Neurosurgical Intensive Care

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THE NEXT DECADE in critical care will be marked by a flurry of activity directed toward the neurologic patient. During the past 20 years, our clinical ability to support cardiac, respiratory and renal function in acutely ill patients has dramatically improved, while development and clinical application of central nervous system (CNS) monitoring and treatment modalities have lagged. The introduction of advanced neurologic monitoring techniques has placed neurologic intensive care at a critical crossroad. Clinical quantitation of regional cerebral blood flow (CBF), intracranial pressure (ICP), and electrical activity of the brain is now practical. With computerized tomography (CT), an analysis of the intracranial contents can be obtained.[1-3] These monitoring advances permit improved application and/or re-evaluation of the standard neurotherapeutic procedures recently reviewed in this journal.[4]

This review seeks to provide the practicing anesthesiologist with a data base enabling him to participate rationally in the treatment of acute neurologic disease and to evaluate new concepts and techniques being directed toward this group of patients. To accomplish this, we examine the basic goals to be considered in the establishment of a neurologic intensive care environment. This discussion focuses on staffing as well as monitoring requirements. In the following section we utilize head trauma as a prototype disease entity and review the problems and recent progress in the management of these patients. In the last section, we evaluate the evidence that barbiturates may be useful adjuncts in the management of cerebral ischemia due to a variety of etiologies.

Neurosurgical Intensive Care Environment

A Specialized Unit?

The critical element in establishing a neurologic intensive care environment is not space and mortar,

but rather, the presence of a staff with combined skills in neurologic and intensive care techniques.[5] It is our experience that the enhanced monitoring capabilities and physician input associated with a neurologic intensive care facility do much to facilitate the recruitment of nursing personnel. Currently, specialized neurologic intensive care units (NICU) should probably be limited to designated regional care centers, each equipped with a CT head scanner. Studies of therapeutic-cost effectiveness in these institutions should be performed prior to a generalized expansion of these facilities.

ADMISSION/DISCHARGE CRITERIA

Patients admitted to a neurologic intensive care area usually have one or a combination of the following abnormalities: altered level of consciousness, fluctuating neurologic signs, inappropriate ventilatory capacity and/or a loss of airway protective reflexes. The most common admitting diagnoses are stroke, head injury, brain tumor, and post-hypoxic encephalopathy[5,6]; admission may also be for immediate postoperative observation and stabilization. Less commonly encountered problems include spinal-cord injury, status epilepticus, myasthenia gravis, and the various infectious, metabolic, and hypertensive encephalopathies.

Recovery from a neurologic disorder is frequently prolonged compared with other disease states requiring intensive supportive care. Acute intracranial disorders such as head injury and stroke may require intensive care for one to three weeks before reaching a stabilized phase. Thereafter, an intermediate care facility, providing a less intense, but highly vigilant and supportive, environment becomes more appropriate.[7] In the absence of such a facility, neurosurgeons are reluctant to discharge their stabilized, but still dependent, patients to general surgical wards. This often leads to bed availability problems in the NICU.

Central Nervous System Monitoring

RECORDING NEUROLOGIC STATUS

Accurate continuing assessment and recording of clinical neurologic status has first priority in neurosurgical intensive care. Methods of clinical assessment of comatose patients have recently been reviewed.[8-12] The initial clinical neurologic examination provides the most accepted basis for prognostication[13,14] and
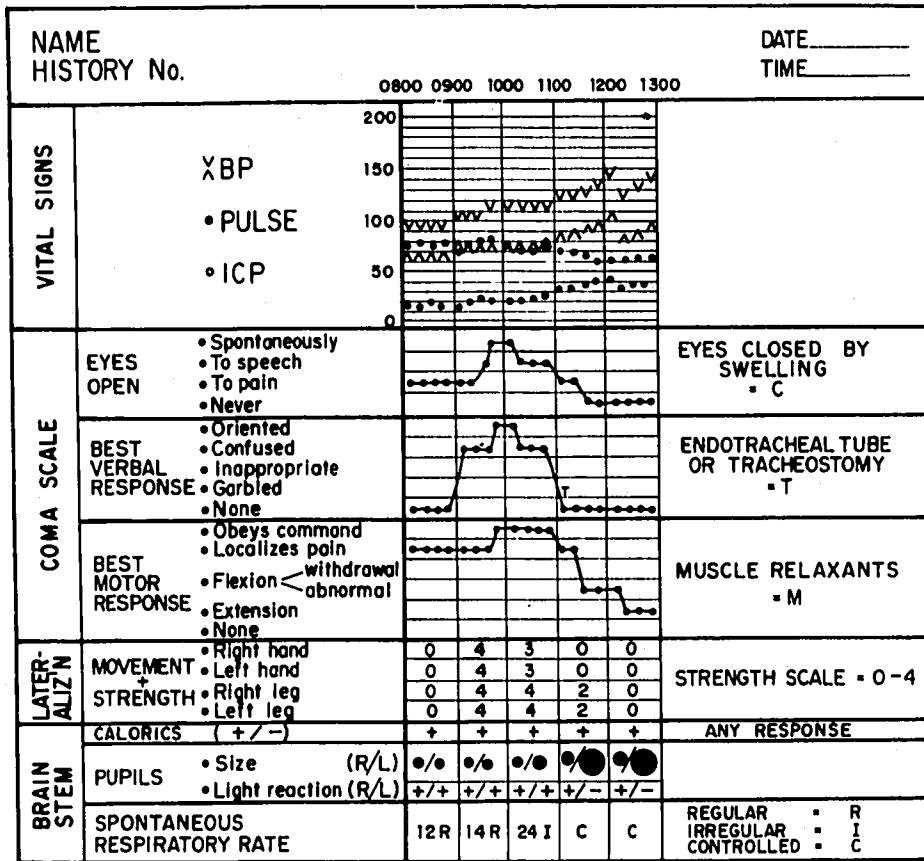
FIG. 1. Example of a neurologic status record, showing the course of a patient admitted to the NICU following a head injury. The initial examination revealed a comatose patient lacking spontaneous movements, but responding to pain. After an hour, the patient emerged from the coma, only to experience an exacerbation with concurrent ICP elevation and clinical evidence of impending transtentorial herniation. The trachea was intubated and the patient hyperventilated prior to surgical evacuation of a large hematoma.

for comparing the outcomes of variations in therapeutic approaches among centers.

Following Jennett's[9] lead in Glasgow, a number of centers have cooperated in evaluating a coma-scoring system in head-injured patients.[10,15] The coma-scoring system is very simple in design, requiring only a recording of the best possible responses (without stating laterality preferences) to vocal or noxious stimuli, as characterized by eye opening, verbalization, and motor activity. The Glasgow coma scale is an important tool for inter-institutional comparisons. This scale, however, does not provide a comprehensive
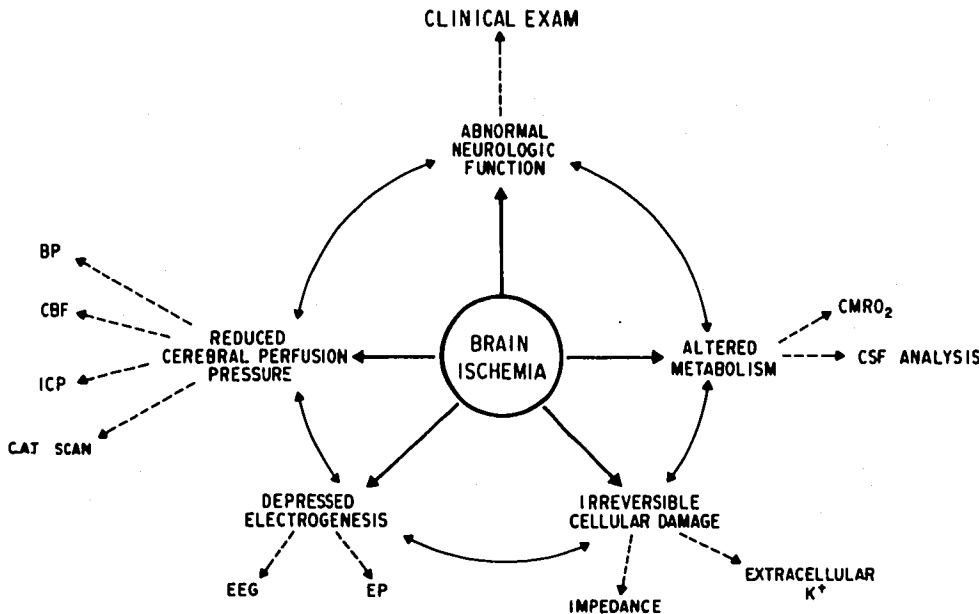

FIG. 2. Summary of the pathophysiologic consequences of cerebral ischemia and the specialized monitoring involved in detecting these changes. The outer circle represents the physiologic disorders caused by cerebral ischemia. The dashed arrows indicate the monitoring methods used to delineate these derangements. See text for elaboration.

FIG. 3. Serial CT scans of a 67-year-old patient with an acute subdural hematoma who was admitted unresponsive, with fixed dilated pupils. The clot was evacuated and barbiturate coma was induced on the operating table. *A*, The CT scan obtained preoperatively revealed the large right-sided subdural hematoma, massive edema, and midline shifting with acute hydrocephalus secondary to horn entrapment. *B*, CT scan two days after operation and coma shows virtually complete resolution of the edema and restoration of brain symmetry. The patient's recovery was complete except for slight spasticity of the left hand.
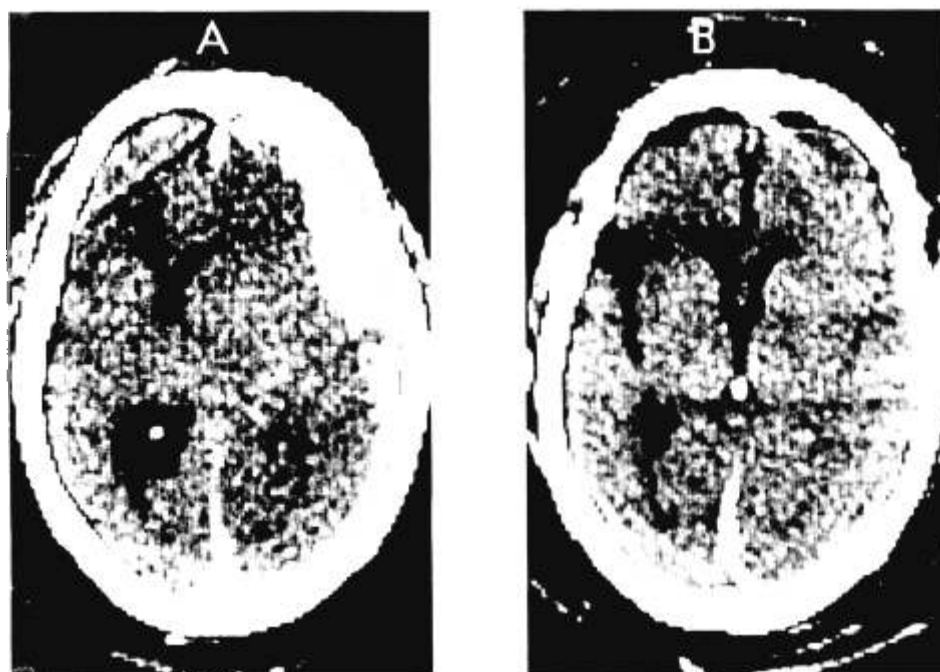
enough picture of an individual's overall neurologic and medical status to guide critical care management decisions. For instance, there is no provision for recording basic criteria, such as vital signs, pupillary size and reactivity, oculovestibular response, and ICP. We incorporated the Glasgow coma score in our neurologic status recording form, as shown in figure 1. This record is designed to illustrate trends in neurologic status. The format incorporated in this method of recording neurologic status quickly teaches the elements of neurologic evaluation.

SPECIALIZED CNS MONITORING

Detection of intracranial events challenging cerebral homeostasis remains a difficult problem because of the complex functional and structural arrangement of the CNS and its relative inaccessibility. Many circumstances threatening survival of the brain result from absolute or relative imbalances between cerebral metabolic demands and supplies. When such a mismatch occurs, specialized monitoring techniques are necessary to quantitate the nutrient supply deficit and to measure the functional/metabolic result. Most CNS monitoring is directed toward quantifying cerebral ischemia or its consequences. In neurosurgical patients, cerebral ischemia may be local or generalized and caused by intracranial hypertension, systemic hypotension, vascular occlusion, or combinations thereof. Figure 2 indicates some of the metabolic and functional aberrations associated with cerebral ischemia and suggests monitoring methods that may be useful in their detection.

CT Scan and ICP

Important elements in neurosurgical monitoring consist of a combination of appropriately timed CT scans and continuous ICP recording.[1,16–19] CT scanning can provide accurate information about surgically amenable lesions, midline position, intracranial hemorrhage or cysts, ventricular size, and cerebral edema (fig. 3). The CT scan, however, does not provide direct information about ICP and blood flow dynamics. ICP measurement permits continuous computation of overall cerebral perfusion pressure (CPP, when $CPP = \overline{BP} - ICP$) and may forewarn of impending cerebral ischemia. Direct total and regional CBF measurements complement the above-mentioned monitoring methods. However, the cost and complexity of making CBF measurements limit their application to a few centers.

| ABBREVIATIONS	
ADH	= antidiuretic hormone
AER	= auditory evoked response
BP	= blood pressure
CBF	= cerebral blood flow
CNS	= central nervous system
CPP	= cerebral perfusion pressure
CT, CAT	= computerized axial tomography
EEG	= electroencephalography
EP	= evoked potential
ER	= evoked response
ICP	= intracranial pressure
NICU	= neurologic intensive care unit
PCAE	= post-circulatory arrest encephalopathy
PEEP	= positive end-expiratory pressure
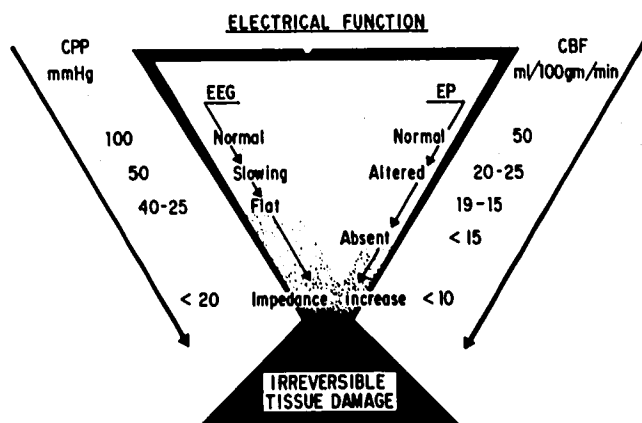
Fig. 4. CPP and CBF thresholds for changes in EEG and EP (evoked potential, ER, evoked response) activity. EP (ER) can be detected in the absence of a spontaneous EEG. However, neither measurement accurately predicts irreversible tissue damage. An increase in brain tissue impedance indicates Na and K transport failure and may immediately precede cellular death. (Modified from data in Astrup J, et al.: Cortical evoked potential and extracellular K^+ and H^+ at critical levels of brain ischemia. Stroke 8:51–57, 1977.)

CBF and Electrophysiology

In normal brain, relationships among CPP, CBF, and the electroencephalogram (EEG) exist, as shown in figure 4. Following a severe hypoxic–ischemic insult, these relationships are uncoupled.[20] For instance, post-ischemic cerebral hyperemia can be accompanied by an isoelectric EEG. The initial uncoupling of the CBF–EEG relationship is followed by a variable recovery time span, which is related to the severity of the insult. Thereafter, EEG activity resumes and CBF normalizes if irreversible tissue changes have not occurred.

There has been a resurgence of interest in applying electrophysiologic monitoring techniques to neurologic patients. The reasons are many. Continuous EEG monitoring provides a non-invasive measurement of cerebral function that can be performed in paralyzed, ventilated patients. The EEG can provide some localization of pathologic processes, and does so at a relatively low cost. Introduction of computer-assisted processing and displaying of EEG information has greatly improved its clinical utility.[21,22]

Recent investigative interests in monitoring of neurophysiologic function in man have focused upon cortical and subcortical evoked responses (ER). To elicit an ER, an appropriate stimulus is applied to a peripheral or cranial nerve and the electrical propagation of this stimulus in the brainstem and cerebral cortex recorded via scalp electrodes. Repeated stimuli and responses are electronically stored and averaged to screen out spontaneous EEG activity and background

noise. The responses are classified in terms of characteristic positive deflections (peaks) and interpeak periods (latencies). For instance, to record the auditory evoked response (AER), 2,048 standardized clicks are presented to each ear through a set of headphones.[23] Appropriately situated scalp electrodes then record the sequential potentials generated by successive structures along the auditory pathway.

Ablation studies in cats have provided anatomic localization of the seven characteristic waves.[24] These relationships are summarized in table 1. Similar localization schemes have been developed for the somatosensory and visual systems.

Initial experiences with this monitoring technique have been encouraging. Using a combination of visual evoked and somatosensory responses, Numoto found that an absence or reduction of the somatosensory responses from all extremities, combined with an abnormal visual evoked response, implied diffuse hemispheric abnormalities.[25] When the visual response alone was normal, then the brainstem could be implicated as the primary site of dysfunction. Our clinical experience with the AER is promising. As shown in figure 5, the serial acoustic response studies in a head-injured patient treated with EEG-suppressing doses of barbiturates (see below) were useful in monitoring the progression and remission of his brainstem dysfunction.

Head Injury: Prototype for Neuro-Intensive Care

The socioeconomic impact of trauma to the head is great, as it is a major cause of death and disability in young people. We have chosen the management of the head-injured patient as a prototype for neuro-intensive care. Many facets of treating head injury are common to other management problems in neurosurgical intensive care. In the past, nonspecific resusci-

TABLE 1. Correlation of Auditory Evoked Response Peaks and Normal Latencies with Anatomic Origin*

Wave Peak	Normal Latency (msec)	Anatomic Origin
I	1.9 ± 0.3	Auditory nerve
II	3.0 ± 0.3	Cochlear nucleus
III	4.1 ± 0.3	Superior olive
IV	5.2 ± 0.2	Areas in and about the nucleus of the lateral lemniscus
V	5.9 ± 0.3	Brachium of the inferior colliculus
VI	7.6 ± 0.3	Probably the medial geniculate
VII	9.2 ± 0.3	

* AER recorded in the cat by Buchwald and Huang.[24] Human latencies have been found to be similar.

tative efforts on behalf of head-injured patients seemed to increase the number of persistent vegetative survivals. The following represents what we consider to be a high standard of care for the head-injured. Improved neurodiagnostic techniques now permit therapy to be matched specifically with a particular neuropathologic process. In this circumstance, our clinical objectives for head-injured patients include: 1) rapid, accurate diagnosis, 2) early surgical treatment, 3) prevention of hypoxemia and hypercarbia, 4) normalization of cerebral perfusion, and 5) prompt recognition and management of medical complications. Figure 6 illustrates the treatment pathway employed in our institution.

INITIAL STABILIZATION

The severely brain-injured patient requires the same initial resuscitative efforts whether at a rural dispensary or a large medical center. The airway must be protected, if necessary by an endotracheal tube, and adequate oxygenation and ventilation assured. A large dose of dexamethasone (50–100 mg, iv) should be administered as soon as possible. A descriptive statement indicating the time and circumstances of the trauma and the patient's initial neurologic state should be entered on the chart.

INITIAL DIAGNOSTIC STUDIES AND THERAPY

On the patient's arrival at the regional center, a thorough neurologic examination and functional classification into one of four therapeutic groups is performed. Subsequent therapy is based upon the following classifications:

Group I: Minimal disturbance of consciousness or history of loss of consciousness.

Group II: Moderate disturbance of consciousness, but without focal neurologic deficit.

Group III: Significant alteration of consciousness combined with appropriate response to painful stimuli and focal neurologic deficit; cannot follow simple commands.

Group IV: Comatose, with obviously severe head injury.

Those falling into Groups I and II are closely observed in an intermediate care facility and may be scheduled for neurodiagnostic studies. Any clinical deterioration in these patients warrants an immediate study, followed by NICU admission and, perhaps, surgery.

Groups III and IV demand specialized monitoring and precautions, including placement of a Foley catheter and a nasogastric tube. In comatose patients,
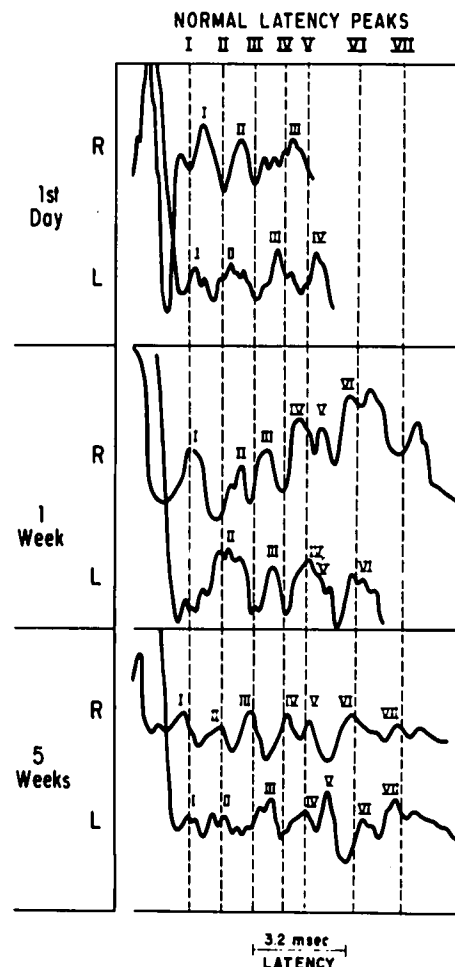

FIG. 5. A series of brain-stem auditory evoked responses in a comatose 27-year-old head-injured patient with a right-sided subdural hematoma. The first two recordings (first day and one week) were made during the administration of high-dose barbiturate therapy accompanied by an EEG frequency of less than 3 Hz. In the first record, the greater delay on the right side was thought to be the result of right cochlear nerve compression. Moderate brainstem dysfunction between the midbrain and the auditory connections in the pons is indicated by the generalized delay in peak performance. One week later, all peak latencies approached normal values, indicating improved brainstem function. At five weeks, when the patient had largely recovered from his head injury, the auditory responses were interpreted as normal.

blood samples should be obtained for a toxicology screen and glucose determination. Occasionally, ICP monitoring will be initiated in the emergency room, but in most cases, a CT scan will be performed as soon as possible. Frequently, muscle relaxation with controlled ventilation is necessary to obtain a high-quality scan. Usually, a single bolus dose of pancuronium (0.1 mg/kg) combined with thiopental–nitrous oxide–oxygen anesthesia suffices. Mannitol infusion and hyperventilation are used to control ICP before and during the neurodiagnostic procedure. During
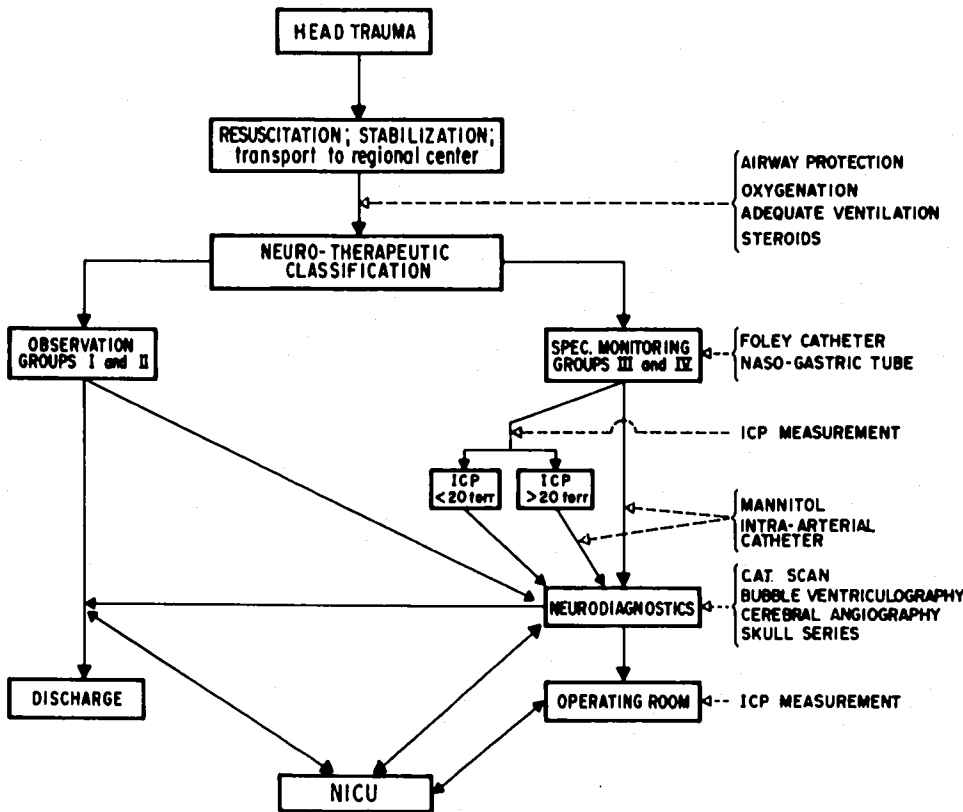
FIG. 6. Idealized disposition of head-injured patients who are treated at a regional care center.

NEUROTHERAPEUTIC CLASSIFICATION

GROUP	I	MINIMAL DISTURBANCE OF CONSCIOUSNESS OR HISTORY OF LOSS OF CONSCIOUSNESS
GROUP	II	MODERATE DISTURBANCE OF CONSCIOUSNESS BUT WITHOUT FOCAL NEUROLOGIC DEFICIT
GROUP	III	SIGNIFICANT ALTERATION OF CONSCIOUSNESS COMBINED WITH APPROPRIATE RESPONSE TO PAINFUL STIMULI AND FOCAL NEUROLOGIC DEFICIT, CANNOT FOLLOW SIMPLE COMMANDS.
GROUP	IV	COMATOSE WITH OBVIOUSLY SEVERE HEAD INJURY

performance of the CT scan (30–45 minutes), additional intravenous and arterial catheters can be placed for later use in the operating room or intensive care unit. When a CT scan is not available, other efforts at radiographic definition of the intracranial process, namely bubble ventriculography, cerebral angiography, or a skull x-ray series (calcified pineal shift) can be performed.

Lateralizing signs, in the presence of significant midline shifts (>5 mm) may necessitate surgical intervention.[26] The procedure is directed toward evacuation of clots and necrotic brain tissue. At the completion of the operation, when the brain is soft and readily contained by the calvarium, the skull flap is replaced. In the presence of swelling, some surgeons prefer to leave the dura open; the bone flap may or may not be replaced. Diffuse cerebral edema, without hematoma, may necessitate a decompressive procedure at some time in the acute post-injury phase.

In postoperative head-trauma patients, an intraventricular catheter or subarachnoid bolt is placed for ICP measurement.

NON-SURGICAL MANAGEMENT

ICP Reduction: Approximately 60 per cent of head-injured patients experience some intracranial hypertension (ICP > 15 torr).[26–29] Uncontrolled intracranial hypertension can result in secondary brainstem compression. Sixty to eighty per cent of patients who have transtentorial herniation and brainstem abnormalities die without evidence of a brainstem lesion directly related to the trauma.[27,30]

Osmotic diuretics, induced respiratory alkalosis, and corticosteroids have become the mainstays in the reduction of elevated ICP. Mannitol is the osmotic diuretic most frequently employed for ICP reduction. It effects water removal from normal, rather than edematous, brain.[31] Since its introduction by Wise and

Chater,[32] a dose of 1.0–1.5 g/kg has been considered standard. This dose of mannitol represents an extrapolation from an average dose of urea found effective in earlier studies, and is based upon molecular size differences. When treating patients with severe intracranial hypertension, frequent administration of this dose of mannitol can induce a hyperosmolar state (serum osmolarities > 350 mOsm). Extreme hyperosmolarity can cause CNS dysfunction and death. Furthermore, in patients with widespread blood–brain barrier disruptions, mannitol penetrates into the brain, aggravating rather than ameliorating existing cerebral edema.[33]

Recognizing these problems in osmo-therapy, we studied the efficacy of smaller doses of mannitol in a series of severely head-injured patients with marked intracranial hypertension. A gradient of 10 mOsm, readily achieved with a 0.25 g/kg dose, was associated with the same initial reduction in ICP as a larger dose when both doses were administered over a 5-min period. Control of ICP was maintained for a slightly longer period (4–5 hours vs. 3–4 hours) in patients given the larger dose of 1 g/kg. We concluded that smaller doses, given slightly more frequently, are effective in reducing ICP while avoiding the risks of hyperosmolarity.

Controlled hyperventilation is a recognized treatment for intracranial hypertension.[34] The acute beneficial effects of moderate hypocapnia (Pa_{CO_2} 25–30 torr) on reducing cerebral blood volume and ICP have been well documented. There is less agreement as to the effectiveness of long-term hyperventilation. With time, CSF pH returns toward normal, and this may attenuate the cerebrovascular constriction induced by continued hyperventilation.[35] When ICP control is lost at a previously established low Pa_{CO_2}, a trial of more extreme hypocapnia may be indicated.

Until recently, the effectiveness of steroids in management of traumatic cerebral edema had not been established. Two well-controlled studies[36,37] demonstrate a remarkable increase in the number of survivals among head-injured patients treated with very high doses of dexamethasone. In a double-blind study, Gobiet et al.[36] found that patients given high doses of dexamethasone had a 23 per cent mortality rate, compared with 41.5 per cent in the low-dose group, and 45.5 per cent in the placebo group. Figure 7 gives the dose schedules and graphic results of this study, in which significantly fewer episodes of intracranial hypertension occurred in patients treated with high doses of dexamethasone. In an independent study, Faupel et al. reported a similar increase in survival with high-dose steroid therapy.[37] The increased survival rates in both studies were associated with high-quality recovery.[36,37]
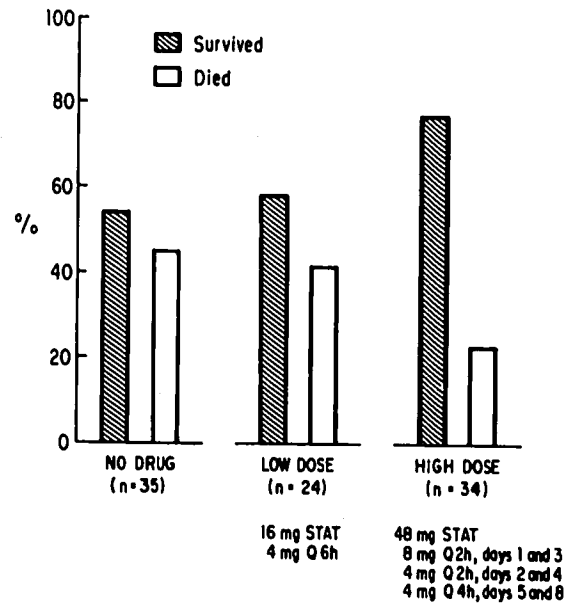

Fig. 7. Summary of effects of dexamethasone on overall survival in 93 head-injured patients studied by Gobiet et al.[36] Survivals in the non-treatment and low-dose-therapy groups did not differ significantly. However, survival rates in both of the groups were significantly lower than that of the high-dose-therapy group.

It is appropriate to issue some practical guidelines concerning ICP control. Head position is critical. Neurosurgeons have long recognized that the head-up position improves venous drainage and thereby contributes to acute ICP reduction. As another manifestation of this phenomenon, it has been demonstrated that extreme rotation of the head may stimulate a sudden increase in ICP.[38,39] This kind of head-turning commonly occurs in patients maintained on mechanical ventilation.

Cerebral venous pressure and ICP can also be elevated by positive end-expiratory pressure (PEEP).[40] In hypovolemic patients PEEP can also decrease arterial pressure. These changes can summate to decrease CPP profoundly. Figure 8 summarizes the effects of PEEP upon CPP in 12 head-injured patients with intracranial hypertension. All patients had coexisting respiratory failure (of undetermined etiology) as evidenced by alveolar–arterial oxygen gradients >200 torr. When PEEP (4–8 cm H_2O) was applied, ICP increased by 10 torr or more in six patients. The CPP fell in seven patients, rose in four others, and remained unchanged in one patient. The CPP gains were small (<6 torr), while losses were much greater (6–35 torr). Interestingly, when the ICP data are examined alone, it appears that seven of the 12 patients experienced reductions of ICP with PEEP therapy.

During endotracheal toilette, precipitous increases in ICP can occur. These are associated with overzeal-
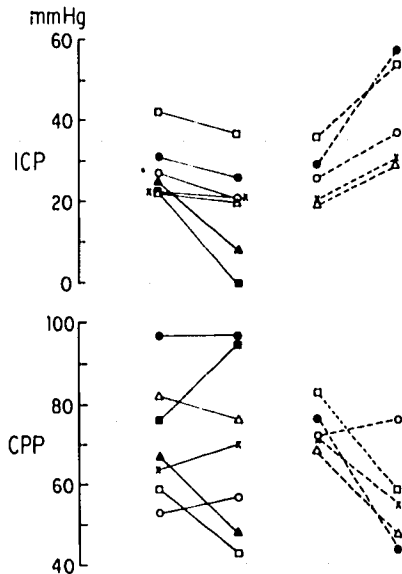
Fig. 8. Graphic summary of the effects of modest positive end-expiratory pressure (PEEP) (4–8 cm H$_2$O) on ICP and CPP in 12 patients with acute head injuries and respiratory failure. Seven patients experienced ICP reductions and five patients showed ICP elevations with application of PEEP. Despite these reductions in ICP, seven patients had decreases in CPP.

ous manual hyperventilation (in effect, PEEP) and prolonged suctioning, leading to Pa$_{CO_2}$ elevation and arterial hypertension secondary to the noxious stimulation. In patients who have highly reactive and critically elevated ICP, respiratory care should coincide with periods of maximal sedation–narcosis, muscle relaxation, and intracranial compliance.

Normal ICP monitoring standards can be misleading when the bony flap has not been replaced after craniotomy. In this situation, a marked shift of the intracranial contents can occur at ICP levels at or below the established norm of 15 torr. Brain deformation in such situations can be extreme and associated with clinical deterioration. It is suggested that absolute ICP levels are difficult to interpret when the skull is open. Changes in the ICP, combined with palpation of the bulging flap, may be more informative.

Blood-pressure Control: Cushing believed that the arterial pressor response to intracranial hypertension was homeostatic.[41] Observations now suggest that arterial hypertension in the presence of cerebral trauma can lead to enhanced cerebral edema formation and intracranial hypertension.[42] These deleterious effects can be primarily attributed to two factors. In patients who have low intracranial compliance and defective CBF autoregulation, an increase in blood pressure (BP) increases cerebral blood volume. Within damaged brain tissue, the blood–brain barrier is disrupted and a high BP increases water and protein leakage

into the brain.[43] Adequate sedation and antihypertensive therapy are directed toward maintaining reasonable BP control. Such treatment should not be undertaken in the absence of ICP monitoring, which allows titration to an acceptable CPP (usually 60–70 torr).

Medical Complications

Adequate cerebral perfusion presupposes a stable cardiovascular system; therefore, arrhythmias, hypotension and ventricular failure are treated vigorously. While the use of hypothermia in the treatment of acute cerebral injury is out of vogue, we emphasize that hyperthermia must be avoided because intracranial hypertension may preclude the normal augmentation of CBF to meet the elevated nutrient requirements of the hyperthermic brain.

Fluid and electrolyte imbalances frequently complicate the management of the comatose head-trauma and/or postoperative patient. Both excesses and deficiencies in antidiuretic hormone (ADH) secretion, *i.e.*, the syndrome of inappropriate ADH and neurogenic diabetes insipidus, may add to the already delicate problem of water balance. Frequent serum and urinary electrolyte and osmolarity determinations and daily patient weighings help to titrate fluid therapy. Hypotonic solutions, *e.g.*, dextrose 5 per cent in water, should be avoided, as glucose metabolism results in free water, which enters the brain.

Prognostic Indices

More than 50 per cent of comatose patients with diagnoses of stroke, post-cardiac-arrest encephalopathy (PCAE) or head injury remain dependent, enter a persistent vegetative state, or die. Allocation of intensive care resources makes the development of reliable neurologic prognostic indices imperative. Efforts in this direction, although numerous, have been frustrating. Virtually every clinical sign, laboratory result, and vital statistic has been evaluated as a prognostic tool. Considerable controversy still exists in defining brain death, let alone in predicting this outcome early.[44–45]

CLINICAL EXAMINATION

In one area of prognostication, general agreement exists: early neurologic classification based upon the bedside physical examination remains the best predictor of outcome in head-injured and post-cardiac-arrest patients.[13,55,56] From a prospective study of more than 100 patients examined within 12 hours of the onset of coma due to metabolic abnormality, stroke, cardiac arrest, or infectious encephalitis, Caronna *et al.* concluded that it should be possible

to develop accurate criteria to predict neurologic outcome.[57] They evaluated a combination of the coma profile, oculocephalic reflexes, and breathing activity. Absent oculovestibular and motor responses to noxious stimuli predicted a poor prognosis: 94 per cent of such patients died. Walker *et al.*, in a retrospective study, found that prolonged apnea and unresponsiveness lasting more than 15 minutes following cardiac arrest were associated with a mortality rate of more than 90 per cent.[51] Teasdale and Jennett employed the Glasgow coma score to predict outcome in a series of 92 patients who had sustained trauma to the head. They correlated an overall score of 7 or less (of a possible 15) within the first 24 hours of injury with poor qualitative survival.[10] Utilizing multiple linear-regression analyses of a large number of neurologic and non-neurologic variables, Tofović and co-workers were able accurately to predict (85 per cent confidence level) outcome based upon the type of insult and initial clinical examination in a group of 200 head-trauma patients.[56]

INTRACRANIAL PRESSURE

Vapalahti and Troupp reviewed a series of 15 head-injured patients with sustained ICP's of more than 60 torr and found no recovery of social function, except in two children.[58] In 12 of the patients, sustained ICP waves were ultimately associated with respiratory arrest and death. In support of Troupp's findings, Bruce[59] observed that an ICP of 70 torr was associated with a poor prognosis. However, Tindall and Fleischer[60] failed to confirm the prognostic importance of ICP.

The pattern of intracranial tension changes may also have prognostic implications. A number of centers have developed computer-assisted ICP data storage and retrieval systems.[1,16–19] McDowall and associates analyzed ICP distributions about a modal value. "Skewing" of the ICP distribution histogram toward a higher modal value provided an early warning of an impending and major sustained ICP increase.[16]

CARDIOVASCULAR SIGNS

Overgaard *et al.*[13] found that when maximum systolic pressure exceeded 200 torr, 70 per cent of their patients died. In our experience, in an otherwise unstimulated comatose patient, fluctuations of BP and pulse rate occur long before the appearance of Cushing's triad (↑BP, ↓pulse, ↑ICP). These changes herald cerebral ischemia and may, therefore, indicate the need for ICP monitoring. ECG changes are often recorded in the brain-injured. The significance of these abnormalities remains unknown. However,

Drory *et al.*[61] described three ECG characteristics in brain death: 1) the presence of a J-wave that is isoproterenol-sensitive, 2) ST-T depression of nonspecific ischemia, and 3) failure to respond to atropine (2 mg, iv).

CBF AND CEREBRAL METABOLISM

Most cerebral insults result in alterations in cerebral blood flow and metabolism. In the extreme, total absence of CBF is one of the indices used to define brain death. The unique prognostic value of isolated CBF measurements has not been established. However, in a series of patients studied in the University of Pennsylvania Head Injury Center, a reduction of flow in the fast compartment to less than 40 ml/100 g/min was associated with death in 50 per cent of the patients.§

More prognostic information may be gathered by combining CBF and cerebral metabolism determinations. Hass[62] states that brain death or failure to recover consciousness occurred in all of his head-injured patients who had CMR_{O_2}'s less than 1.2 ml/100 g/min. Seventy-five per cent who had values of 1.2–2.2 ml/100 g/min died; no death occurred when CMR_{O_2} exceeded 2.7 ml/100 g/min. Ingvar[63] found similar metabolic depression ($CMR_{O_2} = 0.7$ ml/100 g/min) in apallic patients and those who had discrete reticular formation infarction. Thus far, CBF/brain metabolism data in head-injured patients are preliminary, and their role in prognostication remains speculative.

OTHER PROGNOSTIC INDICES

Electrophysiology: In the absence of CNS depressants and hypothermia, a sustained isoelectric EEG recorded with high amplification (2 μv/mm) suggests neocortical death.[52] The AER, which has emerged as a valuable diagnostic adjunct in delineating brainstem disease, has yet to prove its value as a prognostic tool.

Respiration: A terminal relationship between ataxic respirations and lower pontine failure is not disputed. The predictive value of other less severe respiratory abnormalities is controversial.[64,65] In head-injured persons, Vapalahti and Troupp found that persistent Cheyne-Stokes respiration was associated with a persistent vegetative outcome.[58]

Temperature: Thermo-instability is an ominous sign in the acutely brain-injured. Tindal[5] found that persistent hypothermia, especially when accompanied by hypotension, was a grave sign of irreversible hypothalamic damage. Vapalahti and Troupp[58] linked sustained hyperthermia (>39 C) with a persistent vegetative status.

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§ Obrist W, Langfitt TW: Personal communication.

TABLE 2. Differences among Three Types of Neurologic Disease Leading to Cerebral Ischemia

	Stroke	Post-circulatory-arrest Encephalopathy	Head Injury*
Onset pattern	Abrupt Regional	Abrupt Pan-encephalic	Variable Multifocal
Cause of ischemia	Intravascular occlusion	Extracranial loss of perfusion pressure	Extravascular compression
Time course	Irreversible changes in 2–3 hours	Irreversible changes in 5–15 minutes	Primary changes with impact—secondary changes in 24–72 hours
Recovery factors	Development of adequate collateral circulation	Rapid restitution of cardiovascular stability	Timely prevention and/or reduction of intracranial hypertension

* Complicated by ICP > 20 torr.

Age: It is generally thought that in severely ill neurologic patients more than 20 years of age, the potential for neurologic recovery is reduced.[13,56,58] Becker *et al.*[26] suggest that, in the older NICU patient, death may result from medical complications as often as from the primary neurologic disorder.

Barbiturates and Neurologic Intensive Care

Barbiturates have been used to control ICP in head-injured persons and have been shown to reduce ischemic brain damage in monkeys following stroke and cerebral circulatory arrest. However, the mechanism(s) by which barbiturates ameliorate ischemic cerebral disease is unknown. Table 2 summarizes some of the differences among stroke, post-circulatory-arrest encephalopathy (PCAE), and head injury. It is critical to recognize these differences, because barbiturates may be effective through different mechanisms in the evolution of a specific neuropathologic process. In this light, we first describe the pathologic circumstances associated with each type of brain ischemia, and then indicate the influence of barbiturate therapy upon these states. Possible mechanisms for barbiturate protection of ischemic brain are reviewed.

Stroke

In primates and cats, retro-orbital occlusion of the middle cerebral artery produces a lesion that is generally larger than that observed in thrombosis of the human middle cerebral artery.[66–68] This occlusion causes cerebral infarction in about 80–90 per cent of the animals and permanent neurologic dysfunction in 60–70 per cent. The magnitude of intracranial pressure elevations following experimental stroke parallels the size of the infarct.[69] When the vascular clamp is removed within two hours, the expected functional neurologic deficit can be obviated or greatly reduced.[66–68,70] This indicates that therapy initiated within two hours of the onset of stroke may be effec-

tive in reducing tissue destruction. While microvascular changes may contribute to local re-perfusion deficits in this focal stroke model, neuronal changes indicative of cell death can precede development of local "no-reflow" areas.[71]

Smith and Michenfelder and their co-workers, employing middle cerebral artery occlusion techniques in dogs and primates, have independently shown that barbiturates reduce the anticipated area of brain infarction, morbidity, and mortality.[72–74] In the canine studies of Smith *et al.*, pentobarbital (56 mg/kg), given *before* middle cerebral artery occlusion, and thiopental (40 mg/kg), administered either *before* or 15 minutes *after* the occlusion, reduced the mean area of hemispheric infarction from 10 per cent to less than 3 per cent.[72] In another series of studies in primates, Hoff and Smith found that the protective effect of pentobarbital, given *prior* to occlusion of the middle cerebral artery, was dose-related. The area of infarction in these studies decreased as the dose of pentobarbital was increased from 60 to 120 mg/kg.[73] However, great difficulty was encountered in maintaining cardiovascular stability at the higher doses. This indicates that extreme caution must be exercised in establishing equivalent human dose schedules, especially in the presence of cardiac disease.

Michenfelder and Sundt employed pentobarbital treatment of stroke in a more clinically relevant dose schedule.[74] Thirty minutes following middle cerebral artery occlusion in paralyzed, sedated Java monkeys, a relatively low dose (14 mg/kg) of pentobarbital was given. This was followed by 7 mg/kg given every two hours to maintain a 48-hour period of anesthesia. Again, statistically significant reductions in cerebral infarction, morbidity and mortality occurred in the barbiturate-treated group.

Post-circulatory-arrest Encephalopathy

It is believed that neurologic damage ensues after 5 minutes of circulatory arrest in unanesthetized, nor-

mothermic man. However, the spectra of survival, neurologic function, and neuropathologic consequences resulting from experimental global ischemia are broad.[75-79] In some laboratory models of global ischemia, a 3-5-minute arrest causes minimal multi-focal neuronal loss. In other models, functional survival of a few neurons is possible after 60 minutes of absent CBF.[79] Thus, the neuropathologic spectrum following experimental ischemia of the total brain ranges from an insult exposure of 3-5 minutes, where some cells are irreversibly damaged, to ischemia for as long as an hour, where some cells survive with enough integrity to demonstrate functional electrical activity. It is the time gap between these extremes that presents the clinical challenge in treating patients who have acute ischemic brain disease. For example, in monkeys, functional neurologic survival associated with minimal tissue abnormalities followed 14 minutes of total cerebral circulatory arrest.[77]

The differences in the neurologic impact of circulatory arrest between man and monkey may relate to intra- and extracranial physiologic events occurring during and following the arrest. In monkeys that have healthy hearts, the return to cardiovascular stability is normally a step function.[76,77] When cerebral perfusion pressure is not restored rapidly in monkeys due to cardiac decompensation, neurologic abnormalities are greatly increased.[77] Post-cardiac-arrest victims often fall into the latter category. Low post-arrest CPP's may aggravate the microcirculatory dysfunction that begins in the arrest period.[80] Induced arterial hypertension in post-circulatory-arrest dogs can reduce brain damage.[75] This indicates that cardiovascular performance in the post-arrest period may contribute to the quality of survival of the brain.

Most post-ischemic therapeutic regimens are directed at improving cerebral blood flow and/or reducing the brain's metabolic requirements. Improvement of cerebral blood flow is sought by elevating total or local cerebral perfusion pressures, altering cerebral vascular resistance, or improving the rheologic properties of the blood.[75] Cerebral metabolism may be reduced with hypothermia. Following induction of hypothermia to 15 C, infants can tolerate as much as an hour of circulatory arrest without gross neurologic dysfunction.[81] Hypothermia to 30-32 C is suggested as an adjunct to post-cardiac-arrest supportive care, though its efficacy in this situation remains unproven.

Recognizing the protective action of barbiturates in stroke, the University of Pittsburgh group treated monkeys subjected to 16 minutes of selective cerebral circulatory arrest with large doses of thiopental.[76] Thiopental was administered 5, 30, and 60 minutes following recirculation, and the animals were given

TABLE 3. Effects of Pentobarbital in the Treatment of 25 Comatose Head-injured Patients

	Comment
Pentobarbital responders (n = 19) 13	(ICP reduced by 10 torr or more within 10 minutes) ICP reduced to <15 torr without significant BP decrease (<5 torr)
7	Late loss of barbiturate ICP control
10	Return to productive life
4	Deaths
Pentobarbital non-responders (n = 6) 1	Persistent vegetative state
5	Deaths

intensive care for five to seven days. Thiopental (90 mg/kg) given 5 minutes after cerebral circulatory arrest was associated with remarkable neurologic recoveries compared with untreated controls. Delaying therapy for 30 to 60 minutes resulted in reductions in therapeutic efficacy, even when the dose was increased to 120 mg/kg. These data are preliminary and originate from only one laboratory. Although they indicate that the neurologic damage following 15 minutes of cerebral circulatory arrest can be dramatically reduced by barbiturates, they do not provide clear-cut guidelines for clinical applications.

Head Injury

Recoveries of head-injured patients may be complicated by increased intracranial pressures. Provided that surgical lesions have been treated adequately, intracranial hypertension is due to cerebral edema and/or increased cerebral blood volume caused by loss of CBF autoregulation. When the ICP rise is sustained, a pathophysiologic cycle can be initiated wherein intracranial hypertension reduces cerebral blood flow, leading to more tissue ischemia. Eventually, either the ICP becomes so high that CBF is drastically reduced or arrested, and/or compression and herniation ischemia of vital brain structures occurs. Therefore, intracranial hypertension caused by vascular engorgement and edema can lead to generalized or multifocal cerebral ischemia. The latter develops over a relatively prolonged period compared with stroke or PCAE.

Following the observation that thiopental could abruptly reduce increased ICP during anesthesia,[82] we employed barbiturates and hypothermia to reduce persistently elevated ICP's in five critically ill patients.[83] Pentobarbital was given to achieve plasma levels of about 3 mg/100 ml in combination with hypothermia to 30 C, and this treatment was maintained for five days. ICP's were reduced and unexpected
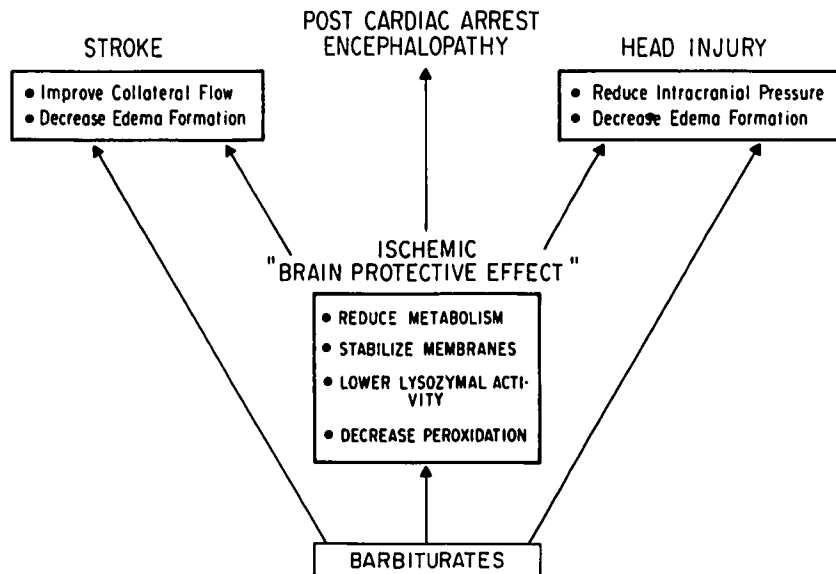
Fig. 9. Schematic summary of the proposed mechanisms by which barbiturates protect ischemic brain tissue following stroke, cardiac arrest, and head injury.

neurologic recoveries occurred in this group. Other investigators have confirmed that thiopental is useful in reducing ICP in intensive care patients.[84]

Based on these preliminary results, we evaluated the effect of pentobarbital, without hypothermia, as an adjunct for ICP control in a group of 25 adult comatose head-injured patients. Prior to barbiturate loading, all had significant midline shifts (>1.0 cm) and intracranial hypertension (ICP > 40 torr for >15 minutes) despite aggressive therapy with hyperventilation, steroids, and mannitol. Table 3 summarizes our results.

The initial pentobarbital loading dose (3–5 mg/kg) effectively reduced ICP in 76 per cent of the patients. Chronic pentobarbital treatment, associated with blood barbiturate levels of about 2 mg/100 ml and EEG activity in the 2–5-Hz range, permitted long-term ICP control in 12 patients. Prior to barbiturate therapy, the average dose of mannitol needed to maintain the baseline ICP below 30 torr was 4.5 g/kg/day. In patients responding to barbiturates, the daily mannitol requirement was reduced to 0.5 g/kg; it increased to 5.9 g/kg in the non-barbiturate-responders. In some, the acoustic evoked responses improved during barbiturate-induced coma (fig. 5). These observations further confirm our opinion that barbiturates are useful in the care of head-injured patients, and indicate that further evaluation is needed.

Mechanisms of Barbiturate Protection

We do not understand how barbiturates act on ischemic cerebral tissue. A number of theories explaining the brain-protective effects of barbiturates have emerged. These are summarized in figure 9.

Initially it was presumed that barbiturates protected the ischemic brain by reducing its metabolic requirements. Although barbiturates slow cerebral energy-state depletion during critical reductions in CBF,[85,86] it is reasonable to assume that this protection is finite and dependent upon severity and duration of ischemia. There is little indication that the modest perturbations in tissue carbohydrate intermediates and high-energy compounds caused by barbiturates will result in a lasting protective effect.[87] Most of the reduction in cerebral metabolism caused by barbiturates occurs at low doses and prior to marked suppression of spontaneous cortical electrical activity.[88] However, the greatest ischemia protection in experimental PCAE and stroke occurs at extremely high doses.[72,73,76] This lack of a parallel dose relationship between barbiturate amelioration of cerebral ischemic damage and metabolic depressive properties suggests that other mechanisms, aside from a simple reduction in brain energy requirements, are associated with its protective effect.

Ischemia may be characterized by an increase in tissue free radicals. These free oxygen radicals are known to cause lipid peroxidation and destroy lipid-rich membranes. Siesjö et al. suggest that the free radical-scavenging ability of barbiturates may be related to their cerebral ischemia-protecting actions. If this were the case, then other antioxidants, without the side effects associated with barbiturate therapy, might also protect ischemic brain.[87]

In stroke, barbiturates may offer some protection to the regionally ischemic zone by diverting blood flow to that area. Increased cerebrovascular resistance, caused by barbiturates in healthy areas of brain, may shunt blood toward ischemic regions that have a fixed low vascular resistance, and improve collateral flow

development.[72,89] Halothane, on the other hand, lowers cerebrovascular resistance and increases the area of infarction in experimentally induced stroke.[72] Hyperventilation therapy should have vascular actions similar to those of barbiturates. However, studies in stroke patients do not support the use of induced hypocapnia in the treatment of this disease.[90]

The most straightforward explanation of how barbiturates act to protect ischemic brain in certain instances may be found in their ability to reduce high ICP. The mechanism of barbiturate-induced ICP reduction is related to the ability of barbiturates to increase cerebrovascular resistance and lower cerebral blood volume. Therefore, they decrease ICP, increase CPP, and may actually improve cerebral blood flow. Whether this occurs in both normal and ischemic tissues is unknown.

Large infarcts and head injuries are frequently accompanied by cerebral edema. Barbiturates have been shown to reduce the formation of cerebral edema following an experimental cryogenic cortical lesion.[91] This may result from barbiturate enhancement of precapillary vascular tone, which reduces the hydrostatic pressure head in damaged areas. In our head-injured patients receiving barbiturates, the reduction in the absolute blood pressure level, as well as in noxious stimuli-related arterial pressure fluctuations, may have the same effect in reducing edema formation.

In Summary: The evidence that barbiturates reduce the pathologic impact of global cerebral ischemia is based upon reports of animal experiments from three laboratories. The total number of primate trials in stroke and PCAE is fewer than 100, and we have, at best, only a fragile grasp on the mechanism of this presumed protective action. More studies are needed before large-scale clinical trials begin.

The environment for additional clinical trials of barbiturates for ICP reduction is different. Here the therapeutic goal is ICP reduction, and barbiturates can accomplish this in the operating room as well as in the intensive care unit. Besides providing a rapid, but transient, reduction in ICP (thiopental bolus), barbiturates can control ICP for prolonged periods in certain patients. In these situations, one does not have to cite a special ischemic brain-protective effect as a reason for employing barbiturates, although one may exist.

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