Comprehensive Predictions of Outcome in Closed Head-Injured Patients

The Development of Prognostic Equations

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INTRODUCTION

Accurate prognostic evaluation of patients with severe head injury is of importance for acute patient management, the establishment of appropriate long-term treatment and rehabilitation, as well as in family counseling. It is critical to obtain diagnostic and prognostic information as soon as possible after injury in order to optimize therapeutic approaches.[1,2] There are two major categories of prognostic information that are needed: (1) acute prognostics for the immediate physical/physiological evaluation and (2) long-term prognostics for the purposes of physical and/or occupational rehabilitation and family counseling. Obtaining the information has been attempted using single measures[3-11] such as the CT-scan,[12,13] EEG,[14-17] or evoked potentials.[18-21] Other studies have utilized a multimodal approach to acute prognostic evaluation by combining diverse measures such as some of the indicants listed above.[22-25] An emphasis on comprehensive or multimodal evaluations has recently arisen because it has been shown that combined measures are more reliable and accurate than any single measure alone.[25] These latter studies have focused primarily on acute prognostic indices that help determine the probability of survival and gross morbidity. In contrast, very few comprehensive or multimodal studies have been conducted to establish long-term prognostic indices, for example, at one year following injury.[25]

Most prognostic studies of patients with head trauma have concentrated on the ability to predict membership in diagnostic categories of the Glasgow Coma Score

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(GCS)[3,26] or a variation of it which lumps the entire spectrum of outcome into two-to-four outcome categories such as complete recovery versus death or vegetative state, etc. In contrast, few studies have utilized multiple regression statistical procedures to predict the quality of function in patients whose outcome is intermediate between complete recovery versus death or disability.[27] The latter is important because an increasing proportion of trauma victims survive, and thereby exhibit survival instead of death. Accordingly, a multimodal prognostic index for a wide range of disability needs to be developed. For these reasons the purpose of the present paper is twofold: (1) to compare the ability of single and multimodal measures obtained shortly after injury to predict outcome at one year following injury, and (2) to begin the development of a heuristic regression equation capable of accurately predicting a wide range of outcome measures. The first step toward this goal will involve the evaluation of two different prognostic prediction techniques in two different categories of patients: (1) in patients in the two extremes of complete recovery versus death and (2) in patients in the intermediate range between the extremes of complete recovery and/or death.

METHODS

Patient Population

A total of 162 patients were included in the study. All of the patients were admitted to the Neurotrauma Service of the Maryland Institute for Emergency Medical Services Systems (MIEMSS). Patients with gunshot wounds to the head or primary anoxia brain injury or who fulfilled the criteria of brain death were not included in the study. All of the patients had initial care by emergency medical system paramedics at the scene of the accident and transportation to MIEMSS within 24 hours. Although the majority of patients arrived directly from the scene of the accident by helicopter, some were stabilized at a local facility before transfer to MIEMSS several hours after the accident. Of the 162 patients 60% were motor-vehicle accident victims, another 10% were pedestrians, and the remainder were victims of industrial or home accidents, or violent crime. All of the patients were diagnosed as having a closed head injury.

Patient Management

Approximately 70% of the patients arrived at the Shock Trauma Center by helicopter. The patient was met at the MIEMSS heliport by an anesthesiologist, general surgeon, and specially trained admitting nurses. Acute respiratory insufficiency was treated with intubation and manual ventilation on the heliport prior to transporting the patients. Patients with a GCS less than or equal to eight received an endotracheal tube and mechanical ventilation after a neurologic evaluation or earlier if required by ventilatory status. If the patient required specific central nervous system studies, such as a CT-scan or angiogram, then these were performed after initial protocol admission workup, which included cervical spine and chest X-rays. Patients were not transferred for CT-scan of the head until cardiopulmonary stability had been obtained in the

admitting area. A carotid stick angiogram was performed occasionally in the resuscitation area when the patient was not transferable because of cardiopulmonary instability.

Patients with a GCS less than or equal to eight had a subarachnoid bolt or intraventricular catheter inserted to monitor the intracranial pressure; approximately 31% in this study had initial intercranial monitoring. If a patient was spastic or restless on a ventilator, sedation was used to calm him. Narcotics were used as the principal sedatives during the initial respiratory management phase of medical care because their action can be reversed for neurologic and clinical evaluation.

The first computerized EEG and evoked potential tests were obtained at the patient's bed in one of the intensive care units or subacute step-down units at MIEMSS depending on the patient's status. Electrophysiologic testing occurred within 1 to 21 days following injury (mean, 7.5 days; SD, 7.6 days).

CT-scan Measures

The CT-scan data for each patient was collected using a modified version of the Traumatic Coma Data Bank (version 2).[11] According to this scheme, lesions were classified by location as extracerebral or intracerebral. Extracerebral lesions were further classified as right, left, midline, or posterior fossa (left or right). Intracerebral lesions were placed in subcategories by region as frontal, temporal, central, parietal, occipital, cerebellum, basal ganglia (all the above noted as left or right hemisphere), and brainstem. Extracerebral and intracerebral lesions were classified as 0 (none), 1 (low density), 2 (isodense), 3 (high density), 4 (mixed density [mottled]), 5 (distinct high and low areas), or 6 (not visible or unknown). All lesions were rated by approximate size in millimeters.

In addition, data were collected on the presence or absence of bone lesion, intraventricular blood, diffuse brain atrophy, intracranial air, and subarachnoid hemorrhage. The ventricular system was rated according to a scale of 0 (normal), 1 (enlarged), 2 (small), and 3 (absent). The ventricular system was also rated as either 0 (symmetric) or 1 (asymmetric). Midline structures were rated as 0 (normal), 1 (< 5), 2 (5-10), or 3 (> 15). Brainstem cisterns were rated as 0 (absent), 1 (present), or 2 (compressed). Posterior fossa were rated as 0 (normal), 1 (left-to-right infratentorial shift), or 2 (right-to-left infratentorial shift). Missing or unknown data for the above categories were classified as 9. In addition to the above information, lesions were classified as subdural, epidural, or neither.

Several CT-scans were read by the trauma surgeons for each patient. The CT-scan which correlated most closely with the date of the electrophysiologic test was used for the analysis. TABLE 1 shows the number of patients in the various categories of CT-scan classification.

Electroencephalographic Measures

Silver disk electrodes (Grass Instrument Co., Quincy, MA) were applied to the 19 scalp sites of the international 10/20 system.[28] A transorbital eye channel (electrooculogram [EOG]) was used to measure eye movements, and all scalp recordings were

referenced to linked ear lobes. Impedance measures for all channels were generally less than 5,000 ohms. Amplifier bandwidths were normally 0.5-30.0 Hz, the outputs being 3 dB down at these frequencies. The EEG activity was digitized on-line by a PDP 11/03 data acquisition system. An on-line artifact rejection routine was used which excluded segments of EEG if the voltage in any channel exceeded a preset limit determined at the beginning of each session to be typical of the subject's resting EEG and EOG.

One minute of artifact-free EEG was obtained at a digitization rate of 100.0 Hz. The EEG segments were analyzed off-line by a PDP 11/70 computer and plotted by a Versatec printer/plotter. Each subject's EEG was then visually examined and edited to eliminate any artifacts that may have passed through the on-line artifact rejection process.

A second-order recursive digital filter analysis was used to compute the auto- and cross-spectral power density[29] for each channel. This procedure is essentially identical to the fast Fourier transform (FFT) method of computing power spectral density. The advantage of using the recursive digital filter when a limited number of bands are analyzed is increased computational efficiency and a simpler design, since the recursive filters provide a natural form of windowing and leakage suppression. The procedure involved using a first-difference, prewhitening filter and a two-stage (four-pole) Butterworth band-pass filter.[29] Frequency bands, including the center frequencies and one half of power B values were as follows: delta (0.5-3.5 Hz; fc = 2.0 Hz, and B = 2.0 Hz), theta (3.5-7.0 Hz; fc = 4.25 Hz, and B = 3.5 Hz), alpha (7.0-13.0 Hz; fc = 9.0 Hz, and B = 6.0 Hz); beta (13.0-22.0 Hz; fc = 19.0 Hz, and B = 14.0 Hz). Degrees of freedom = 2 × BwT, where Bw = the bandwidth and T = the length of the record (e.g., for 20 sec of EEG there are 160° of freedom) and the start-up and trail-off periods of the filter are in seconds, 2/BW (e.g., 0.5 sec for a 4.0 Hz bandwidth). The artifact rejection routines precluded EEG segments less than 0.8 sec in length and the range of total EEG length/subject varied from 16-60 sec (mean, 34.37; SD, 13.34).

Coherence and phase were computed for all pairwise combinations of electrodes.[29,30] Coherence is analogous to a cross-correlation in the frequency domain and reflects the number and strength of connections between spatially distant generators.[29,31] Measures of phase provide estimates of lead- and lag-times between spatially separate but connected systems of generators, as well as measures of frequency dispersion and conduction velocity.[30–32] Mathematical equations describing the method of computing coherence and phase are provided elsewhere.[29,30,32]

In order to reduce the coherence and phase measure set, three different categories of electrode combinations were employed: (1) left intrahemispheric combinations, (2) right intrahemispheric combinations, and (3) homologous interhemispheric combinations.

EEG Amplitude Differences

Because the recursive filter analysis was performed over specific frequency bands, the absolute power of the EEG was computed in μV^2 for each frequency band. Differences in absolute amplitude were computed between the same pairs of electrodes as in coherence described in the previous section (i.e., left and right intrahemispheric and interhemispheric electrode combinations). The formula for amplitude differences was (left − right) for the interhemisphere comparison and (anterior derivation − posterior derivation) for intrahemisphere comparisons.

Brainstem Auditory Evoked Potentials

Auditory click stimuli 100 μsec in duration were delivered through air-conducting tubes from piezoelectric transducers (Motorola #KSM20004A) at 10 clicks/sec. The stimulus intensity was 90 dB SPL to each ear. The vertex signal was led to an amplifier with a gain of 100,000, a noise level of 4 μV peak-to-peak; a common mode rejection ratio of 200 dB, and a bandwidth from 100.0-2.9 Hz at −4 dB points. The prefiltered analog signal was digitized at a rate of 10,000 samples/sec with 12-bit resolution. Digital data were collected for a set of 10 "trials" or subaverages. Each such trial consisted of the average of 200 evoked potentials using an analysis epoch of 12 msec and a sampling interval of 200 msec. Averages of brainstem evoked potentials were thus based upon 1,000 responses.

Brainstem auditory evoked response (BAER) peak detection first involved spectral analyzing each trial using a 512-point fast Fourier transform (FFT) and computing the mean amplitude of each spectral component across all 20 trials. In order to enhance the signal-to-noise ratio the BAERs were digitally filtered with frequency components outside of 440-2400 Hz band set to zero.[32] The enhancement of the BAER signal by digital filtering permitted reliable peak detection by locating the zero crossing of the first derivative. The standard deviation, amplitude, and latency of waves 1 through 5, as well as the interpeak latencies of waves 1-3, waves 3-5, and waves 1-5 for each ear were calculated. Only analyses using the absolute and interpeak latencies were used in order to maintain a high subject:variable ratio for multivariate regression analyses.

Since it was possible to have some peaks missing while others could be present, it was not desirable to code the absolute latency of a particular wave as a "0" latency. This would bias the mean severely. Additionally, we did not want to code absent waves as missing data because the absence of a wave (e.g., wave 3) in the presence of clearly discernible waves (e.g., waves 1 and 5) indicated likely neuropathy for the corresponding brain region. Thus, in order to code absent waves as indicators of pathology, all absolute latencies were Z-score transformed using the standard Z-score equation

$$Y_z = \frac{X - M}{SD_x}$$

where X is the absolute latency for a given wave and M and SD_x are the means and standard deviations derived from a normative study.[33] Abnormality was considered to be increasingly more severe with increasing Z-score values.

Glasgow Coma Score

Two different GCS scores[34] were obtained: one at the time of admission (GCS-A) and a second at the time of computerized EEG and evoked potential testing (GCS-T). The mean time between injury and GCS-T was 7.5 days and the standard deviation was 7.6 days.

The distribution of GCSs at the time of admission for the patients in this study is shown in FIGURE 1.

Disability Outcome Measures

TABLE 1 shows the Rappaport Disability Rating Scale (DRS),[35] which measures disability in six different diagnostic categories of (1) eye opening, (2) best verbal response, (3) best motor response, (4) self-care abilities, (5) level of daily functioning, and (6) employability. TABLE 1 shows the categories and items used for assessing functional outcome. Studies have demonstrated reliability and validity in the DRS and good interrater reliability.[35]

TABLE 1. Rappaport Disability Rating Scale

Eye Opening		Best Verbal Response	
Spontaneous	0	Oriented	0
To speech	1	Confused	1
To pain	2	Inappropriate	2
None	3	Incomprehensive	3
		None	4
Best Motor Response		Self Care Items	
Obeying	0	Complete	0
Localizing	1	Partial	1
Withdrawing	2	Minimal	2
Flexing	3	None	3
Extending	4		
None	5		
Level of Functioning			
Completely independent		0	
Independent in special environment		1	
Mildly dependent		2	
Moderately dependent		3	
Markedly dependent		4	
Totally dependent		5	
Employability			
Not restricted		0	
Selective jobs, competitive		1	
Sheltered workshops, noncompetitive		2	
Nonemployable		3	

The method of scoring and exact definitions of each of the six items are discussed in detail by Rappaport *et al.*[20,21,35] Scores range from 0 (for complete recovery) to 30 (for death). These evaluations were obtained through telephone interviews with the guardians or caretakers of the patients. To minimize errors in the estimates of patient status, the interviews with guardians and parents were structured so as to obtain both yes and no answers to specific questions as well as to provide descriptions of the patient's behavior and progress within a given category. Reliability of the Rappaport scores was obtained by both the simple nature of the score and the accuracy by which it separated functional and independent patients from nonindependent patients.

STATISTICAL METHODS

Data Screening and Transforms

Data analyses involved first double-checking all scores before and after entry into the PDP 11/70 computer files. Each measure category was then screened for extreme values (outliers) and for normality of distribution (BMDP-P7D; P2D).[36] All univariate and multivariate statistical analyses utilized the BMDP Biomedical Computer Programs.[36] Previous work with EEG and evoked potential measures have resulted in the use of standard transforms[7,37] to insure Gaussian normality. For relative power and

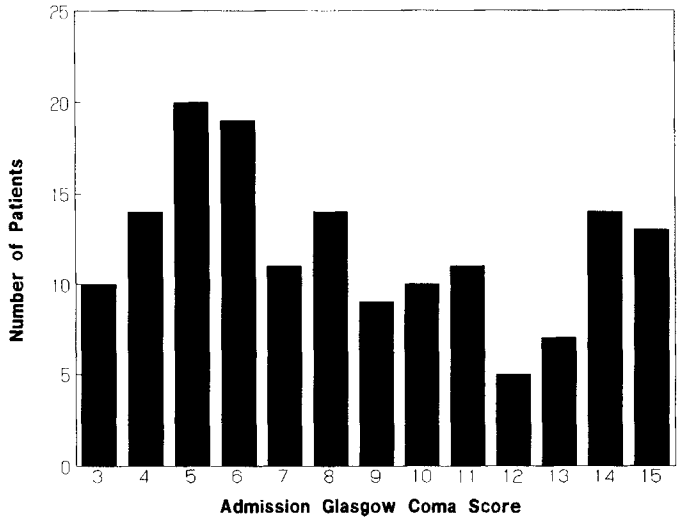

FIGURE 1. Distribution of Glasgow Coma Scores obtained at time of admission (GCS-A).

coherence variables, the transforms were $\log_{10}\frac{(X)}{(100-X)}$. For the amplitude asymmetry variables, the transform was $\log_{10}\frac{(200+X)}{(200-X)}$. After applying the appropriate transforms, all variables approximated the normal distribution.

Discriminant Analyses

Stepwise discriminant analyses with a leave-one-out (for jackknife) replication (BMDP = 7M) were used to determine the ability of individual variables as well as

groups of variables to categorize patients into the two extreme categories of (1) complete recovery (i.e., DRS = 0) or (2) a vegetative state and/or death (i.e., DRS = 30) at one year following injury. Of the 162 patients in the study there was a total of 77 with DRS outcome scores of 0 or 30. Fifty-seven patients had DRS scores of 0, and 20 patients had DRS scores of 30. Initially, each diagnostic measure was evaluated individually (i.e., CT-scan, BSAEP, EEG, GCS, etc). Once the best discriminating variables from each independent variable category were identified, then these variables were combined into a final analysis in order to derive an optimal discriminant function based upon a multimodal analysis.

Multivariate Regression Analysis

The ability of the various diagnostic measures to predict outcome at one-year postinjury in patients with an intermediate Rappaport DRS (i.e., between 1 and 29) was evaluated using multivariate regression analyses (BMDP-2R). Of the 162 patients in the study, a total of 85 patients had DRS scores from 2 to 29. The multiple regression analyses involved first conducting separate analyses of each variable category in order to compare the predictive ability of each independent variable category. Once the best predictor variables from each independent variable category were determined, then these variables were entered into a combined or multimodal stepwise regression analysis. The final analysis adjusted for the intercorrelations between the variables and resulted in a regression equation that contained the strongest predictor variables from the previous analyses.

Prediction Accuracy of Multivariate Analyses

A primary concern is determining how well the discriminant and regression analyses from a sample of patients predict outcome in the population at large. Large sample sizes and multiple cross-validation are necessary to accurately measure prediction accuracy. However, if only a small sample size is available, then constraints must be placed on the ratio of subjects to variables. Recently, Sawyer[38] showed that when a prediction equation is based on a sample from a multivariate normal population, the mean absolute error of prediction can be closely approximated by a simple function of the number of predictor variables and the base sample size. The mean absolute error (MAE) of prediction is equal to the product of $\sigma\sqrt{(2/\pi)}$ and an inflation factor $K = \dfrac{(n + 1)(n - 2)}{[n(n - p - 2)]}$ that is greater than 1. In other words, the inflation factor is a linear function of N and the number of predictor variables p. With this formulation it is possible to estimate the prediction accuracy of a given base sample using a limited number of predictor variables. In all of the discriminant and regression analyses, care was taken to limit the number of predictor variables entered into the discriminant and regression equation to a prediction accuracy of greater than 90%. Thus, in the analyses to follow, the subject:variable ratios were determined by the sample size capable of yielding greater than 90% prediction accuracy.

RESULTS

Discriminant Analyses of Extreme DRS Scores

Individual Discriminant Analyses

TABLE 2 shows the discriminant accuracy of the different independent variable categories to classify patients into the two ends of the Rappaport DRS (good outcomes versus death). The best overall discriminant was provided by EEG phase with 90.2% leave-one-out replication accuracy, and the worst discriminant was provided by EEG relative and total power with 67.1% jackknife accuracy. The order of accuracy of the leave-one-out replicated discriminant (i.e., evaluating both false positives and false negatives) was EEG phase > BSAEP > GCS-T > EEG coherence = amplitude asymmetry > CT-scan > GCS-A > EEG relative and total power. The peak latency of waves 1, 3, 5 and the interpeak latencies between waves 1-3 and 3-5 were the best discriminating variables from the brainstem auditory evoked potential. For CT-scan the best discriminating variables were cerebral atrophy and intraventricular bleeding. For the EEG variables the left and right hemisphere were equally represented with most of the significant variables involving the frontal, central, and temporal leads. The subject:variable ratios of the discriminant analyses ranged from 6:1 for EEG phase to 40:1 for GCS-A and GCS-T.

Combined Discriminant Analyses

The results of the jackknife discriminant analyses using various combinations of independent variables is shown in TABLE 3. Because of listwise deletion in the BMDP analyses, the number of subjects was relatively small in many of the combined analyses and, therefore, the subject:variable ratio was unfavorable (e.g., N = 36 for BSAEP + GCS-T in TABLE 3). However, a relatively large sample size (N = 48) was available in the combined EEG + GCS-T analyses, which yielded the most reliable leave-one-out replicated discriminant (e.g., the subject:variable ratio was 6:1) with a total jackknife discriminant accuracy of 95.8% (TABLE 3).

Regression Analyses of Intermediate DRS Scores

Age

Age ranged from 12.49 to 97.44 yr with a mean of 30.07 and a standard deviation of 17.95. The distribution of age was not skewed; however, it was somewhat kurtotic (e.g., kurtosis = 5.69) with the majority of patients being less than 25 yr of age. A direct relationship was noted between age and the intermediate range of the disability

TABLE 2. Individual Discriminant Analyses

Variable	Predicted Good			Predicted Poor			Total Actual Outcome		
	% Correct	Actual Good (N)	Actual Poor (N)	% Correct	Actual Good (N)	Actual Poor (N)	% Correct	Good (N)	Poor (N)
GCS-A	68.6	35	16	76.5	4	13	70.6	39	29
GCS-T	80.6	29	7	78.6	3	11	80.0	31	28
CT-scan	86.1	31	5	47.1	9	8	73.6	40	13
BSAEP	94.3	50	3	53.8	6	7	86.4	56	10
EEG relative power	69.4	43	19	60.0	8	12	67.1	51	31
EEG amplitude asymmetry	83.0	52	10	65.0	7	13	79.3	59	23
EEG coherence	79.0	49	13	80.0	4	16	79.3	53	29
EEG phase	91.9	57	5	85.0	3	17	90.2	60	22

TABLE 3. Combined Discriminant Analyses

Variables	Predicted Good			Predicted Poor			Total Actual Outcome		
	% Correct	Actual Good (N)	Actual Poor (N)	% Correct	Actual Good (N)	Actual Poor (N)	% Correct	Good (N)	Poor (N)
EEG + GCS-T	94.4	34	2	100.0	0	12	95.8	34	14
BSAEP + GCS-T	100.0	28	0	87.5	1	7	97.2	29	7
CT-scan + GCS-T	94.7	18	1	70.0	3	7	86.2	21	8
EEG + BSAEP	98.1	52	1	92.3	1	12	97.0	53	13
CT-scan + BSAEP	93.5	29	2	70.0	3	7	87.8	32	9
EEG + CT-scan	92.3	34	2	66.7	2	4	87.5	26	6

rating scale. At 12 months postinjury, age was correlated with the Rappaport DRS at .3812, and it accounted for 14.53% of the variance. Examination of residual scatter plots showed that age was a relatively poor predictor of outcome with a large number of both overly optimistic and overly pessimistic predictions. To control for the severity of injury, the regression analyses were repeated with the severity of injury equated across age by forcing the GCS-T into the regression equation at the first step. The results of this analysis showed that age was correlated at .513 and accounted for 26.32% of the variance. The results indicate that the major determiner of outcome is the severity of injury; however, if severity of injury is held constant, then the older an individual the poorer the prognosis.

GCS

As can be seen in FIGURE 2, GCS-A correlated with the intermediate range of the DRS at .5013 and accounted for 25.13% of the variance, while GCS-T correlated with the intermediate range of the DRS at .5907 and accounted for 34.89% of the variance.

CT-scan Measures

As described previously, the CT-scan measures were grouped into three gross anatomic categories: cortical, subcortical, and diffuse. The comparative ability of the different categories of CT-scan measures to predict intermediate outcome scores at 12 months postinjury is shown in FIGURE 3. None of the univariate analyses of subcortical measures was significantly related to outcome. However, there was a significant mutlivariate F in which the multiple $R = 0.2637$ and the $R^2 = 6.95\%$. Of the cortical measures only lesions of the parietal lobes were statistically significant. The multivariate R was 0.4017 and the R^2 was 16.13%. The most significant univariate CT-scan measure was obtained from the diffuse category in which diffuse cortical atrophy was highly significant ($R = 0.5113$, $R^2 = 26.14\%$). Multivariate analyses of the diffuse category yielded an $R = 0.6897$ and $R^2 = 47.57\%$.

Brainstem Auditory Evoked Potential

FIGURE 4 shows the ability of the brainstem auditory evoked potential peak latency and amplitude measures to predict intermediate outcome DRS scores. Peak latency measures exhibited a multiple $R = 0.5209$ and accounted for 27.13% latency and amplitude measures to predict intermediate DRS scores. Peak amplitude measures exhibited a multiple $R = 0.3891$ and accounted for 15.14% of the variance. The variance of peak amplitude was not significantly predictive of outcome. Of the peak latency measures, the interpeak latency between waves 3 and 5 and the latency between waves 1 and 5 accounted for the most variance. Of the peak amplitude measures, the

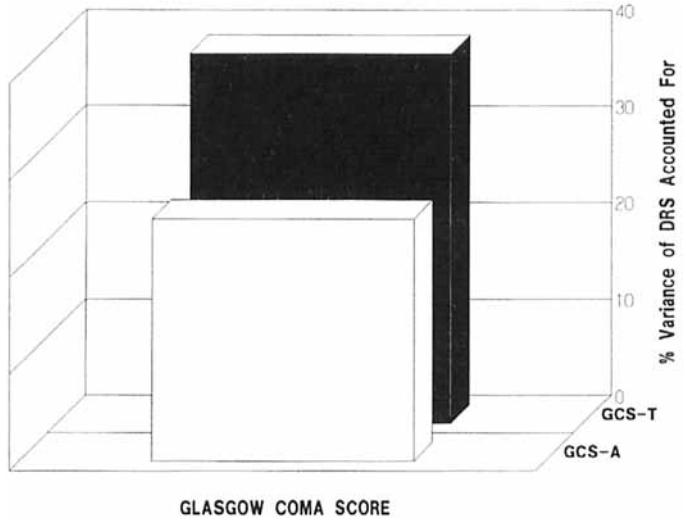

FIGURE 2. Percent variance of the intermediate range of Rappaport Disability Rating Scores (DRS) accounted for by Glasgow Coma Scores obtained at admission (GCS-A) and at the time of computerized EEG and evoked potential testing (GCS-T).

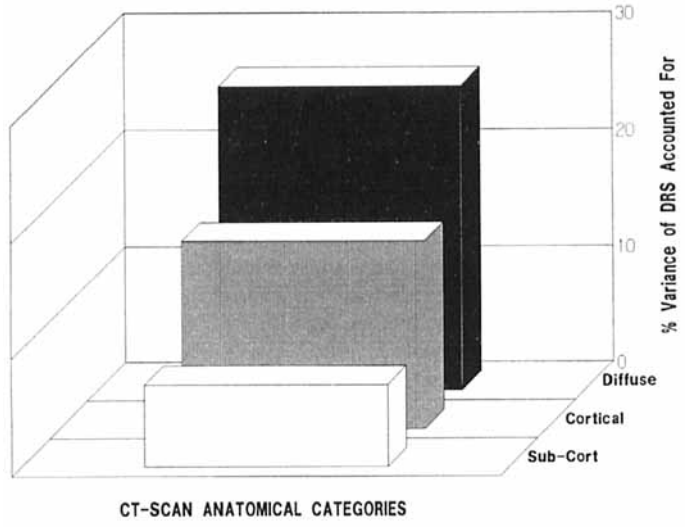

FIGURE 3. Percent variance of the intermediate range of Rappaport DRS accounted for by CT-scan measures. The CT-scan measures were divided into subcortical damage, cortical damage, and diffuse damage (*see* METHODS for details).

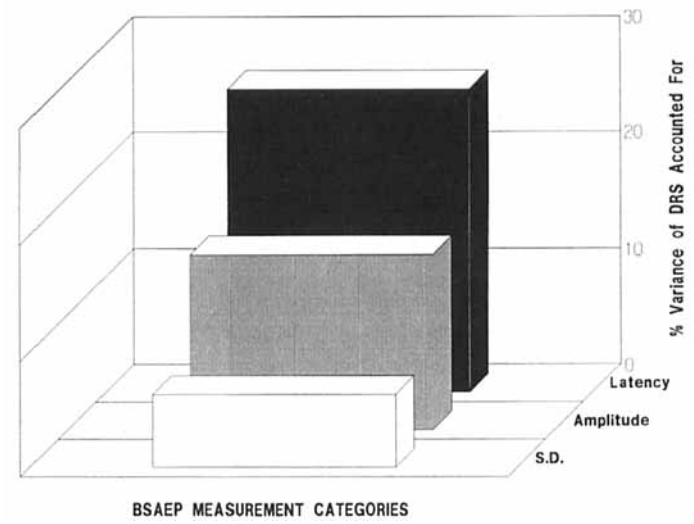

FIGURE 4. Percent variance of the intermediate range of Rappaport DRS accounted for by brainstem auditory evoked potential measures. Amplitude represents the baseline to peak μV amplitude value of waves 1, 2, and 3, while latency represents the absolute latency of waves 1, 3, and 5 as well as interpeak latencies between waves 1-3, 1-5, and 3-5.

absolute amplitude of peaks 2 and 5 accounted for the most variance. The direction of the partial correlations indicate an inverse relationship between peak latency and outcome, that is, the longer the latency the worse the prognosis. Similarly, for peak amplitude, the lower the peak amplitude the worse the prognosis.

Computerized EEG

The ability of the EEG to predict outcome was assessed in separate regressions of five different categories of EEG variables: (1) relative power, (2) total power, (3) amplitude asymmetry, (4) EEG coherence, and (5) EEG phase.

FIGURE 5 shows the ability of the various EEG measures to predict intermediate outcome scores at one year postinjury. It can be seen that the best predictor was EEG phase which had an $R = 0.664$ and accounted for 44.21% of the variance of the disability rating scale, while the least predictive was absolute power with $R = 0.437$ and an $R^2 = 19.14\%$. When the statistically significant EEG variables obtained from the individual analyses were combined into a final EEG analysis, then the multiple R equaled 0.725 and accounted for 52.56% of the variance of the disability rating scores. In the final multivariate regression analysis none of the relative power or total power variables were entered into the regression equation, because these variables were weaker predictors than the amplitude asymmetries, coherence, and phase measures.

Ability of Combined Measures to Predict Outcome

FIGURE 6 shows the comparative strength of predictability of intermediate DRS scores for the various clinical measures. It can be seen that the best predictor of intermediate outcome was the EEG, the second strongest predictor was GCS, the third was brainstem far-field evoked potentials, the fourth strongest was CT-scan measures, and the least predictive was patient age. The final multiple regression analyses were performed on various combinations of the statistically significant variables obtained from the individual analyses shown in FIGURE 6. TABLE 4 shows the results of the combined analyses. It can be seen that the best predictor of outcome was the combination of EEG and GCS-T with R = 0.864 and accounted for 74.65% of the variance of the intermediate range of the Rappaport DRS. The second best combination of variables were from the EEG and brainstem auditory evoked potentials with a multiple R = 0.839 and accounted for 70.53% of the variance. The addition of age, CT-scan, and GCS did not significantly improve predictability.

DISCUSSION

The results of the present study support the view that multimodal measures are more predictive of functional outcome in neurotrauma patients than any one measure set alone.[14–16,29] The results also indicated that EEG measures of cerebral symmetry

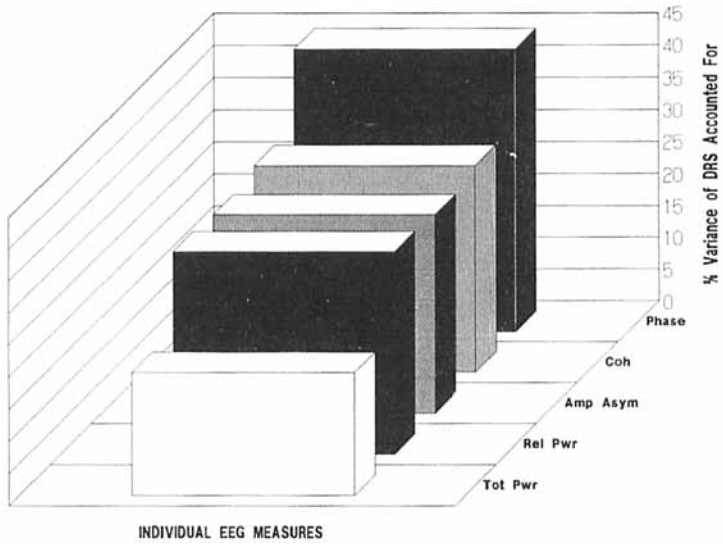

FIGURE 5. Percent variance of the Rappaport DRS accounted for by individual EEG measures. The measures were total EEG power (μv^2), relative power, amplitude asymmetries, coherence, and phase.

(i.e., coherence, phase, and amplitude symmetry) were the best predictors of outcome whether a discriminant analysis of extreme outcome scores was used or a multiple regression analysis of the mid-range of outcome scores was employed. This represents a cross-validation in that entirely different subjects were used in the two different multivariate analyses. The best combination of variables was EEG and GCS, which accounted for 74.65% of the variance with a multiple R = 0.864 and which also exhibited a discriminant accuracy between good outcome and death of 95.8% (TABLE 3).

One difficulty in establishing and evaluating long-term prognostic indices is the fact that many nonneurologic factors, such as associated somatic injuries, sepsis, and medical complications, influence a patient's course and outcome. These factors tend to increase false-positive predictions or errors on the side of overoptimism. The opposite category of error is the false-negative error or the error of overpessimism. Although both categories of error are undesirable, their consequences are different depending on their direction and whether they influence acute management or long-term rehabilitation planning or both. For example, false-positive predictions due to nonneurologic causes have only minimal adverse implications with regard to treatment for recovery of cognitive function. More serious consequences of false-positive predictions occur when they are due to inaccurate measurements of neurologic status.[25] On the other hand, false-negative predictions or errors due to undue pessimism have a bearing on patient outcome if the prediction is for vegetative state or death. A major objective of any program of patient prognostication is to evaluate the consequences of errors and, where possible, to minimize both false positives and false negatives by improving the reliability of measures.

Since different patients with different outcomes were used in the two different analyses, the reliability of the predictor measures can be evaluated by comparing the

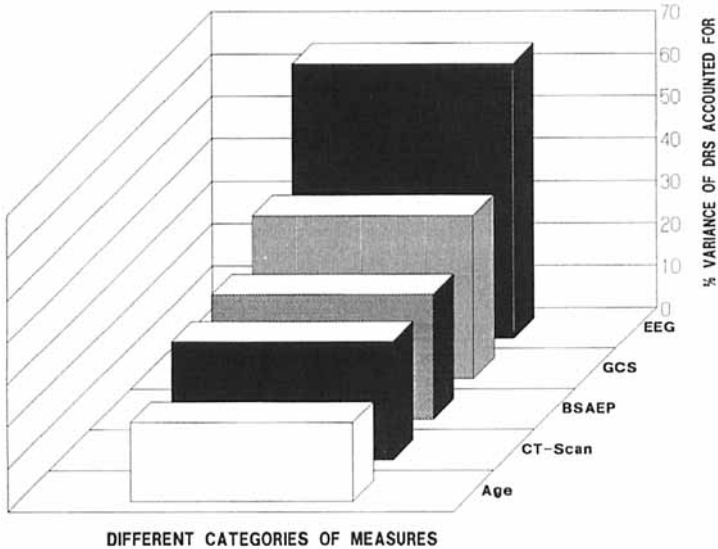

FIGURE 6. Comparison of percent variance of the Rappaport DRS accounted for by various measures. In this figure, measures from each category were combined into a single multiple regression analysis.

TABLE 4. Percent Variance of Rappaport Disability Rating Scale Accounted for by Combined Analyses

Variables	N* (p)**	% Variance
EEG + GCS	129 (12)	74.65
EEG + BSAEP	107 (11)	70.53
EEG + Age	129 (12)	66.82
EEG + CT-scan	80 (7)	60.96
EEG + GCS + Age	129 (12)	74.65
EEG + BSAEP + Age	107 (11)	70.53
EEG + BSAEP + CT-scan	65 (5)	66.09
EEG + Age + CT-scan	80 (7)	61.87
EEG + BSAEP + GCS + Age	88 (7)	72.59
EEG + BSAEP + CT-scan + Age	64 (5)	71.98
EEG + GCS + CT-scan + Age	68 (6)	66.57
EEG + BSAEP + CT-scan + Age + GCS	54 (5)	71.67

* N = Number of subjects; ** p (in parentheses) = Number of variable predictors.

measures that were entered into the final discriminant analysis to the measures that were entered into the final regression analysis. Examination of the variable lists revealed relatively good replication of the measures for the two groups of patients. In particular, the same EEG phase, coherence, and amplitude asymmetry variables exhibited the highest F values in the discriminant analyses and the highest R^2 values in the multiple regression analyses, thus indicating that these measures are reliable and relatively robust in their ability to predict outcome over the entire range of Rappaport DRS. Further, the gradient of prognostic strength from EEG phase > EEG coherence and amplitude asymmetry > CT-scan > EEG relative and total power was also replicated. The reliability and predictive strength of the EEG measures were further demonstrated by the observation of no statistically significant correlation between the date of injury and the date of EEG test (e.g., $R = -0.052$). Thus, the EEG coherence and phase measures appear to be relatively independent of changes in brain edema and other acute injury dynamics.

Diffuse Axonal Injury

Several studies have shown that a predominant pattern of injury in cerebral trauma is of a diffuse and nonspecific nature,[39–41] with the most common substrate for the diffuse effects being diffuse axonal injury (DAI). DAI is the consequence of the shear-strain forces on brain tissue that result from rapid acceleration and deceleration which accompany high velocity impact.[42] The shear-strain forces result in torn axonal fibers, damage to supportive structures (e.g., glia and vascular), and degeneration of neuronal fibers that are often distal to the point of impact.[43] Severe DAI can sometimes be imaged on CT or magnetic resonance imagery (MRI)[43] as a collection of 2.0- to 5.0-mm lesions in deep white matter, brainstem, or basal ganglia. However, CT and MRI do not reliably image mild DAI and hence cannot provide quantitative measures of the neurophysiologic consequences of DAI. In contrast, EEG coherence and phase have been shown to reflect the topographic patterning of human corticocortical fiber bun-

dles.[30–32] Based upon these studies, the most concise explanation of the consistently strong prognostic measures of EEG phase and coherence on the one hand and the latency of brainstem auditory evoked potentials on the other hand is that these measures reflect, to some extent, the magnitude of diffuse axonal injury in the cerebral cortex and brainstem.

Topography of EEG Features

The most significant EEG predictors of outcome were from frontal scalp leads. This is consistent with the features of the skull-brain interface, which place the frontal lobes at risk for injury in high velocity accidents.[43] For example, of the scalp variables that were entered into the final regression analysis, 41.4% involved the frontal leads, 20.6% involved the central leads, 13.7% involved the temporal leads, and 10.3% involved the occipital leads. In all cases there was an approximately equal distribution for the left and right hemispheres. Of the EEG features that were most predictive of outcome, EEG phase exhibited the highest discriminant accuracy (TABLE 2) as well as being the most frequently entered variable in the final regression analysis (e.g., 50%). Coherence was the next most frequently entered variable in the final regression analysis (e.g., 35%), amplitude asymmetry the next (e.g., 10%), and EEG relative and total power were the least represented (0.5% for relative power and 0% for total power). The relatively weak prognostic value of relative and total power is consistent with the fact that these variables tend to reflect the effects of medication as well as global variables such as cerebral swelling. Relative and total power are strongly influenced by the general level of cortical excitability,[31] which is nearly always attenuated following severe-to-moderate closed head injuries, and thus relative and total power have limited ability to discriminate and predict outcome in closed head-injured patients. On the other hand, EEG phase and coherence appear to be relatively insensitive to global cerebral phenomena such as swelling and medication and tend to reflect more accurately the magnitude of structural damage, including damage to the white matter.[30,31]

SUMMARY

A comprehensive diagnostic evaluation was administered to 162 closed head-injured patients within 1 to 21 days (mean, 7.5 days) after injury. Each evaluation consisted of (1) power spectral analyses of electroencephalogram (EEG) recorded from 19 scalp locations referenced to age-matched norms, (2) brainstem auditory evoked potentials, (3) computed tomography (CT)-scan, and (4) Glasgow Coma Score (GCS) at time of admission (GCS-A) and at time of EEG test (GCS-T). Functional outcome at one year following injury was assessed using the Rappaport Disability Rating Scale (DRS), which measures the level of disability in the six diagnostic categories of (1) eye opening, (2) best verbal response, (3) best motor response, (4) self-care ability for feeding, grooming, and toileting, (5) level of cognitive functioning, and (6) employability. The ability of the different diagnostic measures to predict outcome at one year following injury was assessed using stepwise discriminant analyses to identify patients in the extreme outcome categories of complete recovery versus death and multivariate regres-

sion analyses to predict patients with intermediate outcome scores. The best combination of predictor variables was EEG and GCS-T, which accounted for 74.6% of the variance in the multivariate regression analysis of intermediate outcome scores and 95.8% discriminant accuracy between good outcome and death. The best single predictors of outcome in both the discriminant analyses and the regression analyses were EEG coherence and phase. A gradient of prognostic strength of diagnostic measures was EEG phase > EEG coherence > GCS-T > CT-scan > EEG relative power. The value of EEG coherence and phase in the assessment of diffuse axonal injury was discussed.

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REFERENCES

1. KNOBLICH, O. E. & M. GAAB. 1979. Prognostic information from EEG and ICP monitoring after severe closed head injuries in the early post-traumatic phase. Acta Neurochir. Suppl. **28:** 58-62.
2. LANGFITT, T. W. & T. A. GENNARELLI. 1982. Can the outcome from head injury be improved? J. Neurosurg. **56:** 19-25.
3. AVEZAAT, C. J., H. J. VAN DEN BERG & R. BRAAKMAN. 1979. Eye movements as a prognostic factor. Acta Neurochir. Suppl. **28:** 26-28.
4. BRAAKMAN, R., G. J. GELPKE, J. D. E. HABBEMA, A. R. MAAS & J. M. MINDERHOUD. 1980. Systematic selection of prognostic features in patients with severe head injury. Neurosurgery **6:** 362-370.
5. GENNARELLI, T. A., G. M. SPIELMAN, T. W. LANGFITT, P. L. GILDENBER, T. HARRINGTON, J. A. JANE, L. F. MARSHALL, J. D. MILLER & L. H. PITTS. 1982. Influence of the type of intracranial lesion on outcome from severe head injury. J. Neurosurg. **56:** 26-32.
6. HABBEMA, J., R. BRAAKMAN & C. AVEZAAT. 1979. Prognosis of the individual patient with severe head injury. Acta Neurochir. Suppl. **28:** 158-160.
7. JENNETT, B., G. TEASDALE, R. BRAAKMAN, J. MINDERHOUD & R. KNILL-JONES. 1976. Predicting outcome in individual patients after severe head injury. Lancet **1:** 1031-1034.
8. MILLER, J.D. 1979. Barbiturates and raised intracranial pressure. Ann. Neurol. **6:** 189-193.
9. OVERGAARD, J., S. CHRISTENSEN, O. HVID-HANSEN, *et al.* 1973. Prognosis after head injury based on early clinical examination. Lancet **2:** 631-635.
10. ROBERSON, F. C., P. R. KISHORE, J. D. MILLER, *et al.* 1979. The value of serial computerized tomography in the management of severe head injury. Surg. Neurol. **12:** 161-167.
11. TABADDOR, K., A. DANZIGER & H. WISOFF. 1982. Estimation of intracranial pressure by CT scan in closed head trauma. Surg. Neurol. **18:** 212-215.
12. CLIFTON, G. L., R. G. GROSSMAN, M. E. MAKELA, M. E. MINER, S. HANDEL & V. SADHU. 1980. Neurological course and correlated computerized tomography findings after severe closed head injury. J. Neurosurg. **52:** 611-624.

13. LOBATO, R., F. CORDOBES, J. RIVAS, M. DE LA FUENTE, A. MONTERO, A. BARCENA, C. PEREZ, A. CABERA & E. LAMAS. 1983. Outcome from severe head injury related to the type of intracranial lesion. J. Neurosurg. **59:** 762-774.
14. NAU, H.E., E. B. BONGARTZ, W. J. BOCK & C. WEICHERT. 1979. Computerized tomography (CT), electroencephalography (EEG), and clinical symptoms in severe cranio-cerebral injuries. Acta Neurochir. **45:** 209-216.
15. COOPER, R. & A. HUYLME. 1969. Changes of the EEG, intracranial pressure and other variables during sleep in patients with intracranial lesions. Electroencephalogr. Clin. Neurophysiol. **27:** 12-22.
16. ASKENAZY, J. J., L. SAZBON, P. HACKETT & T. NAJENSON. 1980. The value of electroencephalography in prolonged coma: a comparative EEG-computed axial tomography study of two patients one year after trauma. Resuscitation **9:** 181-194.
17. JOHN, E. R., B. KARMEL, W. CORNING, P. EASTON, D. BROWN, H. AHN, M. JOHN, T. HARMONY, L. PRICHEP, A. TORO, I. GERSON, F. BARTLETT, R. THATCHER, H. KAYE, P. VALDES & E. SCHWARTZ. 1977. Neurometrics: Numerical taxonomy identifies different profiles of brain functions within groups of behaviorally similar people. Science **196:** 1393-1410.
18. CURRY, S. H. 1980. Event-related potentials as indicants of structural and functional damage in closed head injury. Prog. Brain Res. **54:** 507-515.
19. FEINSOD, M. 1976. Electrophysiological correlates of traumatic visual damage. *In* Head Injuries. Proceedings of the Second Symposium on Neural Trauma. R. L. McLaurin, Ed.: 95-100. Grune and Stratton. New York, NY.
20. RAPPAPORT, M., K. HALL, H. K. HOPKINS & T. BELLEZA 1977. Evoked brain potentials and disability in brain-damaged patients. Arch. Phys. Med. Rehabil. **58:** 333-338.
21. RAPPAPORT, M., K. HALL, H. K. HOPKINS & T. BELLEZA. 1981. Evoked potentials and head injury: I. rating of evoked potential abnormality. Clin. Electroencephalogr. **12:** 154-156.
22. NARAYAN, R., R. GREENBERG, J. MILLER, G. ENAS, S. CHOI, P. KISHORE, J. SELHORST, H. LUTZ & D. BECKER. 1981. Improved confidence of outcome prediction in severe head injury. J. Neurosurg. **54:** 751-762.
23. GREENBERG, R. P., D. J. MAYER, D. P. BECKER & J. D. MILLER. 1977. Evaluation of brain function in severe human head trauma with multimodality evoked potentials. Part 1: Evoked brain-injury potentials, methods, and analysis. Post-traumatic neurological conditions. J. Neurosurg. **47:** 150-162.
24. GREENBERG, R. P., D. P. BECKER, J. D. MILLER & D. J. MAYER. 1977. Evaluation of brain function in severe human head trauma with multimodality evoked potentials. Part 2: Localization of brain dysfunction and correlation with posttraumatic neurological conditions. J. Neurosurg. **47:** 163-177.
25. GREENBERG, R. P., P. G. NEWLON, M. S. HYATT, R. K. NARAYAN & D. P. BECKER. 1981. Prognostic implications of early multimodality evoked potentials in severely head-injured patients. J. Neurosurg. **55:** 227-236.
26. JENNETT, B. 1986. Head Trauma. *In* Diseases of the Nervous System. A. K. Asbury, G. M. McKhaan & W. I. McDonald, Eds.: 1282-1291. W. B. Saunders. Philadelphia, PA.
27. WILLIAMS, J. M., F. GONES, O. W. DRUDGE & M. KESSLER. 1984. Predicting outcome from closed head injury by early assessment of trauma severity. J. Neurosurg. **61:** 581-585.
28. JASPER, H. H. 1958. The ten-twenty electrode system of the International Federation. Electroencephalogr. Clin. Neurophysiol. **10:** 371-375.
29. OTNES, R. K. & L. ENOCHSON. 1972. Digital Time Series Analysis. John Wiley. New York, NY.
30. THATCHER, R. W., P. KRAUSE & M. HRYBYK. 1986. Corticocortical associations and EEG coherence: A two-compartmental model. EEG Clin. Neurophysiol. **64:** 123-143.
31. NUNEZ, P. 1981. Electrical Fields of the Brain: the Neurophysics of EEG. Oxford University Press. New York, NY.
32. THATCHER, R. W., R. A. WALKER & S. GIUDICE. 1987. Human cerebral hemispheres develop at different rates and ages. Science **236:** 1110-1113.
33. STARR, A. & L. J. ACHOR. 1975. Auditory brainstem responses in neurological disease. Arch. Neurol. **32:** 761-768.

34. JENNETT, B. & M. BOND. 1975. Assessment of outcome after severe brain damage. A practical scale. Lancet **1:** 480-487.
35. RAPPAPORT, M., K. M. HALL, K. HOPKINS, B. S. BELLEZA & D. N. COPE. 1982. Disability rating scale for severe head trauma: Coma to community. Arch. Phys. Med. Rehabil. **63:** 118-123.
36. DIXON, W. & M. BROWN. 1979. Biomedical Computer Programs P-Series. University of California Press. Los Angeles, CA.
37. THATCHER, R. W., R. MCALASTER, M. L. LESTER, R. L. HORST & D. S. CANTOR. 1983. Hemispheric EEG asymmetries related to cognitive functioning in children. *In* Cognitive Processing in the Right Hemisphere. A. Perecman, Ed: 125-146. Academic Press. New York, NY.
38. SAWYER, R. 1982. Sample size and the accuracy of predictions made from multiple regression equations. J. Ed. Stat. **7:** 91-104.
39. ADAMS, J. H., D. J. GRAHAM & T. A. GENNEARELLI. 1985. Contemporary neuropathological considerations regarding brain damage in head injury. *In* Central Nervous System Trauma Status Report—1985. D. P. Becker & J. T. Povlishack, Eds. National Institutes of Health National Institute for Neurological and Communicative Disorders and Stroke. Washington, D.C.
40. AUERBACH, S. H. 1986. Neuroanatomical correlates of attention and memory disorders in traumatic brain injury: An application of neurobehavioral subtypes. J. Head Trauma Rehabil. **1:** 1-12.
41. JANE, J. A., O. STEWARD & T. GENNARELLI. 1985. Axonal degeneration induced by experimental noninvasive minor head injury. J. Neurosurg. **62:** 96-100.
42. STRICH, S. J. 1961. Shearing of nerve fibres as a cause of brain damage due to head injury. A pathological study of twenty cases. Lancet **2:** 443-448.
43. BIGLER, E. D. 1987. Neuropathology of acquired cerebral trauma. J. Learn. Disabil. **20:** 458-473.