

ELECTRICAL TREATMENT OF COMA

**Recent Experience in the
Eastern United States and Central Japan**

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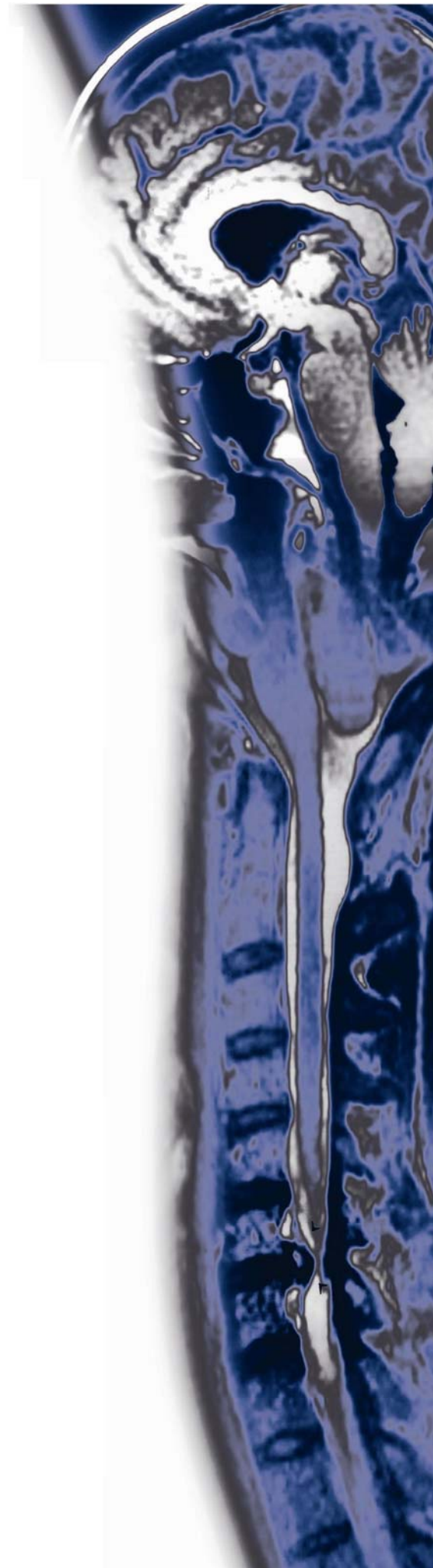


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I. INTRODUCTION

In the third millennium, the useful applications of electricity abound. So accustomed are we to multi-tasking:

- We talk on a cell phone while reading e-mail for the
- few minutes a frozen steak is thawing in a microwave,
- all interrupted by a beeper. . .

The electronic extensions of our brain and body have stretched our abilities which are driven by internal electrochemical reactions. The complicated but finite digital real world processing of information has retrained our infinite minds. No longer do we plan and work in a linear sequence. The cerebrum mimics computer brains. We think in parallel circuits while racing forward and backward to amplify the truth that emerges. But just as sophisticated modern computers can crash and lose data, the human brain can be seriously injured, electrically and structurally, by trauma. Brain trauma in the third millennium comes in two species:

- blunt head injury from motor vehicle collisions and
- penetrating trauma from civilian gunshot wounds.

Neurological salvage is more predictable and more successful in diffuse brain injury resulting from a collision. Usually there is more structural damage when the injury is caused by the violent penetration of a missile.

Just as electricity has been our servant and instructor in the daily world, electrical stimulation can be our rescuer in the post-traumatic coma world.

There exists a certain pessimism regarding the treatment of severe closed head injuries. Physicians are reluctant to offer much hope to the families of the acutely comatose brain injured victim. The patients are often teenagers, inexperienced drivers involved in high speed collisions. Usually there are multisystem injuries that add to the seriousness of the condition.

But deep coma, with sluggish pupils, and abnormal motor responses governed by the brainstem, does not universally indicate a poor outcome. Clinical and computerized tomography (CT) findings have been used to predict outcome. With the advent of intracranial pressure monitoring, and regulation of the elevated pressure by diuresis and chemically induced coma, serial Glasgow Coma Scale (GCS) scores may not be reliable prognosticators in the first few days of coma. In the absence of severe anatomical damage on the initial and follow-up CT scans, but in the presence of cerebral edema, a favorable recovery may still be possible for the patient.

This chapter will present traditional measures of prognosis and standard treatments for closed head injury and a discussion of the anticipated outcomes. This will be followed by a presentation of a novel treatment of coma: electrical stimulation.

Implanted electrical stimulation of the dorsal column cervical spinal cord has been used for over a decade, mainly in Japan, to treat the persistent vegetative state. In the United States

superficial electrical stimulation of the right median nerve has been used for the treatment of acute post-traumatic coma since the early 1990's.¹

A. HISTORY OF ELECTRICAL STIMULATION

Electricity's potent physiological effects have been recognized for most of recorded history. Almost two thousand years ago between 40 A.D. and 100 A.D., the Romans and Greeks adopted electric therapy. The torpedo fish, an electric ray, was applied to patients complaining of headache, hemorrhoids, gout, depression, and epilepsy.² In the mid 1800's, an English surgeon, John Birch, reported the use of electrical stimulation to treat a patient with a hand injury for the purpose of restoring function and decreasing pain.³

The medical advent of neurostimulation in pain control can be attributed to the work of Melzack and Wall in 1965⁴. Stimulation as a means of muscular control and improving function has been researched through the past three decades by Cooper, Hildebrandt, Keith, Kralj, Marsolais, Mortimer, Peckham, Petrofsky, Salmons and Verbova, Vdovink, and others. Most of the research has focused on the clinical and functional applications of electrical stimulation for the control of the paralyzed muscles of persons who are quadriplegic or paraplegic, and stroke victims.

Functional electrical stimulation has been used to assist paraplegic patients in walking.⁵ Much research has been devoted to restoring basic functions to the quadriplegic hand. Grasping objects under computer control has been developed by Peckham, Mortimer, Marsolais, Cooper, McElhaney, and Han.⁶ In the treatment of motor neuron deficits, electrical stimulation is used to mimic cerebral control of muscle fibers.

Implanted or transcutaneous electrodes transfer current to local tissues that is communicated through the axons of nerves. The action potential begins when the plasma membrane of the axon allows passage of certain ions. The ions diffuse along concentration gradients, electrically induced currents flow in complete circuits, and a capacitive current is established.⁷ Once a capacitive current is established in the axon of a nerve, an action potential indistinguishable from those initiated by physiological mechanisms is propagated.⁸ The resultant potential travels down the axon independent of the electrical stimulation.

When the action potential reaches the neuro-muscular junction, acetylcholine streams across the cleft interacting with receptors on the muscle end-plate. The signal is transduced into the muscle fibers through the T-tubules, Ca^{++} is sequestered from the sarcoplasmic reticulum, the actin/troponin/tropomyosin complex is activated, and the muscle contracts. The amplitude and pulse width of the current must be sufficient to exceed the threshold of excitability.⁹

Electrical stimulation induces changes in levels of neurotransmitters, some neural hormones, and cerebral blood flow. Direct stimulation of the nucleus raphe dorsalis was shown to reduce nociception through increased release of serotonin.¹⁰ Pain reducing stimulation often involves chronic stimulation of the spinal cord in conjunction with narcotic treatment. Stimulation of the

thalamus, periventricular gray, and the nucleus raphe dorsalis of the brain have been shown to successfully produce results in pain management.¹⁰

An increase in neurotransmitter release has been hypothesized to mitigate the improvement of patients with Alzheimer's type dementia undergoing transcutaneous electrical stimulation.¹¹

Significant increases in norepinephrine and dopamine in the cerebrospinal fluid and increases in cerebral blood flow have been observed in comatose individuals receiving dorsal column electrical stimulation.¹²

B. ELECTRICAL STIMULATION TECHNIQUES

Two contraindications to the use of transcutaneous electrical stimulation have been stated by the Federal Food and Drug Administration.¹³

TENS (transcutaneous electrical nerve stimulation) should not be used for patients with a demand cardiac pacemaker nor should it be applied over the carotid sinus. Special precaution should be taken with patients and young children with cognitive dysfunction.⁷

Possible adverse reactions to transcutaneous stimulation are infrequent but could include skin irritation from the electrical reaction or allergic reactions to the electrodes, the lubricant, the tape, or the mechanical irritation of the electrodes. Close monitoring is needed for the skin and denervated areas where the patient would not feel the electrical stimulation. Burns could occur if the current density is too high under the electrode.⁸ Electrical stimulation over an electrical implant including pacemakers and defibrillators could interfere with the function of those devices. However, electrical stimulation done at an area away from the implant could be done safely.¹⁴

The safety of TENS during pregnancy has not been established. It was stated by Nelson, "Effects on patients with cerebral vascular accidents, transit ischemic attacks, epilepsy, and seizure disorders, or stimulation on the head or upper cervical regions, are not well established thus close monitoring is required."¹⁴

The manual for the Focus® electrical stimulator (Empi, Inc., St. Paul, Minnesota) stated that neuromuscular electrical stimulation (NMES) is contraindicated for use in patients with implanted demand type cardiac pacemakers or defibrillators.¹⁵ They also suggest caution when stimulating patients with a history of heart disease or epilepsy. NMES should be applied with caution to patients with cardiac conditions such as arrhythmia or conduction disturbances.⁷ Empi also listed contraindicated locations as placement over the carotid sinus region of the neck, transcerebral placement and transthoracic locations.

Electrotherapy for enhancing neuromuscular performance has greatly increased over the past 20 years in the United States.¹⁴ Prior to the mid 1970's electrical stimulation was used mainly to treat atrophy in skeletal muscles. Neuromuscular electrical stimulation (NMES) on the skin over a motor point of the muscle produces active potential in the muscle or nerve fiber identical to the potential generated by a nerve. The evoked potential travels in both directions along the

nerve fiber from the site. NMES involves stimulating peripheral nerves with a mixture of motor and sensory fibers.

For patients who were unable to contract a specific muscle, NMES activates the muscle and may help with muscle reeducation. However, motor units must be intact for this to be useful. Spasticity may be reduced by applying the NMES alternately to the spastic agonist muscle and the antagonist and the combined effect may give reciprocal inhibition, muscle fatigue, and therefore help reduce the spasticity. However, the effectiveness of NMES in the treatment of spasticity is unpredictable.^{14,16}

NMES has been approved by the FDA as safe and effective for treatment of disuse atrophy, increasing in maintenance of range of motion and muscle reeducation and facilitation.^{7,17} Other areas of use include spasticity reduction or orthotic substitution and augmentation of motor recruitment.⁷

The asymmetrical biphasic square waves are suitable for smaller muscles. The symmetric biphasic pulse is for large muscle groups. The duration of 0.3 milliseconds (300 microseconds) is for muscle stimulation.⁷ The frequency in the range of 10-20 pulses per second causes a sensation of vibration or incomplete tetany. Above 30 pulses per second, the muscle contractions become fused (tetanic) so that a smooth contraction is produced.⁷

The amount of resistance (impedance) for dry skin is in the range of 500,000 ohms and 1,000 ohms for wet skin. For our projects we have considered the resistance of the skin under the lubricated electrodes to have an impedance of 1,000 ohms.¹

Various duty cycles are used for balancing the on time and the off time to prevent fatigue. A 1 to 5 ratio of on and off is recommended for the initiation of an NMES program.⁷ For nerve stimulation of coma patients a 1:2 cycle of 20 seconds on and 40 or 50 seconds off has proved useful for the last decade.^{1,18} Up to 100 milliamps of surface stimulation has been used for stimulation of the quadriceps in paraplegics.⁸ Much lower levels are used when the stimulation is over the skin at the wrist.

For median nerve stimulation, the range of 10-20 milliamps has been used as tolerated in the University of Virginia and East Carolina University studies.^{1,18} The delivered dose to the nerve would be measured in microamps. In working with stroke patients, with shoulder subluxation, amplitudes of 30-35 milliamps have been used for muscle strengthening.⁷

Electrical current that is transported through a biological conductive medium causes three effects: electrochemical, electrophysical, and electrothermal. The electrophysical effect could also be termed electrokinetic.¹⁴ Sodium and potassium ions move across the semipermeable cell membrane (of the muscle) producing the action potential which results in the contraction of the skeletal muscle. With peripheral nerve stimulation, afferent stimulation of the sensory nerves to the spinal cord, brainstem, thalamus and cerebrum occurs.

Surface, as opposed to implanted, electrodes are used for the acute coma stimulation for the ease of application, economy, and noninvasive features. Higher currents are required from the stimulator for transcutaneous stimulation than for implanted devices.

Smaller width, smaller duration pulses can be tolerated at relatively higher amplitudes than longer duration pulses.¹⁴ At the 200 microsecond width of pulse, sensation is noted around 10 milliamps, motor function at 20 milliamps or less, and pain at 30 to 40 milliamps.^{1,14}

Neural excitability comes from voltage-gated ionic channels within the semipermeable membranes. The resting threshold of -40 to -60 millivolts (mV), the channels open to allow a quick flow of sodium ions inward thus reversing the membrane potential to +20 to +30 mV. There is also an outflow of potassium ions after that restoring the potential back to the resting level. This rapid sequence is called the action potential and is propagated along the neural membrane.

Monophasic pulses are preferred when the responses need to be accurately quantified. These pulses can be electrically differentiated to retard fatigue. Most physiological studies are done with constant-current electrical stimulators that supply a pulse of constant intensity.¹⁴ This is important as the impedance of the skin may vary, depending on sweating and the amount of lubrication.

C. INCIDENCE OF TRAUMATIC BRAIN INJURY

Traumatic Brain Injury (TBI) is caused by vehicular crashes, falls, violence, and sports injuries. TBI is twice as frequent in males than in females. The estimated incidences is 100 per 1,000 persons with 52,000 annual deaths.¹⁹ The highest incidence is among persons 15 to 24 years of age. There are also peaks in the very young and the elderly. TBI may result in lifelong impairment of physical, cognitive, and psychosocial functions. The prevalence in the United States is estimated to be 2.5 million to 6.5 million individuals.

About two million persons each year have a traumatic brain injury. The number of survivors has increased significantly in recent years secondary to fast and more effective emergency care, more rapid transportation to specialized treatment centers and advances in acute management. But up to 90,000 persons incur a TBI resulting in lifelong impairments: reduced physical, cognitive, and emotional functions. TBI may result in physical impairment. But the more serious consequences involve the person's cognition, emotional function and behavior.¹⁹

D. THE EVOLUTION OF ELECTRICAL STIMULATION FOR TBI

In Japan and in the United States in the 1980's, over 15 years ago, parallel observations were made by unrelated observers, Tetsuo Kanno and Ed Cooper. These revelations led to the concept of electrical stimulation for the treatment of comatose states, chronic and acute.

Kanno was using dorsal column stimulation (DCS) for the relief of spasticity.¹² Near the same time, Cooper was using right forearm stimulation (involving the median nerve and the flexor muscles) to try to decrease right arm spasticity in a young man with spastic quadriplegia. The man was residing at Caswell Center in Kinston, North Carolina's largest facility for persons with mental/motor delays. Both Kanno and Cooper separately observed increased levels of consciousness in their patients who were given electrical stimulation for the purpose of

decreasing spasticity.^{12,20} Almost two decades ago, this important observation led both physicians to research electrical stimulation for the purpose of central nervous system arousal.

A second parallel observation that was made by researchers in the United States and Japan: brief periods of median nerve stimulation led to temporary although slight increases in awareness of comatose patients. This was noted in both countries during median nerve stimulation for sensory evoked potentials.^{21,22}

Cooper also noted gradual improvement in mental function in a semi-vegetative 52 year old male physician who had suffered a brain injury and stroke as a result of head trauma in 1987. After treatment, he was noted to have no rehabilitation potential. This patient was transferred to Duke University Medical Center (Durham, North Carolina) nine months after the onset of severe coma followed by a semi-vegetative state. At Duke, with control of pain and electrical stimulation of his right forearm and both quadriceps, he gradually regained the abilities to walk, talk, and operate his computer and to live at home with his wife.

II. EXPERIENCE IN JAPAN WITH ELECTRICAL STIMULATION FOR COMA

In Japan, Kanno's keen observations led him to become the world pioneer for dorsal column stimulation for patients in the persistent vegetative state after head injury, stroke, hypoxia, and other neurologic etiologies.²³ Cooper's observations in the United States of increased awareness after peripheral nerve stimulation evolved into the coma stimulation projects at East Carolina University in (Greenville, North Carolina, 1992 through the present) and the University of Virginia (Charlottesville, 1994-1995, 1998-1999).^{1,18} This chapter will describe the goals, methods and theories of the techniques of dorsal column stimulation (DCS) for persistent vegetative state (PVS) and right median nerve electrical stimulation (RMNS) for treatment of acute coma.

Kanno in Japan observed that it is clear that neurosurgeons must be familiar with the morbid conditions and therapeutic modalities related to prolonged coma: the persistent vegetative state.²³ He observed although diagnostic instruments and methods of treatment have improved, patients with prolonged coma are still found in most hospital wards. Unfortunately, no special modality of treatment has yet been established, and the condition is being left to follow a natural course. On the other hand, the social climate is increasingly focused on the importance of quality of life, which is naturally problematic in patients with prolonged coma, who are confined to bed without effective treatment.²³

A. DORSAL COLUMN STIMULATION FOR THE PERSISTENT VEGETATIVE STATE

At the first annual meeting of the Society for Treatment of Coma (held in Kyoto in 1992) Kanno, Kamei and Yokoyama at the Department of Neurosurgery, Fujita Health University,

School of Medicine, Toyoake, Japan, reported on their experience for the previous eight years with dorsal column stimulation. Forty-two cases were treated of which 18 (42.9%) showed clinical improvement. This was much higher than expected in the incidence of natural recovery.²³

Previously, dorsal column stimulation was known to be effective for treatment of pain and spasticity. Improvement in the level of activity and also improvement on the electroencephalogram (EEG) was observed in some patients who were treated with DCS for spasticity and cerebral vascular diseases. This led to the use of DCS for treatment of the persistent vegetative state (PVS). Of the 42 patients, 23 were cases of PVS secondary to trauma, 11 were due to cerebrovascular disease, 7 to hypoxia and 1 was a complication of surgery for a brain tumor. Twenty-five patients (60%) were under the age of 30.²³

The clinical conditions that satisfied the definition of the vegetative state include inability to recognize and/or communicate, inability to move or eat, and loss of bowel and bladder control for a minimum period of 3 months. In their study, the patients had been in a morbid condition for 3 to 78 months (an average of 19.2 months) before DCS therapy was commenced. Before and during DCS therapy, 37 patients were studied for changes in rCBF (regional cerebral blood flow) using SPECT (single photon emission computerized tomography), and electroencephalography (EEG) in all 42 cases.

The rCBF was increased by DCS therapy in 22 out of 37 cases. The EEG improved in 23 out of 42 cases. They found that the original disease in the improved group was head trauma in 72.2% of the cases. PVS due to vascular or hypoxic injury rarely improved with DCS. On average, 89.9% of the improved patients were under the age of 30, but patients over the age of 50 did not show any improvement by DCS therapy.

These data show a general trend that computerized tomography (CT) in the improved cases shows no marked cerebral atrophy, no large low density area and no involvement of thalamus.

There was good clinical improvement in 18 of 42 cases. None of the patients showed a return to normal functioning such as being able to walk. But the patients with a good outcome were able to have some communication with the outside world and/or express some emotion. The interval from the start of DCS therapy to the first sign of improvement is variable: from 6 months to 5 years. Therefore, the effectiveness of therapy may not be able to be evaluated for some time. Based on their results, the indications for DCS therapy for patients in a vegetative state are as follows:

1. Young age
2. Head trauma
3. Coma for over 3 months, without improvement by medical treatment
4. Head CT does not show signs of severe damage.

After marked cerebral atrophy has occurred, it appears that DCS therapy is not effective.

The mechanism of action of DCS is not clear but, as already reported: DCS increases rCBF, enhances catecholamine metabolism, and improves EEG. The increase in rCBF appears in all parts of the brain. The rCBF in the cerebral cortex and brainstem in cases of vegetative coma is usually between 10 and 25 ml/min/100 gm which is markedly low compared with controls. After DCS therapy, rCBF increases 10-20% in most areas. The same phenomena was also observed in the experimental model. It appears that DCS enhances the metabolism of catecholamine in the central nervous system.²³

The improvement in the EEG tracing was usually bilateral, dominant on the unaffected side, and characterized by alpha-waves tending to increase. However, improvement in the EEG probably was followed by improvement of the clinical status. DCS enhances catecholamine metabolism and increases r-CBF. This resulted in EEG and clinical improvement.²³

By July of 2000, Kanno's group had treated 131 dorsal column stimulation cases (65 in coma from trauma, 28 from hypoxic cerebropathy, 25 from cerebrovascular accidents, 3 from brain tumors; other causes, 10 cases). The mean age was 33 years. The percent of favorable outcome was the same 43% as had been observed earlier. In cases that were under thirty-five years of age, there was clinical improvement in 58% of the cases.

B. KANNO AT THE UNIVERSITY OF VIRGINIA

In June of 1995, Tetsuo Kanno was the visiting professor at John Jane's Department of Neurosurgery at the University of Virginia in Charlottesville. Kanno gave a lecture on an expanded series of patients in the persistent vegetative state that had been treated by dorsal column stimulation. He explained in detail the physiological mechanisms of the electrical stimulation.

In the discussion, John Jane asked if the targets in the thalamus reached by dorsal column stimulation and by peripheral nerve stimulation were the same. Kanno concluded that they were the same.²⁴

C. UNIVERSITY OF VIRGINIA SERIES PRESENTED IN JAPAN

One year later in Sendai, Japan, at the Fifth Annual Meeting for the Society for Treatment of Coma (August of 1996), Cooper presented the results of the first series of six acutely comatose patients treated at the University of Virginia (1994-1995). Kanno stated: "This was the very first lecture regarding median nerve stimulation in Japan."

In that UVa series, three patients were treated with right median nerve electrical stimulation and three were given sham stimulation.²⁵ All patients were in coma after acute closed head injury. All acute brain injury patients were screened by the neuroclinical nurses. Admission criteria included: acute traumatic brain injury and Glasgow Coma Scale (GCS) 4-8 after resuscitation. Patients with severe cardiac arrhythmia, pacemakers, implanted defibrillators, uncontrolled seizures, cerebral palsy, mental retardation, or pregnancy were excluded. The

neurological exclusions were spinal cord, brachial plexus or right median nerve injury. Patients were randomly assigned to the electrical stimulation or the sham stimulation group.

Battery powered Respond Select[®] (Empi) electrical neuromuscular stimulators were connected by lead wires to a pair of 2.5 by 2.5 cm rubber electrodes in a plastic orthosis cuff applied onto the right wrist over the median nerve. Electrical stimulation was performed at 40 pulses (300 microseconds duration) per second at approximately 20 milliamps, 20 seconds on and 40 seconds off for eight hours per day for a period of two weeks. Stimulation was discontinued if the patient awoke during that time. There were no complications from the stimulation.

Intracranial pressure monitoring was done. No patients had prolonged elevations of the pressure above 20 mm Hg during the first five days after injury. CT scans were noted for the presence of cisterns, midline shift, subarachnoid blood, and cerebral edema. Patients were also evaluated regarding their multisystem injuries. In all cases the brain injury was the most significant injury. The afferent pathway of the right median nerve was chosen in this study because the cortical representation of the hand resides in close proximity to the motor speech planning center. Increases in release of neurotransmitters in areas of the brain may facilitate the progression of individuals from a vegetative or comatose condition to a conscious and more functional state.²⁵

The results of the coma treatment are presented in Table 1:

Insert Table 1

In this small one and a half year pilot study, only six patients met the criteria including informed consents from the families. There were 2 males and 4 females ranging in age from 13 to 42 years old. The GCS for both groups was in the range of 7. The average age of the treated group (32 years) was moderately higher than the control group (24 years). The severity of the multisystem injuries was mildly less in the treated group than the control group (Injury Severity Scores: treated group mean of 28.3, control group mean of 34.3).

The follow-up results after one and two weeks of stimulation are presented in Table 2:

Insert Table 2

After one week of stimulation, the treated group average GCS had risen to 11.3 while the control group was at a level of 7.7. At two weeks the treated group had risen to 13.7 GCS and the control group was at 8.3.

The comparison of the pre-stimulation and post-stimulation status was dramatic in the treated group contrasted to the controlled group (Table 3).

Insert Table 3

Therefore, the mean increase in the GCS for the treated group over a two week period was 6.3 compared to 0.8 in the control group.

At one month all of the treated patients were at a Glasgow Outcome Score (GOS) of III with severe disability. The three patients in the control group had a score of II, the persistent vegetative state (Table 4).

Insert Table 4

Frequent assessments of both groups were done daily by the nurses and once daily by a physical therapist. The physicians, nurses, and evaluators were blinded as to which patients were receiving real or sham electrical stimulation. An interesting difference in length of stay in the ICU was noted (Table 5).

Insert Table 5

When the data were encapsulated in summary form the differences between the treated and the sham treatment group were striking (Table 6).

Insert Table 6

In recent years in the United States, there has been much interest in the economics of medical care. We looked at the length of stay in the intensive care unit for the two groups and there was a significant difference there also. The treated group stayed an average of 7.7 days and the control group 17 days. The decrease in the bed days of the treated group was driven by the significant improvement in the GCS during the first week. The treated group mean GCS increased by 4 points, the control group by 0.7 points. We concluded that early right median nerve stimulation could be an effective treatment for acutely comatose patients.²⁵

D. THE USE OF RIGHT MEDIAN NERVE STIMULATION IN JAPAN

1. Society for Treatment of Coma Meeting, 1996

At the same 1996 meeting in Japan, Yokoyama reported on work that he, Kamei and Kanno had done using the right median nerve stimulation technique for comatose patients.²⁶ They

selected two unconscious patients: a 59 year old female with hypoxic brain damage, and a 40 year old male with severe head trauma. Both of these patients showed increased level of consciousness after two weeks of electrical nerve stimulation.

The 59 year old woman (KJ) was suspected of having a right cerebellopontine angle tumor at another hospital. She was admitted for detailed examination. There were no distinct neurological abnormalities other than numbness of the right upper and lower extremities. Cerebral angiography was performed. The following day the patient had systemic convulsions that deteriorated to respiratory arrest. Despite emergency resuscitation, the patient sustained prolonged consciousness disturbance since the ictus.

Three weeks after the onset, the patient showed a Glasgow Coma Scale (GCS) score of 1.T.3, and median nerve stimulation was initiated. The patient's condition changed from a comatose state to one of arousal within approximately 2 weeks after the start of stimulation. The patient became more oriented, involving both eyes in response to the electrical stimulation.²⁶

2. Society for Treatment of Coma Meeting, 1997

Yamamoto and colleagues from the Department of Neurosurgery at Kurume University School of Medicine in Japan reported on "A case of persistent vegetative state treated with median nerve stimulation."²⁷ They used this technique for an 18-year-old woman who was in a vegetative state after a brain contusion and open head injury from a traffic accident with admission GCS of 4 with decerebrate rigidity and unequal pupils.

The right median nerve stimulation (RMNS) was started three months after the injury when she was in a persistent vegetative state (PVS). The Focus electrical stimulator was set at 20 milliamps and pulses at 40 Hz. There was no change in the level of consciousness (GSC 7) before and after the one month period of stimulation 12 hours per day. There were no marked changes on the EEG nor were there increases in the cerebral blood flow to the left hemisphere (measured by single photon emission computed tomography, SPECT). There were no changes in adrenalin or serotonin in the spinal fluid but GABA and dopamine each almost doubled. These findings suggested one possible mechanism for the therapeutic effects of RMNS.²⁷

At the same meeting, Hayashi from Nihon University in Tokyo, reported on "Prevention of vegetation after severe head injury and stroke by combination therapy of cerebral hypothermia and activation of immune-dopaminergic nervous system."²⁸ It has been their practice to use cerebral hypothermia for 1-2 weeks in the treatment of severely brain injured patients with GCS scores of less than 6 with a high incidence of good recovery (54%). Similar treatments were also used after cerebrovascular accidents.

In this study they treated (RMNS) five cases of vegetation after cerebral hypothermia treatment. All of these persons had suffered cardiac arrest following trauma or a stroke. The RMNS therapy was done to increase cerebral dopamine. Hayashi stated "Our preliminary clinical trials of these combination therapy have revealed very useful effects for the neuronal

recovery."²⁸ One case returned to an ordinary lifestyle while others retained neurological deficits.

3. Society for Treatment of Coma Meeting, 1998

Moriya, Hayashi et al. reported on median nerve stimulation for unconscious patients: "New therapeutic strategies for patients with unconsciousness and neurological deficits in acute stage with median nerve stimulation."²⁹ They used two weeks of median nerve stimulation (MNS) to treat 17 intensive-care patients. Seven had severe head injury, 4 cerebrovascular disease, 4 with encephalopathy following cardiopulmonary resuscitation, 2 with hypoxic encephalopathy due to chronic obstructive pulmonary disease.

Nine (53%) showed improved clinical status within two weeks. They noted significant rises of the dopamine in the spinal fluid within one hour after the stimulation. There were no complications induced by the MNS. Hayashi and Moriya concluded that the MNS may be useful for patients in coma with neurological deficits in the acute stage. This treatment may be a therapeutic strategy for comatose patients and could result in lower hospital costs and shorter hospitalizations.²⁹

4. Society for Treatment of Coma Meeting, 1999

Moriya, Hayashi and other members of the Department Emergency and Critical Care Medicine at Nihon University observed the change of clinical symptoms caused by median nerve stimulation.³⁰ Their protocol was 6 hours a day of RMNS, 20 seconds on and 50 seconds off. Clinical symptoms improved in 17 of 37 cases of severe brain damage. The average admission GCS was in the 3.3-5.6 range and the average was 44 years.

The etiology of the brain damage in the 17 improved cases was trauma (9 cases) encephalopathy after cardiopulmonary resuscitation (4 cases) and 2 cases each of severe subarachnoid bleeding and hypoxic encephalopathy. RMNS was started on an average of three weeks after admission. In the improved cases, changes in the muscles of facial expression occurred after three days of electrical stimulation. They also noted improvements in phonation.

They concluded that median nerve stimulation improved the arousal response. Effectiveness could be expected in cases where increases in spontaneous movement of the extremities and changes of facial expression were observed.³⁰

5. Society for Treatment of Coma Meeting, 2000

Tetsuo Kanno in a special lecture on surgical neurorehabilitation concluded:

"The treatment for severe trauma and vascular diseases at acute stage is carried out very enthusiastically by neurosurgeons, while the treatment at chronic stage is done well by the rehabilitation people. However, at sub-acute stage, the patients do not have any special treatment. But at this time, the brain atrophy is in progress. Some new treatments must develop to awake the patient and inhibit the progress of the brain

atrophy. The author considers that DCS, MNS (Median Nerve Stimulation), and deep brain stimulation could be the modalities for the new treatment. Surgical neurorehabilitation will play an important role in the very near future."³¹

Hirata and Ushio reported on a new application of median nerve stimulation for consciousness disturbance in the chronic phase following subarachnoid hemorrhage in an elderly female. She had already had a ventricular atrial shunt inserted but still had a severe eating disorder taking two hours to finish a meal with help. Xenon-CT scanning revealed decreased cerebral blood flow. However after right median nerve stimulation was started blood flow increase by 40 to 75% in both cerebral hemispheres. The therapy was given three times daily before each meal for 30 minutes each. In two weeks the patient was able to finish ordinary meals in a half-hour with help. More importantly, her phonation and level of intelligence improved. Months later she was able to walk between parallel bars. They concluded "Above all, MNS [median nerve stimulation] therapy is characterized by non-invasiveness, simple procedures, and no complications, and is believed to be more suitable than SCS therapy as the first-choice for elderly patients with complications."³²

The final paper of that meeting pertaining to the nerve stimulation was presented by Moriya, Hayashi and group from Nihon University School of Medicine in Toyoko. He noted the correlation between the median nerve stimulation and changes in the cerebral spinal fluid dopamine in patients with severe traumatic brain injury who responded to the treatment. In those patients whose level of dopamine was low before the startup of the electrical therapy, there was increase in the spinal fluid dopamine concentration and clinical improvement regarding consciousness and motor control. They concluded "Since dopamine is involved in vigilance and motor control via the A-10 nervous system, which centers on the limbic system, consistency with the improvement of clinical symptoms after MNS is believed to be significant when associated with cerebral changes caused by dopamine."³³

6. Society for Treatment of Coma, 2001

At this meeting Isao Okuma gave a lecture and mentioned that both median nerve stimulation and dorsal column stimulation were performed at Fujita Health University in Toyoake City. These electrical therapies were used for patients with prolonged consciousness disturbance.³⁴

7. Society for Treatment of Coma, 2002

At this recent meeting at Tokyo Bay there were two lectures presenting clinical results of acute coma patients treated by right median nerve stimulation. Ed Cooper gave a six year follow up of young coma patients treated with RMNS that had been previously presented by him at the 1996 Society for Treatment of Coma meeting. Better than expected results have been obtained in half of the GCS 4 coma patients treated with RMNS within the first two weeks after

their closed head injuries. Three young patients were presented by videotape. These patients are discussed later in this chapter.

Jun-Tung Liu from Taiwan, R.O.C. (China Medical College Hospital) presented a recent series of six patients ranging from age 1 ½ to 66 years old treated with RMNS in the sub-acute phase. Cerebral perfusion rose in all cases. Neurotransmitter amounts increased in the spinal fluid in five of the six cases.

The details of these and other lectures at Tokyo Bay, July 2002, will be published in supplement of *Acta Neurochirurgica*.

E. OBSERVATIONS OF THE CENTRAL NERVOUS SYSTEM EFFECT OF PERIPHERAL NERVE STIMULATION

1. Neuroimaging in Europe

The central nervous system effect of median nerve electrical stimulation has been demonstrated in several ways. In a recent article from Mainz, Germany, this effect was noted by using functional magnetic resonance imaging (fMRI).³⁵ Increased signals in the contralateral somatosensory cortex were noted during median nerve stimulation at a rate of 30-50 Hz (similar to what was used in the University of Virginia and East Carolina University studies). The stimulation was 200 microseconds and the intensity was at motor threshold. In seven out of nine normal subjects, there was significant activity in the hand area on the side opposite to the median nerve stimulation involving the sensory and the motor strips (see Figure 1).

**Insert Figure 1: CAPTION: Close-up of functional MRI, left hemisphere, showing the uptake in the motor/sensory strips during RMNS.
(Used with permission of Professor R. Treede, Ref. 35.)**

In Austria it was also noted with functional MRI that there was an increase in the signal in the primary and secondary motor and somatosensory areas after mesh-glove electrical stimulation of the hand of normal subjects.³⁶ The pulse frequency was 50 Hz with a pulse width of 300 microseconds. In this study variable amounts of ipsilateral and contralateral hemisphere uptake were noted. Based on this information, it was hypothesized that the stimulation triggered input to the posterior column nuclei of the spinal cord, then to the thalamus and to the cortex of the brain.³⁶

In Munich, Germany functional MRI was used to identify cortical areas dedicated to motor hand function prior to removal of space occupying lesions.³⁷ At the time of brain surgery, electrical stimulation at 50 Hz was done to identify the hand areas. The movements of the

contralateral limbs were observed as well as measuring compound muscle action potentials from the contralateral hand (thenar and hypothenar muscles). The motor hand area was located in each case in the precentral gyrus. By doing this open stimulation technique, the pathways were again stimulated.³⁷

2. Observations in rats

In Minnesota, electrical stimulation of the forepaw of ten male rats produced increases in cerebral blood flow (CBF) in the somatosensory cortex.³⁸ This animal model gives further credence to the theory that peripheral nerve stimulation causes measurable central nervous system effects which might lead toward clinical changes.

III. A REVIEW OF PROGNOSIS AND OUTCOMES IN THE LITERATURE

The following section is a review of articles over the last quarter of the 20th century. This chronological progression will show the evolution of the treatment and prognosis of severe brain injury. The original Glasgow Coma Scale was described in a 1974 article by Teasdale and Jennett "Assessment of coma and impaired consciousness."³⁹

Twenty-five years ago in Italy there was a report of 282 comatose patients, there were 140 fatalities (49%). Age was an important factor in recovery from brain injury. Twenty was the positive limit for complete recovery and 40 represented the positive limit for survival. After age 60 the probability of dying was greater than that of surviving.⁴⁰

Twenty years ago a study was done at the Medical College of Virginia in Richmond doing a competitive analysis with the clinical examination evoked potentials, CT scanning, and measurement of intracranial pressure.⁴¹ Age was also an important factor. The proportion of good versus poor outcomes changed at age 40. In their review they used the Glasgow Outcome Scale of Good, Moderately Disabled (that prevent normal function but allows self care), Severely Disabled (marked deficits that prevent self care), Vegetative (no higher mental function), and Dead.

The proportion of Good/Moderate Disability versus Severe Disability/Vegetative/Dead outcomes reversed after age 40. In patients over age 60, 78% had a Severe Disability/Vegetative/Dead outcome. Under age 20, 72% of patients had a Good/Moderate Disability outcome. Only 30% of patients with abnormal pupillary functions had good outcome contrasted to 76% of those with normal pupil responses.

A higher proportion (83%) of Good/Moderate Disability outcomes was observed in patients with normal computerized tomography (CT) scans on admission. Elevated intracranial pressure (ICP) was predictive of a poor prognosis. If ICP's remained elevated throughout then there was only an 11% Good/Moderate Disability outcome.

With the combination of the age, the Glasgow Coma Scale, pupillary reaction, the presence or absence of a surgical mass lesion, eye movements, and motor responses, the prognosis of

severe head injury could be estimated with 82% accuracy. This study of 133 patients was between the period of 1976-1979.⁴¹

John Jane presented a description of the outcome following head injury based on material from the University of Virginia Head Injury Service and the National Coma Data Bank.⁴² This report from 20 years ago presents the predictive value of the Glasgow Coma Scale motor score alone. Of the three scales, the motor score was the most significant as the patient in deep coma would usually have the eyes closed and would be intubated.

The lower Glasgow Coma Scales of 3, 4 and 5 yielded high mortalities (over 60%). The outcome of patients with GCS less than 8 depended largely on three preventable or treatable factors of hypoxia, shock, and increased intracranial pressure.⁴²

Five hundred and eighty-one patients with severe brain injury (nonpenetrating) with GCS score of 8 or less following resuscitation were described in the follow-up phase of the National Traumatic Coma Data Bank in the *Journal of Neurosurgery* in 1983.⁴³ Experience was gathered from the four participating hospitals: University of Virginia, University of Texas at Galveston, Medical College of Virginia, and University of California at San Diego. In the second year of the study two other centers were added: Albert Einstein College of Medicine in New York and Baylor University in Houston.

The data was stored at Stanford University in Palo Alto, California. The data was collected between 1980 and 1982. The largest group of patients (28%) were white males between the ages of 19-29 with head injury resulting from a motor vehicle accident. This effort served as a model for further multiple center studies of complex neurosurgical problems.

The appearance of the basal cisterns on the initial CT scan was assessed in 218 severely head injured patients (University of California Medical Center, San Diego) in the early 1980's.⁴⁴ When the cisterns were normal the mortality rate was 22%, if they were compressed the death rate was 39% and if the cisterns were absent mortality was 77%. In 25 of 34 patients (74%) in which the ICP's were monitored and the cisterns were absent, there was severe intracranial hypertension exceeding 30 mm Hg.

An important article from 1987 about the outcome after severe head injury reported a series of 330 severely head injured patients at the Medical College of Virginia.⁴⁵ The pediatric patients had a higher percentage of good outcome (43%) than the adult patients (28%). The mortality rate for the children was 24% and for the adults 45%. At one year post injury 55% of the pediatric patients had a good outcome overall compared to only 21% of the adults. The overall percentage of good outcome for all patients in the series was 32% with mortality of 38%. Moderate disability combined with good outcome yielded a 52% favorable result.

For patients in whom ICP was elevated above 20 mm Hg and the pressure did not come down with treatment (pharmacological paralysis, morphine sedation, hyperventilation, CFS drainage, Mannitol, barbiturate coma), there was only an 8% of good outcome in the pediatric group and 0% good outcome in the adult group. Mortality rates were 92% and 95% respectively. If the patient had treatable intracranial hypertension the good outcome was still

low, only 27%. It was concluded that "by the time a severe injury had manifested itself with an increased ICP, it may already be too late to effect an improved outcome." It appeared that the children and the adults both fared badly with increased ICP.⁴⁵

In an article by Lawrence Marshall in 1988, the role of aggressive therapy was discussed.⁴⁶ Aggressive management of intracranial hypertension is important. However, some brain injuries are so severe at the beginning that the outcome is inevitable. Outcome studies elsewhere had indicated a mortality of approximately 35-40%. Of the patients who reached the hospital alive, the neurosurgeon could only influence the outcome in a group no greater than 50%, Marshall estimated.

He concluded that "Further refinements in head injury care await a better understanding of the neurobiology of such injuries and the imaginative application of therapies by young investigators."⁴⁶

A five center study of 73 patients was done to investigate the role of high-dose barbiturate control of elevated intracranial pressure in patients with severe head injury.⁴⁷ Eisenberg noted that when ICP control using other protocols failed, high-dose barbiturates can be effective. Their study confirmed the findings of others: a strong association between controlled ICP and mortality from TBI.⁴⁷

From four hospitals in Barcelona, Spain, a paper emerged on "Diffuse axonal injury after severe head trauma" published in 1989.⁴⁸ DAI is considered to be the cases rendered unconscious at the moment of impact in which the CT scan does not show mass lesions, but there is diffuse axonal damage with rotational acceleration producing shear and tensile injuries. The shear injuries of the brain could explain the poor outcome in certain patients in spite of rapid surgical treatment and control of intracranial pressure. The initial CT scan is important in predicting the clinical evolution and outcome. Those with intracerebral hemorrhages have a worse outcome than those who do not. The most severe forms show lesions in the corpus callosum and/or the dorsolateral rostral brainstem.⁴⁸

In 1990, a multicenter study from the Neurosurgery Departments of the University of Texas, University of Virginia, Medical College of Virginia, University of California (San Diego) and the National Institute of Neurological Diseases and Stroke was reported. This prospective study looked at the initial CT scans of 753 patients with severe head injury.⁴⁹ It was found that the risk of dying in severe head injured patients is increased twofold if the mesencephalic cisterns are obliterated or compressed. In general, if the initial CT scan is normal, then the patient does not develop intracranial hypertension.⁴⁹

In another study from the same multiple centers, neurobehavioral outcome was evaluated one year after severe head injury.⁵⁰ The lowest post resuscitation Glasgow Coma Scale score and the pupillary reactivity were predictive of the one year Glasgow Outcome Scale score and the neurophysiological performance. Patients with the lowest score below 4 all ended up in a vegetative state. Those with scores between 4 and 6 were more likely to end up with severe than moderate disability and only those with scores of 6 and above had a good outcome. One

year after injury, memory for new information was impaired. It was concluded that the 24 hour GCS score was more predictive of neurobehavioral outcome than the GCS score obtained on admission.⁵⁰

From the same centers, a new classification of head injury was based primarily on information from the first computerized tomography scan.⁵¹ In category III, where the cisterns were compressed or absent, or a midline shift of 0-5 mm, but no high or mixed density lesions greater than 25 cc, only 16% made a satisfactory recovery. There was an unsatisfactory result in 50% of these patients and 34% expired for a total of 100%.

It was noted that the CT classification appeared to have significant application to the critical care head injury patients. There was a strong relationship between the CT scan, mortality and elevated intracranial pressure. The authors stated, however, ". . . in patients with less substantial biomechanical injuries, it appears likely that early intervention might prevent the development of other insults and improve both mortality in the overall quality of life."⁵¹ They concluded that the frequency of diffuse head injury with midline shift was relatively low. But the very high mortality rates suggest that these severely injured patients represent a target group in which innovative therapies might first be tested.⁵¹

In Waxman's 1991 article, "Is early prediction of outcome and severe head injury possible?", he noted a poor correlation between the initial Glasgow Coma Scale score at patient arrival and eventual outcome.⁵² But scores six hours after presentation correlated better with the outcome. In patients even as low as GCS 3 there could be a good neurological outcome.

Several factors affect survival including the age, other injuries, blood pressure, mechanism of injury, presence of spontaneous ventilation, CT scan findings. He reasoned that the initial therapy should be aggressive for patients with severe TBI. Regardless of the initial neurologic status, accurate prediction of outcome within six hours of presentation is not possible. This included a review of patient records between 1985 and 1987 at the University of California Irvine Medical Center. Ninety-six percent of patients with initial blood pressure of less than 60 mm Hg died and the one survivor was in a vegetative state.

In patients in the 13-20 year-old group (74 patients), the initial Glasgow Coma Scale score was 5.9. Of this group 32% died, 7% went into a vegetative state, 26% had severe disability, 14% had moderate disability and 20% a good outcome. The improved correlation using scores six hours after admission was due in part to the natural history of the brain injury: some patients had already died by that time. The effects of drugs and alcohol diminished and there was time for the treatment of associated injuries.⁵²

The conclusion by the authors deserves quoting: "To provide appropriate care the patients with potential for good outcome, we conclude that initial therapy should be aggressive, regardless of the initial GCS score . . . the risk of withholding therapy must be considered, namely, that salvageable patient may die or suffer unnecessary disability. We believe this risk offsets any cost savings. . . prolonged hospitalization need not precede death."⁵²

The same multiple centers published an article in 1991, "The outcome in severe closed head injury."⁵³ They studied patients enrolled in the Traumatic Coma Data Bank prospectively from January of 1984 through September of 1987 and this included 1,030 consecutive patients admitted with severe head injury: GCS of 8 or less after resuscitation.

Of these, 284 were brain dead or had a gunshot wound to the brain so those groups were excluded leaving 746 patients. The overall mortality for this group was 36% by 6 months post injury. The highest mortality group were the GCS 3 patients (76%) but only 18% for patients of 6, 7, or 8. Among patients with nonsurgical lesions overall mortality rate was 31%. At the time of hospital discharge 33% of patients had died, 14% were vegetative and only 7% were showing a good outcome at that point. Higher proportions of patients with Diffuse Injury III and IV (swelling and shift) were vegetative. Only the Diffuse Injury I (no visible CT scan pathology) had a high proportion of good outcomes of 27%.

For Diffuse Injury II group patients, 15% of those under 40 years of age had a good recovery, 44% moderate disability for a total of 59% satisfactory. If they were over 40 years old then there were no good category survivors and 8.3% moderate disability.⁵³

Dacey and Winn analyzed a series of 242 consecutive surviving head injured patients and 132 general trauma patients.⁵⁴ The neuropsychological outcome was related to the brain and the injury severity though it is not independently related to other system injuries. The psychosocial outcome was related to both the brain and the non-brain injuries independently. Therefore, both sets of injuries should be considered.

The severity of the brain injury was the dominant factor in determining mortality in patients with multisystem injuries. The mortality was about 30% from patients with major blunt trauma and severe brain injury. When there is major trauma alone the mortality is very low. Cognitive outcome was mainly related to the severity of the brain injury. The psychosocial outcome was affected by both the brain injury and the multisystem injuries.⁵⁴

The usefulness of CT scan in predicting the outcome of TBI patients was discussed by Kido at Rochester Medical Center in New York.⁵⁵ Patients with normal CT scans were more likely to have mild neurological dysfunction or normal recovery than patients with an abnormal CT scan. Norepinephrine levels were higher in patients with severe brain injury and this was associated with the outcome. However, even with a normal CT scan, 41% remained moderately severely disabled. The lesion size was most critical for intracranial hematomas. Prognosis was poor for patients with a lesion larger than 4,100 cubic millimeters.⁵⁵

In 1992 Levin, Jane, and Marshall investigated the outcome at six months and at one year of children (0-15 years old) who had suffered severe head injuries.⁵⁶ The children in 0-4 year old group had a high mortality (62% by one year). Only 1 in 5 obtained a favorable outcome. In the 5 to 10 year old group three quarters had a favorable outcome. In terms of the CT scans, the most common finding was bilateral swelling (36% of the patients). Mass lesions of at least 15 cc and bilateral swelling were associated with elevated ICP and poor outcome. Children with

diffuse axonal injury but without diffuse brain swelling usually did not have increased ICP. More than two-thirds of these children obtained a favorable outcome.⁵⁶

Choi and Barnes noted that extremely good or poor outcomes could be predicted with confidence.⁵⁷ Intermediate outcomes are more difficult to predict. They reviewed 786 patients with severe head injury treated between 1976 and 1991 at the Medical College of Virginia. Comparing GCS scores and age relative to favorable or unfavorable outcome, there was a "J" shaped curve. The turning point was between age 30 and 40 years in terms of more unfavorable outcomes. Above age 40 all patients with a GCS of 5 or less had an unfavorable outcome.⁵⁷

Gruen reported in 1996 on the management of complicated neurologic injuries.⁶¹ An injury was called complicated if associated with an injury of any other organ system which jeopardizes the neurologic outcome. It was noted that of the 60,000 patients each year in the United States with severe head injury who were alive for transfer to the hospital, 50% had intracranial pressure elevation.

Cerebral oxygen delivery can be measured and may be a better indicator of ischemia. Refractory intracranial hypertension with increases in ICP led to neurologic deterioration and death. Gruen noted that all neural tissue is very dependent on an uninterrupted supply of oxygen and glucose, the fuels for sustaining the metabolic machinery.⁵⁸

Baltas and others reported on the outcome in severely head injured patients with and without multiple trauma.⁵⁹ They concluded that the non-shock severely head injured patients with multiple trauma had similar mortality to those without multiple trauma. Mortality was dependent on the severity of the intracranial pathology.

The Guidelines for the Management of Severe Head Injury published in 1996 by the Brain Trauma Foundation and the American Association of Neurological Surgeons gave standards that could improve the outcome.⁶⁰ The understanding of events that determine the functional outcome depend on the 1) primary brain injury, 2) secondary brain injury, 3) inflammation: the cellular inflammatory response adds to the damage begun by the oxygen-free radicals and other toxic chemicals, 4) repair/ regeneration-this is the area that is least known. Future advances will include neuronal regeneration, axonal guidance and central nervous system transplantation. The incidence of gunshot wound to the head has steadily risen during the past 10-20 years as the most common cause of fatal head injury.^{60,61}

Letarte at Loyola University Medical School wrote the article "Neurotrauma care in the new millennium."⁶² He observed: "The dawn of the new millennium occurs as the paradigm for the treatment of patients with head injuries is changing. The treatment of patients with head injuries started in the 1900s as a surgical disease; craniotomy for evacuation of hematoma was the only modality available for the reduction of intracranial pressure (ICP) and the maintenance of cerebral perfusion pressure (CPP). Over the past 50 years there has been the introduction of surgical modalities for treatment of patients' traumatic brain injury (TBI). As the new

millennium dawn, surgery is becoming but one modality in what is now seen as the resuscitation of the injured brain."⁶²

In *Neurology and Trauma* by Evans, chapter 12 entitled "Neurobehavioral outcome of head trauma," the Glasgow Coma Scale and Glasgow Outcome Scale were explained. Age is important: in adults 50 years or older age is a poor prognostic factor partly because of the higher incidence of intracranial hematoma in older patients. Older patients have other medical complications that could contribute to a poor outcome.⁶³

In those patients with nonreactive pupils in the first 24 hours of coma, 95% will die or become vegetative. Only 4% will have a moderate disability or good recovery. If the pupils are reactive, there is a 50% rate of moderate or good recovery.

Cognitive impairments are the most disabling results of head injury. In the recovery from moderate to severe closed head injury, there is a period of post-traumatic amnesia (PTA) that often is accompanied by a reduced level of consciousness or agitation. Initial severity of trauma, age and length of PTA are some of the variables that are predictive of outcome.⁶³

In the textbook *Neurosurgery* by Wilkins and Rengachary (1996), Marshall observed that prediction after severe head injury continues to be an area of intense interest because of the natural curiosity of neurosurgeons and society's attention to resource allocation. The ability to predict outcome becomes very important to the targeting of resources.⁶⁴

IV. RIGHT MEDIAN NERVE ELECTRICAL STIMULATION (RMNS)

The median nerve serves as a peripheral gateway to the central nervous system. The sensory distribution of the hand exhibits disproportionately large cortical representation. Within the brainstem, the ascending reticular activating system (ARAS) maintains wakefulness. The spinoreticular component of the median nerve synapses with neurons of the ARAS. The nearby locus coeruleus releases norepinephrine causing a monoaminergic arousal of the cortex directed to cortical layer 1.⁶⁵ The intralaminar nuclei of the thalamus are activated by acetylcholinergic input from the ARAS. These intralaminar thalamic nuclei provide nonspecific excitatory input to the cortical layer 1 leading to the initiation of awakening. The excited ARAS also stimulates the forebrain basal nucleus of Meynert which delivers diffusely spread acetylcholine to the cerebral cortex.⁶⁶

The right median nerve was chosen as a portal to stimulate the brainstem and cerebrum because increased alertness and better speech have been observed after RMNS.^{1,18} Broca's motor speech planning area in the left frontotemporal region has been shown in positron emission tomography (PET) to become more active when a subject moves, or even contemplates moving his/her hand.⁶⁷ This process is mimicked in RMNS.

The author's interest in stimulation began 30 years ago with a study involving a paraplegic individual at University of Virginia (UVa) in Charlottesville, Virginia. Radio-linked, implanted electrodes strengthened muscles and allowed crude ambulation.⁵ From 1987 to 1989 individuals

suffering from quadriplegia were helped to use their forearm muscles through voice-activated electrical stimulation to produce hand opening and closing at the Department of Biomedical Engineering at Duke University in Durham, North Carolina. Significant improvement was noted in distal motor abilities in response to electrical stimulation in this and previous studies by Cooper and associates.^{5,6,68} Proximal voluntary and contralateral arm increases in performance were also noted during strength testing.⁶

Similar computerized electrical stimulation was applied to adult individuals with severe mental/motor delays at Caswell Center in Kinston, North Carolina, in hopes of improving function and awareness.⁶⁹ While viewing serial videos of patients in the treated group, progressive augmentation of mental awareness was noted. The observed cross-over effect in the quadriplegic population, along with the central arousal of the mentally challenged population, led to the postulation that stimulation of the median nerve causes significant central nervous system activation.^{1,18,69}

The electrical stimulators, Respond Select at the University of Virginia project and Respond II® (Empi) at the East Carolina University project were battery-powered units. They supplied trains of asymmetric biphasic pulses at an amplitude of 20 mA with a pulse width of 300 microseconds at 40 Hz for 20 sec/min. The treatment was done for 12 hours daily at ECU and 8 hours per day at UVa for 2 weeks. The trains of pulses were delivered to the volar aspect of the right distal forearm over the median nerve via lubricated surface rubber electrodes measuring 2.5 by 2.5 centimeters. The electrodes were embedded 2 cm apart in the midline of plastic cuffs from Carolina Ortho Prosthetics, Greenville, North Carolina (see Figure 2).

Insert Figure 2: PHOTO CAPTION: An electrical stimulator connected to a right wrist electrode cuff.

In our UVa and ECU coma projects, electrical treatment was usually started in the first week post traumatic brain injury (TBI).^{1,18} Stimulation was not done in the first two days to allow for time for clearing of any intoxicants and also for emergency surgery.

If there is concern about the dopamine rush in the first week after severe TBI with neuronal cell death, then the coma stimulation may be delayed as needed. However with advancing time post injury, there may be a slower response to the electrical treatment and diminishing returns for the final neurological outcome.

For children and small adults, a setting of up to 15 milliamps is recommended and also for those adults with agitation at the 20 milliamp setting. For safety purposes, a plastic cap or clear tape should be applied over the external power dial on the electrical stimulator to prevent inadvertent overstimulation.

Peripheral nerve electrical stimulation (FDA approved stimulators) was cleared by the institutional review boards of UVa and ECU for the coma projects. Informed consents for the participation of the comatose patients were obtained from the families.

The right median nerve motor stimulation was done at approximately 1.5 times the motor threshold. This usually produced strong right thenar abduction and flexion of the index and middle fingers plus some wrist flexion. In conscious volunteers, obvious tingling (but not painful) was felt in a median nerve distribution in the right hand. Depending on the depth of coma of the TBI patients, RMNS may elicit withdrawal of the right forearm, head turning and partial opening of the eyes. Temporary mild elevation of the vital signs is not unusual, but intracranial pressures usually remain stable. The motor responses gradually diminish during the eight to twelve hour treatment sessions. If the coma patient has been chemically paralyzed, hand movements during the "on" cycles may be absent, but the therapeutic afferent stimulation should continue to be effective.

In the first few days of treatment, mirror movements of the unstimulated left hand may occur. This cross-over effect was first discovered in the Duke quadriplegic hand stimulation study as evidenced by the strength gains in bilateral proximal arm muscles. The effect was noted in the Caswell computerized electrical stimulation projects as evidenced by the generalized motor and emotional improvements.⁶

This dynamic cross-over effect heralds the reactivation of the cerebral hemispheres in the electrically stimulated comatose patient. First the left hemisphere, then the right, are reanimated via the corpus callosum.⁷⁰ Usually the first simple command ("touch your thumb to your finger") to which the patient will respond after one or two weeks of RMNS is a sluggish opposition of the right thumb and index finger. *This unique "O sign" is the earliest signal of the progressive emergence from deep coma.*

In computer parlance, this voluntary hand response while the TBI patient still appears to be semi-comatose, demonstrates that the 5 million electrical pulses delivered to the nervous system in the first ten days of treatment have been copied and stored in the hard drive of the brain. The message can be retrieved on command: purposeful hand movement, a very human and not a vegetative function. It is the outward and physical sign of internal electrochemical partial healing.¹

As reported earlier in this chapter, in the UVa study at 1 week, the treated group had improved by an average of 4.0 on the GCS and the control group had improved by an average of 0.7 on the GCS. By 2 weeks, the treated group had improved by an average of 6.4 on the GCS and the control group had improved by an average of 1.3 on the GCS (refer to Tables 1 & 2). The treated group stayed in the intensive care unit for an average of 7.7 days and the control group stayed in the ICU for an average of 17.0 days (refer to Table 6).

In a more recent study (1998-1999) with similar methods and similar comatose patients, Cristian Peri noted that the electrically treated group required a shorter period of endotracheal intubation/respirator than the sham treatment group.¹⁸ Although the statistical significance has not been determined, it appears that the difference in intubation time is an even more refined measure of brainstem function than the previously observed total days in the ICU for the two groups.²⁵

Right median nerve stimulation (RMNS) by way of the afferent pathways through the spinal cord and brainstem probably activates the cells of the medullary "respiratory centers."⁷¹ Injuries to the brainstem particularly in the medulla may result in ataxic or irregular respiration or a cessation of respiration.⁷²

A. HISTORY OF RMNS IN THE EASTERN UNITED STATES

1. Four selected American cases

The following four young patients with severe TBI from motor vehicle collisions were treated with right median nerve electrical stimulation (RMNS) at two university medical centers in North Carolina within the last few years. These cases are presented to show the possibility of functional recovery with RMNS in situations where the initial prognosis was very grim.

1. CP, a 16 year old female, was involved in an motor vehicle crash (MVC 1993) and sustained a severe closed head injury. She had a mandibular fracture and an intracranial pressure of 18. After resuscitation she continued with decerebrate posturing. Her initial head CT scan was normal. She was dependent on a respirator and had a brief cardiac arrest. One week later she remained comatose and RMNS was commenced. After 1 week of stimulation her GCS had improved to 9. After a total of 2 weeks of stimulation she scored 14 on the GCS, an improvement of 9 and near the fully alert state. Within 1 month of her injury, CP could speak, eat, and walk with assistance. CP was discharged to home within 2 months of her trauma. She made a full recovery by one year. She has had held a full-time job as a cashier and has been promoted to the administrative office.
2. AT, a 14 year old female, was involved in an MVC (1995) and sustained a severe closed head injury. She had a hemothorax and a pulmonary contusion. Her right mandibular condyle penetrated the base of her skull through the temporal bone into the middle cranial fossa. CT scan showed haemorrhagic foci in the left cerebral hemisphere. She exhibited alternating decerebrate and decorticate posturing and received a GCS of 4. Within the first week of stimulation she began gripping spontaneously. After 1 week of stimulation her GCS was 6. After 2 weeks of stimulation she began to open her eyes spontaneously and received a GCS of 8. At 2 months post-injury she was eating well and speaking. Within 5 months she was playing volleyball and doing well in school. She recently graduated from college ("B" average) and is now married.
3. CI, a 16 year old female, was involved in an MVC (1994) and sustained severe closed head injury. She suffered a basilar skull fracture, cerebrospinal fluid otorrhea, left facial fracture, and left pelvic fracture. CT scan revealed left internal capsule contusion, right cerebellar subarachnoid hemorrhage, and blood in the

fourth ventricle. Decerebrate posturing was observed and she received a GCS of 4. She was briefly given electrical stimulation but intracranial pressures continued to rise. With her extremely poor prognosis, she was expected to die and was extubated. She breathed spontaneously and electrical stimulation was resumed to the right median nerve. Within 1 week of stimulation, she exhibited semi-purposeful movement of her right arm and leg and scored 7 on the GCS. After a total of 2 weeks of stimulation, she scored 10 on the GCS. This increase of 6 was consistent with the UVa pilot project observation.^{1,25}

One month after the injury, CI followed simple commands. At 2 months post-injury CI could walk with assistance and read aloud. Two years later CI talked and walked well. She resumed dancing and driving. She completed high school and college with a "B" average. Now she is the recreation/activities director at a rest home.

4. In March of 2000, a 12 year old boy (KF) was struck by a van and had severe brain and intra-abdominal injuries plus multiple extremity fractures including compound fractures of the pelvis. On his initial CT scan there was left frontal contusion, a small amount of subarachnoid hemorrhage in the interpeduncular cistern and a non-depressed skull fracture of the left parietal bone. There was also a fracture of the left temporal bone. On the follow-up scan two days later, a right frontal ventricular catheter was noted. There were several contusions (right frontal and left temporal), increased edema with marked effacement of the cortical sulci, and intraventricular hemorrhage. On the scan one week post-injury there was diffuse brain swelling and multiple hemorrhagic shearing injuries and hemorrhagic contusions of the left frontal lobe extending into the temporal lobe.

He underwent multiple abdominal and orthopaedic operations.

He remained comatose with elevated intracranial pressures (over 70 mm Hg) in spite of two courses of barbiturate therapy. Pupils remained unequal. Survival was very questionable. Surface electrical stimulation in the 15 milliamps range to the left median nerve was commenced two weeks post injury. The right forearm was in a cast. After two weeks of daily stimulation, he began to emerge from the coma. He progressively improved and regained his ability to speak. He could use his hands in spite of a right hemiparesis.

Two months post-injury, he was transferred to a rehabilitation center. Electrical stimulation was resumed, but switched to the right median nerve to help reduce the right hemiparesis. He continued to improve and was discharged to home six weeks later. He started home schooling and made good grades.

On his final neurosurgical evaluation four months post injury KF was noted to have made a very good recovery.

On a home visit eight months post injury, his speech was almost normal. His right hemiparesis was very mild, walking with only a slight limp. Two post injury in the spring of 2002 his junior high school grade average was a "B". He returned to some athletic activities.

B. ANALYSIS OF GCS-4 DECEREBRATE PATIENTS

At the heart of the controversy regarding electrical stimulation for coma lies the stark question:

Does early electrical stimulation improve the outcome of severely comatose patients?

To best answer this question a series of 100 comatose patients from acute brain injury would be needed. They would be randomized so that approximately 50 would be in a treated group and 50 in a control group with sham electrical stimulation, double blinded. With the large number of patients, variations in the severity and types of injuries would balance out.⁷³ To accomplish such a study, a multicenter effort in the USA, Asia and Europe would be needed. This work needs to be done in the near future. To provide a quick answer to the efficacy of early stimulation, looking at a group of patients with an extremely poor prognosis when treated by conventional methods would be helpful.

Within our series of 22 comatose patients treated with electrical stimulation at the medical center at East Carolina University from 1993 through 1999, 12 of the patients were in the Glasgow Coma Scale 4 category. They exhibited decerebrate posturing. These patients were in deep coma for more than a week. It is known that GCS 4 patients have a very poor prognosis.^{41-46,48-57}

In the textbook by Wilkins and Rengachary, *Neurosurgery*, 1996, there is a chapter written by Marshall and Marshall on "Outcome prediction in severe head injury." The outcome at the last contact was discussed by categories of the post resuscitation Glasgow Coma Scale scores.⁶⁴ Out of 111 patients in the GCS 4 category, 62 expired. This left 49 patients for comparison to our 12 GCS 4 patients who survived. Of their 49 patients, 7 had a Good outcome (14%), 9 had Moderate Disability (18%) for a total of 32% favorable outcome of the GCS 4 patients who survived. Other survivors included 21 with Severe Disability (43%) and 12 Vegetative patients (25%) for a total of 100% for the surviving group of 49 patients.

Using the Glasgow Outcome Scale, Good recovery is characterized as "Resumption of normal life even though there may be minor neurologic and pathologic deficits."^{74,75} A patient in the category of Moderate Disability is "Disabled but independent." The person could work in a sheltered environment and travel by public transport. However, various degrees of neurological deficit and also intellectual and memory deficits and personality change would remain. Those in the Severe Disability category are dependent for daily support, usually with a combination of mental and physical disabilities.

In our small uncontrolled series at East Carolina University, the comatose patients were treated with RMNS as described in the protocol plus traditional neurosurgical aggressive

management with intracranial monitoring.^{1,18} The right median nerve electrical stimulation was usually started at 1 week post-injury and continued for 2 to 3 weeks. The outcome of the surviving GCS 4 subset of patients (12) is as follows in Tables 7 and 8:

Insert Table 7

Insert Table 8

In summary, a satisfactory result (Good plus Moderate) was reached by one year in 58% of the GCS 4 patients treated with right median nerve electrical stimulation.²⁵

In the chapter by Marshall, the outcome scoring was done at "last contact."⁶⁴ The outcomes in our series as noted in Tables 7 and 8 were at one year or less. In the Severe cases (42%), the outcome was judged much earlier, usually several months post injury when the patient was transferred from the rehabilitation center to a long term facility elsewhere. It is not known whether some of the patients in the Severe category might have progressed to the Moderate category by one year.

As demonstrated by one of the Severe category patients, (PD, age 21) by last report a little over one year post injury was making progress toward Moderate Disability. He was living in an apartment, receiving physical therapy, but was having difficulty walking because of heterotopic ossification in his hips. But he was able to talk.

There were three patients in the Moderate outcome category, (25%). In the Good recovery group at one year there were four patients (33%). One of the teenage patients (CI) in the Moderate category progressed to the Good outcome group by three years post injury.

EW (Moderate Disability) is now almost two years post severe brain injury making A's and B's in high school, playing basketball, but has short term memory deficits. But based on her rate of progress, she too will probably be in the Good outcome category by three years post injury.

The time required to reach the Good category in our patients corresponded inversely to the severity of the findings on the early CT scans.^{1,25} This relationship between the early CT scans and the final outcome has been well reported in the literature.^{49,55,76} The Good outcomes were judged on the basis of physical and speaking abilities, resuming driving an automobile and making good grades in school. Most of these good outcome patients went on to be fully employed.

There was a satisfactory outcome (Good plus Moderate) in 58% of the GCS 4 patients treated with right median nerve electrical stimulation. Three of our Good outcome patients had excellent outcomes, virtually normal according to the families.

While the number of treated patients was quite small and not randomized, there was a definite trend toward Good recovery. This would suggest a significant treatment effect by the early electrical stimulation.^{1,25}

V. DISCUSSION

Electrical stimulation of the right median nerve may help acutely brain-injured persons to recover from coma more rapidly. The patients receiving RMNS suffered no ill consequences.^{1,25,77} Many have recovered more quickly than was anticipated.

Through maintenance of existing neuronal circuitry, earlier awakening from coma may lead to a higher final level of function. Increased cerebral activity, as observed in RMNS, may also facilitate synaptogenesis in damaged cerebral cortex.^{78,79,80} The clinical observations indicate that RMNS has a beneficial effect on the resumption of language capabilities, possibly through stimulation of Broca's motor speech area.^{1,25}

The pilot project at the University of Virginia reflects the observations at ECU: treated patients' Glasgow Coma Scale scores rose more quickly than those in the control group.^{1,25} But the burden of proof in establishing a cause and effect relationship in the comatose population is immense. Both the treated group in the UVa pilot project and the three cases presented from the ECU series showed a mean improvement of 6.4 on the GCS after two weeks of treatment. This suggests that the treatment may show dose-dependent efficacy.¹ Future clinical trials at the University of Virginia and other medical centers in the United States and Japan should produce more substantial results.

VI. CONCLUSION

Electrical stimulation is not a panacea for all severe head injuries. Those patients with extensive cerebral structural damage and/or intractable intracranial hypertension may not respond to the electrical stimulation. Those patients with mild and moderate brain injury can be expected to respond to standard neurosurgical protocols. But there is a subset of severe TBI patients, usually in the Glasgow Coma Scale post-resuscitation range of 4 and 5 with a mixture of decerebrate and decorticate movements. They may benefit from early electrical stimulation. Especially in comatose teenagers with CT scans that do not show excessive structural damage, electrical stimulation may yield a better than expected outcome.

Anecdotally our patients' history show a tendency toward better recovery than expected in the literature. The strong message gained from the last ten years of clinical research is that there is a subset of young patients who appear at first to have a hopeless neurological injury. With the proper treatment, the majority of persons who survive their brain injuries may make a semi-functional recovery. About half of the patients could make a good recovery, a few excellent.

For patients with severe traumatic brain injury, electrical stimulation can be a therapeutic adjunct to the standard neurosurgical treatment. Through peripheral nerve stimulation, cerebral blood flow may be increased, catecholamine output enhanced, and maintenance of neuronal circuitry in spite of massive blunt trauma to the brain.

The reawakening and partial healing of the non-fatally injured brain can be driven from below.^{78,79,80} The median nerve is an available portal to the brainstem and cerebral cortex.⁸¹ Electrical stimulation provides a strong force to unmask a subset of salvageable patients whose grim clinical picture exceeds the amount of anatomical brain damage. Right median nerve stimulation, by avoiding disuse atrophy, may allow patients to begin rehabilitation with fewer deficits.

These patients may obtain a better outcome as a result of the stimulation. The observations gained from the treated series of patients at ECU, Fujita Health University, and the pilot projects at UVA suggest that RMNS may have a positive effect on brain-injured comatose individuals. Non-invasive RMNS is easily employed with little risk and is cost effective. This new technique *can* improve neurological outcomes.

In the words of Shakespeare:

*Diseases desperate grown
By desperate appliance are relieved,
Or not at all.*

*Hamlet Act IV, scene iii*⁸²

To empower brains that have crashed, median nerve stimulation will be an easy, safe, and economical adjunctive treatment for severe brain injury.

Insert Figure 3: PHOTO CAPTION: Endoscopic photo of right median nerve, *Una via futura* .

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Table 1: Initial Glasgow Coma Scale (GCS) ratings

Treated Group		
Patient Name	Age	GCS
SI	16	7
DS	37	8
AC	42	7
Mean	32	7.3
Control Group		
Patient Name	Age	GCS
RB	13	7
WM	42	7
JB	18	7
Mean	24	7

Table 2: Follow-up

Treated Group		
Patient Name	7 Day	14 Day
	Glasgow Coma Scale	Glasgow Coma Scale
SI	10	14
DS	11	14
AC	13	13
Mean	11.3	13.7
Control Group		
Patient Name	7 Day	14 Day
	Glasgow Coma Scale	Glasgow Coma Scale
RB	9	9

WM	7	5
JB	7	11
Mean	7.7	8.3

Table 3: Change over 14 days

Patient	Group	Change
SI	Treated	+7
DS	Treated	+6
AC	Treated	+6
RB	Control	+2
WM	Control	-2
JB	Control	+4

**Table 4: Glasgow Outcome Scale (GOS)
One Month Post Injury**

Patient	Group	GOS	Score
SI	Treated	Severe Disability	III
DS	Treated	Severe Disability	III
AC	Treated	Severe Disability	III
RB	Control	Persistent Vegetative State	II
WM	Control	Persistent Vegetative State	II
JB	Control	Persistent Vegetative State	II

Table 5: Days in Intensive Care Unit

Patient	Group	Days
SI	Treated	6
DS	Treated	9
AC	Treated	8
RB	Control	8
WM	Control	28
JB	Control	15

Table 6: Glasgow Coma Scale change and intensive care days

Group	Positive Change GCS	Bed Days
Treated	6.3	7.7
Control	0.8	17.0

Table 7: 12 GCS-4 Survivor patients treated with early RMNS at ECU

Initials	Age	Sex	Injury Year	Outcome at \leq 1 yr.
1. CP	16	F	1993	Good Recovery
2. PW	21	M	1994	Severe Disability
3. MS	22	M	1994	Severe Disability
4. CI	16	F	1994	Moderate Disability
5. AT	15	F	1995	Good Recovery
6. AP	17	F	1995	Good Recovery
7. MC	26	F	1996	Moderate Disability
8. KB	19	F	1996	Good Recovery
9. KB	7	M	1997	Severe Disability
10. RR	14	M	1997	Severe Disability
11. DV	21	M	1997	Severe Disability
12. EW	15	F	1999	Moderate Disability

Table 8: Outcome at one year or less

Good	4	33%
Moderate Disability	3	25%
Severe Disability	5	42%
Vegetative	0	-
Dead	Not Included	-

Total	12	100%
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