for studies with GC benefit = 45%; average for studies without GC benefit = 40%).
6. Variability in steroid side effects – Side effects of GC treatment (e.g., diabetes, susceptibility to infection, gastric ulceration) were inconsistently reported among the studies and were usually non-quantitative when available. Where available, the reports of GC side effects were insufficiently detailed to indicate if CHT with and without ICH were afflicted differently.

[3]In the GC treatment group, CT scan identified intracerebral hemorrhage in 55%, subarachnoid hemorrhage in 39%, epidural hemorrhage in 10%, and subdural hemorrhage in 22%. Clearly these data indicate that multiple forms of hemorrhage were identified within individual patients.

[4]In the GC treatment group, CT scan identified subdural hemorrhage in 26% and epidural hemorrhage in 15%. Cases of subarachnoid and intraparenchymal hemorrhage were included with those of traumatic brain swelling and no visible lesion, amounting to 13% of the GC treatment group.

As mentioned earlier, one possible explanation for the inconsistent results obtained from the studies of GC treatment in CHT may be the incidence of ICH. As shown in Table 1, studies with ICH rates less than 25% (shown in light gray) exhibited some clinical benefit of steroid treatment, whereas studies with ICH rates greater than 25% (shown in dark gray) either showed no long-term benefit of treatment or a worsened outcome with treatment.

The hypothesis that GC treatment is useful in CHT patients with ICH, but ineffective in patients without ICH, is further supported by several minor findings from the studies listed in Table 1. GCs worsened clinical outcome in patients strongly suspect for ICH: in Gutterman and Shenkin (11) and elsewhere in Dearden et al. (22) (shown in white in Table 1), patients that required surgical intervention, which in most cases can be assumed to be drainage of ICH; in Cooper et al. (14), patients with 'focal' brain injuries; and in Gutterman and Shenkin (11), decerebrate patients, a condition frequently associated with ICH (12). Saul et al.'s (9) report of improved outcome with steroid treatment in patients that responded to surgical drainage of ICH further shows that removal of the factor of ICH promotes GC therapy. In addition to being consistent with the CHT literature, the hypothesis advanced in this communication is supported by the repeated observations that GCs fail to improve outcome after atraumatic intracerebral hemorrhage (23,24).

It is hypothesized that some factor associated with ICH antagonizes GC therapy in CHT. ICH may then (i) induce GC-insensitive pathological mechanisms that do not exist in CHT devoid of ICH, and/or (ii) increase an otherwise GC-sensitive pathological burden of CHT beyond the therapeutic efficacy of GC treatment. Potential mechanisms underlying the hypothesis will be discussed briefly in the next section.

MECHANISMS OF GLUCOCORTICOID INACTION

Evidence has been presented that in absence of ICH, GCs are an effective treatment for CHT, and that some factor associated with ICH may reduce the effectiveness of GC therapy. An extensive study on the relation between intracranial pressure and clinical condition after CHT (25) supports the conclusion that different pathophysiological mechanisms operate in CHT with and without ICH. In CHT without ICH, the patient's neurological condition and clinical outcome are predicted by the degree of intracranial hypertension: no such relationship exists in CHT with ICH, highlighting the importance of factors other than intracranial hypertension in this condition. Furthermore, some of these ICH-dependent mechanisms may account for the GC insensitivity of this condition.

If the hypothesis laid out earlier is acceptable then the question arises as to what factors distinguish CHT with

and without ICH. Several possible explanations will now be briefly discussed.

Vasospasm

Vasospasm is classically associated with subarachnoid hemorrhage from ruptured cerebral aneurysms, but it also can develop after CHT (26). Angiographic evidence of vasospasm was observed in 19% of CHT patients (27) and subsequently was associated with a worsened clinical outcome (28). Vasospasm has been reported after traumatic subdural, epidural, subarachnoid, or intraparenchymal hemorrhage, as well as after nonhemorrhagic CHT (29,30). These studies failed to describe the incidence of vasospasm after each type of ICH, and no report of the frequency of vasospasm after non-ICH CHT is available; however, Lee et al. (28) have reported that vasospasm is six times more common after traumatic subarachnoid hemorrhage than after all other types of traumatic ICH combined. Vasospasm is then an additional complication of CHT that falls predominantly on those cases with ICH. Since considerable evidence exists that vasospasm after aneurysmal subarachnoid hemorrhage is reduced by GCs (31–33) – albeit at unusually intense dosing (hydrocortisone 3g q2h for 12 h (34) – CHT vasospasm might similarly prove susceptible to GC treatment.

Blood coagulation, the complement system, and the Hageman factor-kallikrein-kinin system

After CHT, activation of the coagulation cascade at sites of endothelial injury produces microthrombi and small vessel occlusion in the brain (35,36). This would be expected, to some degree, after most CHT irrespective of radiographically detected ICH. However, severe malfunction of blood coagulation, as occurs in disseminated intravascular coagulation, is more commonly found in CHT with ICH (particularly subdural hemorrhage) than in nonhemorrhagic brain injury (37,38). Furthermore, the development of disseminated intravascular coagulation is promoted by GCs (39).

Proteins of the complement system are also carried into contact with brain parenchyma during ICH. Complement complexes are found in the brain after subarachnoid hemorrhage in patients who were treated with betamethasone (40). In brain parenchyma complement is activated by myelin and subsequently attacks oligodendrocytes (41), resulting in demyelination (42). Such actions are quite possibly worsened by GC treatment, since the production of complement proteins from endothelium is increased by GCs (43).

In addition to its hemostatic role at sites of injured endothelium, the Hageman factor (Factor XII) self-activates after contacting certain membrane glycolipids that are concentrated in the central nervous system (44). The Hageman factor activates kallikrein, which attracts neutrophils and causes them to produce free radicals (45,46). Kallikrein, in turn, proteolytically activates bradykinins, substances that directly induce brain edema by promoting vasodilation and blood–brain barrier disruption (47–49). GCs decrease production and activation of kallikrein in the kidney [50] and induce angiotensin converting enzyme production (51), the inactivating enzyme of bradykinin.

Free radicals

Oxygen free radicals damage membrane lipids, inhibiting cellular function and ultimately causing cell death by disruption of lipid bilayer integrity. Oxygen free radical production is initiated and amplified by extracellular iron (52,53), which presumably increases after ICH (54; demonstrated with zinc in 55). Thus, the extent of lipid peroxidation and cell death that occurs after hemorrhagic CHT is expected to be greater than that occurring after nonhemorrhagic CHT. GCs, which counteract lipid peroxidation in experimental brain contusion (56), may simply be overwhelmed in CHT with ICH by the oxidative potential that develops in the presence of high extracellular iron levels.

Another free radical, nitric oxide, is also associated with brain injury (57–59), though its role in CHT has not been specifically addressed. Nitric oxide has both damaging (60,61) and protective (62–65) actions. Since nitric oxide is regulated both by hemoglobin (66) and GCs (67), it is in a potentially important position to distinguish between CHT with and without ICH.

Glutamate neurotoxicity

Exposure to high levels of glutamate kills neurons in culture and in vivo (68,69). Glutamate binding to NMDA- or kainate-specific receptors[5] stimulates production of nitric oxide (73,74) (discussed above) and increases intracellular calcium levels (75). High intracellular calcium levels (i) stimulate the production of prostaglandins, compounds with established roles in nervous system injury (76) and (ii) disrupt the mitochondrial membrane potential, thereby arresting cellular metabolism and allowing damaging levels of free radicals to accumulate (77). High levels of intracellular calcium are controlled in part by sequestration into mitochondria (78).

[5] The metabotropic glutamate receptor also is responsible for some of glutamate's neurotoxic properties (70), although its activation opposes the neurotoxicity of ionotropic glutamate receptors (71). Receptor binding studies in rats suggest that glutamate release after CHT is predominantly onto NMDA receptors, however (72).

Glutamate release is increased after experimental brain injury by fluid percussion (*79*,*80*) and direct cortex compression (*81*), and after subdural hematoma formation (*82*–*85*). Unfortunately, the neurological condition of the experimental animals after injury was not described, so the various models cannot be compared to determine if glutamate release is differently affected by the presence of blood. Glutamate in the extracellular space of the brain is also increased in patients after CHT (*86*). Here, however, accurate comparison of the levels of glutamate in the various types of CHT is complicated by the release of glutamate-rich blood into the brain parenchyma after surgical removal of contused brain.

Glutamate neurotoxicity is independently amplified by both blood substances and GC treatment. Incubation of primary cortical neurons with hemoglobin increased the neurotoxic potency of NMDA, AMPA, and kainate (*87*), independent of hemoglobin's own neurotoxic potential (*88*). Other substances from the blood that may be important in CHT with ICH include as-of-yet uncharacterized serum proteins that inhibit calcium buffering by mitochondria (*89*). GCs potentiate glutamate neurotoxicity (*90*), possibly by decreasing glial glutamate reuptake (*91*) or augmenting glutamate release (*92*). It should be noted that GCs themselves have some neurotoxic potential on hippocampal neurons in vitro (*93*,*94*) and in vivo (*95*): the duration and dosage of these experimental GC treatments are in excess of any GC therapeutic protocols, however, and so this is not likely a clinical factor.

CONCLUSIONS

In summary, an analysis of the relevant literature suggests that GC treatment may be effective in the treatment of CHT when it is not complicated by ICH. This suggests that ICH either reduces or eliminates the beneficial effect of GCs. Several mechanisms are available to explain why ICH could render GC therapy ineffective. Some of these mechanisms are not affected by GCs, or perhaps are even made worse by GCs. Such mechanisms include glutamate neurotoxicity, complement cytotoxicity, and the development of disseminated intravascular coagulation. The qualitative difference that these factors may bring to hemorrhagic CHT would necessitate the use of distinct therapeutic modalities.

Alternatively, the addition or amplification of GC-sensitive mechanisms (e.g., vasospasm, activation of the Hageman factor-kallikrein-kinin system, cell injury from free radicals) by ICH might increase the pathological effect to levels that cannot be contained by currently employed steroid treatments. The existence of such mechanisms may indicate that CHT with ICH exists on a continuum with nonhemorrhagic CHT and that CHT with ICH may also be susceptible to GC treatment albeit at doses above those used in the reviewed clinical studies.

REFERENCES

1. Galicich J. H., French L. A. The use of dexamethasone in the treatment of cerebral edema resulting from brain tumors and brain surgery. *Am Pract* 1961; **12:** 169–174.
2. Rassmussen T., Gulati D. R. Cortisone in the treatment of postoperative cerebral edema. *J Neurosurg* 1962; **19:** 535–544.
3. Greenberg M. S. In: Handbook of Neurosurgery, Third Edition. Greenberg Graphics, Lakeland. 1994; 559–562.
4. Koehler P. J. Use of corticosteroids in neuro-oncology. *Anticancer Drugs* 1995; **6:** 19–33.
5. American College of Neurological Surgeons, Joint Section on Neurotrauma and Critical Care. Guidelines for the Management of Severe Brain Injury. *J Neurotrauma* 1996; **13:** 641–734.
6. French L. A., Galicich J. H. The use of steroids for control of cerebral edema. *Clin Neurosurg* 1969; **10:** 212–223.
7. Gobiet W., Bock W. J., Liesegang J., Grote W. Treatment of acute cerebral edema with a high dose of dexamethasone. In Intracranial Pressure III. Beks J. W. F. et al. eds. Springer-Verlag, 1976; 231–235.
8. Ransohoff J. The effects of steroids on brain edema in man. In Steroids and Brain Edema. Reulen J. H. and Schurmann K., eds. Springer-Verlag 1972; 211–217.
9. Saul T. G., Ducker T. B., Saleman M., Carro E. Steroids in severe head injury. A prospective randomized clinical trial. *J Neurosurg* 1981; **54:** 596–600.
10. Gobiet W. The influence of various doses of dexamethasone on intracranial pressure in patients with severe head injury. In Dynamics of Brain Edema. Pappius H. M. and Feindel W. eds. Springer-Verlag 1976; 351–355.
11. Gutterman P., Shenkin H. A. Prognostic Features in Recovery from Traumatic Decerebration. *J Neurosurg* 1970; **32:** 330–335.
12. Bricolo A., Turazzi S., Alexandre A., Rizzuto N. Decerebrate rigidity in acute head injury. *J Neurosurg* 1977; **47:** 680–698.
13. Gudeman S. K., Miller J. D., Becker D. P. Failure of high-dose steroid therapy to influence intracranial pressure in patients with severe head injury. *J Neurosurg* 1979; **51:** 301–306.
14. Cooper P. R., Moody S. Clark W. K. et al. Dexamethasone and severe head injury. A prospective double-blind study. *J Neurosurg* 1979; **51:** 307–316.
15. Gennarelli T. A., Spielman G. M., Langfitt T. W. et al. Influence of the type of intracranial lesion on outcome from severe head injury. *J Neurosurg* 1982; **56:** 26–32.
16. Gaab M. R., Trost H. A. Alcantara A. et al. "Ultrahigh" dexamethasone in acute brain injury. Results from a prospective randomized double-blind multicenter trial (GUDHIS). *Zentralbl Neurochi* 1994; **55:** 135–143.
17. Grumme T., Baethmann A., Kolodziejczyk D. et al. Treatment of patients with severe head injury by triamcinolone: A prospective, controlled multicenter clinical trial of 396 cases. *Res Exp Med* 1995; **195:** 217–229.
18. Krozowski Z. S., Funder J. W. Renal mineralocorticoid receptors and hippocampal corticosterone binding species have identical intrinsic steroid specificity. *PNAS* 1983; **80:** 6056–6060.
19. Veldhuis H. D., van Koppen C., van Ittersum M., de Kloet E. R. Specificity of the adrenal steroid receptor system in rat hippocampus. *Endocrinol* 1982; **110:** 2044–2051.
20. Faupel G., Reulen H. J., Muller D. et al. Double-blind study on the effects of steroids on severe closed head injury. In Pappius H. M. and Feindel W. (eds), Dynamics of Brain Edema. Springer-Verlag, 1976; 337–343.
21. Reulen H. J. and Schurmann K. Nonsurgical management of severe head injuries. *Prog Neurolog Surg* 1981; **10:** 291–322.

22. Dearden N. M., Gibson J. S., McDowall G. et al. Effect of high-dose dexamethasone on outcome from severe head injury. *J Neurosurg* 1986; **64:** 81–88.
23. Poungvarin N., Bhoopat W., Viriyavejakul A. et al. Effects of dexamethasone in primary supratentorial intracerebral hemorrhage. *NEJM* 1987; **316:** 1229–1233.
24. Tellez H., Bauer R. B. Dexamethasone as treatment in cerebrovascular disease. 1. A controlled study in intracerebral hemorrhage. *Stroke* 1973; **4:** 541–546.
25. Miller J. D., Becker D. P., Ward J. D. et al. Significance of intracranial hypertension in severe head injury. *J Neurosurg* 1977; **47:** 503–516.
26. Martin N. A., Patwardhan R. V., Alexander M. J. et al. Characterization of cerebral hemodynamic phases following severe head trauma: hypoperfusion, hyperemia, and vasospasm. *J Neurosurg* 1997; **87:** 9–19.
27. Suwanwela C., Suwanwela N. Intracranial arterial narrowing and spasm in acute head injury. *J Neurosurg* 1972; **36:** 314–323.
28. Lee E. J., Chio C. C., Chang C. H., Chen H. H. Prognostic significance of altered cerebrovascular blood flow velocity in acute head trauma. *J Formosan Med Assoc* 1997; **96:** 5–12.
29. Kordestani R. K., Counelis G. J., McBride D. Q., Martin N. A. Cerebral arterial spasm after penetrating craniocerebral gunshot wounds: Transcranial Doppler and cerebral blood flow findings. *Neurosurg* 1997; **41:** 351–359.
30. Martin N. A. Post-traumatic cerebral arterial spasm. *J Neurotrauma* 1993; **10:** S84.
31. Clarisse J., Jomin M., Andreussi L., Lain E. Prognostic significance of cerebral arterial spasm in the course of meningeal haemorrhage. *Neuroradiol* 1972; **3:** 150–152.
32. Fox J. L., Yasargil M. G. The relief of intracranial vasospasm: An experimental study with methylprednisolone and cortisol. *Surg Neurol* 1975; **3:** 214–218.
33. Suzuki S., Ogane K., Ohkuma H., Iwabuchi T. Efficacy of steroid hormone in solution for intracranial irrigation during aneurysmal surgery for prevention of the vasospasm syndrome. *Acta Neurochir* 1994; **131:** 184–188.
34. Hashi K., Takakura K., Sano K. et al. Intravenous hydrocortisone in large doses in the treatment of delayed ischemic neurological deficits following subarachnoid hemorrhage – results of a multicentered controlled double-blind clinical study. *Brain Nerve* 1988; **40:** 373–382.
35. Huber A., Dorn A., Witzmann A., Cervos-Navarro J. Microthrombi formation after severe head trauma. *Internatl J Legal Med* 1993; **106:** 152–155.
36. van der Sande J. J., Emeis J. J., Lindeman J. Intravascular coagulation: A common phenomenon in minor experimental head injury. *J Neurosurg* 1981; **54:** 21–25.
37. Kaufman H. H., Hui K. S., Mattson J. C. et al. Clinicopathological correlations of disseminated intravascular coagulation in patients with head injury. *Neurosurg* 1984; **15:** 34–42.
38. Kumura E., Sato M., Fukuda A., Takemoto Y. et al. Coagulation disorders following acute head injury. *Acta Neurochir* 1987; **85:** 23–28.
39. Latour J. G., Prejean J. B., Margaretten W. Corticosteroids and the generalized Schwartzman reaction. Mechanisms of sensitization in the rabbit. *Am J Pathol* 1971; **65:** 189–202.
40. Lindsberg P. J., Ohman J., Lehto T. Complement activation in the central nervous system following blood-brain barrier damage in man. *Ann Neurol* 1996; **40:** 587–596.
41. Cyong J. C., Witkin S. S., Reiger B. et al. Antibody-independent compliment activation by myelin via the classic complement pathway. *J Exp Med* 1982; **155:** 587–598.
42. Silverberg D. H., Manning M. C., Schreiber A. D. Tissue culture demyelination by normal human serum. *Ann Neurol* 1984; **15:** 575–580.
43. Coulpier M., Andreev S., Lemercier C. et al. Activation of the endothelium by IL-1 alpha and glucocorticoids results in major increase of complement C3 and factor B production and generation of C3a. *Clin Exper Immunol* 1995; **101:** 142–149.
44. Tans G., Rosing J., Griffin J. H. Sulfatide-dependent autoactivation of human blood coagulation Factor XII (Hageman factor). *J Biol Chem* 1983; **258:** 8215–8222.
45. Schapira M., Despland E., Scott C. F. et al. Purified human plasma kallikrein aggregates human blood neutrophils. *J Clin Invest* 1982; **69:** 1199–1202.
46. Zimmerli W., Huber I., Bouma B. N., Lammle B. Purified human plasma kallikrein does not stimulate but primes neutrophils for superoxide production. *Thromb Haemost* 1989; **62:** 1121–1125.
47. Unterberg A., Dautermann C., Baethmann A., Muller-Esterl W. The kallikrein-kinin system as mediator in vasogenic brain edema. *J Neurosurg* 1986; **64:** 269–276.
48. Uterberg A., Wahl M., Baethmann A. Effects of bradykinin on permeability and diameter of pial vessels in vivo. *J Cereb Blood Flow Metab* 1984; **4:** 574–585.
49. Uterberg A., Wahl M., Baethmann A. Effects of bradykinin on blood-brain-barrier function and pial microcirculation. *Advances Neurosurg* 1983; **11:** 355–358.
50. Jaffa A. A., Miller D. H., Silva R. H. et al. Regulation of renal kallikrein synthesis and activation by glucocorticoids. *Kidney Internatl* 1990; **38:** 212–218.
51. Ialenti A., Calignano A., Carnuccio R., di Rosa M. Glucocorticoid induction of angiotensin converting enzyme. *Agents Actions* 1986; **17:** 294–295.
52. Hall E. D., Braughler J. M. Free radicals in CNS injury. In: Waxman S. G. (ed) Molecular and Cellular Approaches to the Treatment of Neurological Diseases. Raven Press, 1993.
53. Wilmore L. J., Rubin J. J. Formation of malonaldehyde and focal brain edema induced by subpial injection of FeCl2 into rat isocortex. *Brain Res* 1982; **246:** 113–119.
54. el-Yazigi A., Al-Saleh I., Al-Mefty O. Concentrations of zinc, iron, molybdenum, arsenic, and lithium in cerebrospinal fluid of patients with brain tumors. *Clin Chem* 1986; **32:** 2187–2190.
55. Palm R., Hallmans G. Zinc concentrations in the cerebrospinal fluid of normal adults and patients with neurological diseases. *J Neurol Neurosurg Psych* 1982; **45:** 685–690.
56. Ildan F., Polat S., Oner A. et al. The effect of the treatment of high-dose methylprednisolone on Na(+)–K(+)/Mg(+2) ATPase activity and lipid peroxidation and ultrastructural findings following cerebral contusion in rat. *Surg Neurol* 1995; **44:** 573–580.
57. Yu W. H. A. Nitric oxide synthase in motor neurons after axotomy. *J Histochem Cytochem* 1994; **335:** 563–575.
58. Chen S., Aston-Jones G. Cerebellar injury induces NADPH diaphorase in Purkinje and inferior olivary neurons in the rat. *Brain Res* 1994; **492:** 237–244.
59. Huang Z., Huang P. L., Panahian N. et al. Effects of cerebral ischemia in mice deficient in neuronal nitric oxide synthase. *Science* 1994; **265:** 1883–1885.
60. Garg U. C., Devi L., Turndorf H. et al. Effect of nitric oxide on mitogenesis and proliferation of cerebellar glial cells. *Brain Res* 1992; **592:** 208–212.
61. Dawson V. L., Dawson T. M., London E. D., Bredt D. S. Nitric oxide mediates glutamate neurotoxicity in primary neuronal cultures. *Proc Natl Acad Sci USA* 1991; **88:** 6368–6371.
62. Kim H., Kim K. H. Effects of nitric oxide on hydrogen peroxide-induced damage in isolated rabbit gastric glands. *Pharmacol* 1998; **57:** 323–330.
63. Brune B., Dimmeler S., Vedia L. M., Lapentina E. G. Nitric oxide: A signal for ADP-ribosylation of proteins. *Life Sci* 1994; **54:** 61–70.

64. Chang J., Rao N. V., Markewitz B. A. et al. Nitric oxide donor prevents hydrogen peroxide-mediated endothelial cell injury. *Am J Physiol* 1996; **270:** L931–940.
65. Bautista A. P., Spitzer J. J. Inhibition of nitric oxide formation in vivo enhances superoxide release by the perfused liver. *Am J Physiol* 1994; **266:** G783–788.
66. Doyle M. P., Hoekstra J. W. Oxidation of nitrogen oxides by bound dioxygen in hemoproteins. *J Inorg Biochem* 1981; **14:** 351–358.
67. Szabo C. Regulation of the expression of the inducible isoform of nitric oxide synthase by glucocorticoids. *Ann NY Acad Sci* 1998; **851:** 336–341.
68. Finkbeiner S., Stevens C. F. Applications of quantitative measurements for assessing glutamate neurotoxicity. *Proc Natl Acad Sci USA* 1988; **85:** 4071–4074.
69. Ignatowicz E., Vezzani A. M., Rizzi M., d'Incalci M. Nerve cell death induced in vivo by kainic acid and quinolinic acid does not involve apoptosis. *Neuroreport* 1991; **2:** 651–654.
70. Gong Q. Z., Delahunty T. M., Hamm R. J., Lyeth B. G. Metabotropic glutamate antagonist, MCPG, treatment of traumatic brain injury in rats. *Brain Res* 1995; **700:** 299–302.
71. Wang Y., Qin Z. H., Nakai M., Chase T. N. Glutamate metabotropic receptor agonist 1S.3R-ACPD induces internucleosomal DNA fragmentation and cell death in rat striatum. *Brain Res* 1997; **772:** 45–56.
72. Miller L. P., Lyeth B. G., Jenkins L. W. et al. Excitatory amino acid receptor subtype binding following traumatic brain injury. *Brain Res* 1990; **526:** 103–107.
73. Cheng Y., Sun A. Y. Oxidative mechanisms involved in kainate-induced cytotoxicity in cortical neurons. *Neurochem Res* 1994; **19:** 1557–1564.
74. Almeida A., Heales S. J., Bolanos J. P., Medina J. M. Glutamate neurotoxicity is associated with nitric oxide-mediated mitrochondrial dysfunction and glutathione depletion. *Brain Res* 1998; **790:** 209–216.
75. Itoh T., Itoh A., Horiuchi K., Pleasure D. AMPA receptor-mediated excitotoxicity in human NT2-N neurons results from loss of intracellular Ca2+ homeostasis following marked elevation of intracellular Na+. *J Neurochem* 1998; **71:** 112–124.
76. Shohami E., Glantz L., Nates J., Feuerstein G. The mixed lipoxygenase/cyclooxygenase inhibitor SK&F 105809 reduces cerebral edema after closed head injury in the rat. *J Basic Clin Physiol Pharmacol* 1992; **3:** 99–107.
77. Perez-Velazquez J. L., Frantseva M. V., Carlen P. L. In vitro ischemia promotes glutamate-mediated free radical generation and intracellular calcium accumulation in hippocampal pyramidal neurons. *J Neurosci* 1997; **17:** 9085–9094.
78. Wang G. J., Thayer S. A. Sequestration of glutamate-induced Ca2+ load by mitochondria in cultured rat hippocampal neurons. *J Neurophysiol* 1996; **76:** 1611–1621.
79. Faden A. I., Demediuk P., Panter, S. S., Vink R. The role of excitatory amino acids and NMDA receptors in traumatic brain injury. *Science* 1989; **244:** 798–800.
80. Katayama Y., Becker D. P., Tamura T., Hovda D. A. Massive increase in extracellular potassium and the indiscriminate release of glutamate following concussive brain injury. *J Neurosurg* 1990; **73:** 889–900.
81. Nilson P., Hillered L., Ponten U., Ungersteadt U. Changes in cortical extracellular levels of energy-related metabolites and amino acids following concussive injury in rats. *J Cereb Blood Flow Metab* 1990; **10:** 631–637.
82. Bullock R., Inglis F. M., Kuroda Y. et al. Transient hippocampal hypermetabolism associated with glutamate release after acute subdural haematoma in the rat: A potentially neurotoxic mechanism? *J Cerebral Blood Flow Metab* 1991; **11:** S109.
83. Bullock R., Butcher S. P., Chen M. et al. Correlation of the extracellular glutamate concentration with extent of blood flow reduction after subdural haematoma in the rat. *J Neurosurg* 1991; **74:** 794–802.
84. Bullock R., Butcher S., McCulloch J. Changes in extracellular glutamate concentrations after acute subdural haematoma in the rat – evidence for an "excitotoxic" mechanism? *Acta Neurochir Suppl* 1990; **51:** 274–276.
85. Kuroda Y., Inglis F. M., Miller J. D. et al. Transient glucose hypermetabolism after acute subdural hematoma in the rat. *J Neurosurg* 1992; **76:** 471–477.
86. Bullock R., Zauner A., Woodward J. J. et al. Factors affecting excitatory amino acid release following severe human head injury. *J Neurosurg* 1998; **89:** 507–518.
87. Regan R. F., Panter S. S. Hemoglobin potentiates excitotoxic injury in cortical cell culture. *J Neurotrauma* 1996; **13:** 223–231.
88. Regan R. F,. Panter S. S. Neurotoxicity of hemoglobin in cortical cell culture. *Neurosci Lett* 1993; **153:** 219–222.
89. Dux E., Oschlies U., Uto A. et al. Serum prevents glutamate-induced mitochondrial calcium accumulation in primary neuronal cultures. *Acta Neuropathol* 1996; **92:** 264–272.
90. Supko D. E., Johnson M. V. Dexamethasone potentiates NMDA receptor-mediated neuronal injury in the postnatal rat. *Euro J Pharmacol* 1994; **270:** 105–113.
91. Virgin C. E., Ha T. P., Packan D. R. et al. Glucocorticoids inhibit glucose transport and glutamate uptake in hippocampal astrocytes: Implications for glucocorticoid neurotoxicity. *J Neurochem* 1991; **57:** 1422–1428.
92. Moghaddam B., Bolinao M. L., Stein-Behrens B., Sapolsky R. Glucocorticoids mediate the stress-induced extracellular accumulation of glutamate. *Brain Res* 1994; **655:** 251–254.
93. Behl C., Lezoualc'h F., Trapp T. et al. Glucocorticoids enhance oxidative stress-induced cell death in hippocampal neurons in vitro. *Endocrinol* 1997; **138:** 101–106.
94. Flavin M. P. Influence of dexamethasone on neurotoxicity caused by oxygen and glucose deprivation *in vitro*. *Exp Neurol* 1996; **139:** 34–38.
95. Sapolsky R. M., Uno H., Rebert C. S., Finch C. E. Hippocampal damage associated with prolonged glucocorticoid exposure in primates. *J Neurosci* 1990; **10:** 2897–2902.