Can the outcome from head injury be improved?

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In the past few years, considerable progress has been made in describing patients with head injuries in such a manner that comparisons in morbidity and mortality can be made among neurosurgical centers according to the seriousness of the injury. Less progress has been made in classifying the type of pathology, especially by computerized tomography. The authors have introduced a classification that includes both the type and the seriousness of the injury. There appear to be two principal causes of the brain damage produced by head injury: 1) mechanical damage to neurons and their processes, especially axons, and 2) ischemia. Mechanical damage produces axonal degeneration. Although central regeneration generally is quite limited, perhaps many of the axons damaged by head injury degenerate in continuity, a circumstance in which functional regeneration by axoplasmic outgrowth is much more likely to occur than in most experimental situations where the axons are physically divided. The ischemic brain damage that is so common in head injury appears to be due to mass lesions and brain swelling that both cause intracranial hypertension. The more the brain swells, and the higher the intracranial pressure, the more difficult it is to control the swelling and the pressure. In patients with acute subdural hematoma in particular, the brain swelling and the high mortality appear to be due to ischemic brain damage. There is recent evidence that the mortality rate in patients with acute subdural hematoma is a function of the time from injury to evacuation of the hematoma. Therefore, outcome from head injury can be improved by the earliest possible removal of space-occupying hematomas and by early, vigorous management of intracranial hypertension.

KEY WORDS • head injury • cerebral ischemia • intracranial pressure • subdural hematoma • brain swelling

ALTHOUGH it is clear that the mortality rate from serious head injury is still very high, there continues to be a problem in defining it, because in order to be meaningful a mortality rate should be expressed in terms of the characteristics and the seriousness of the head injury. Therefore, there is uncertainty whether differences in mortality among series of head-injured patients are due to differences in management or variability in the mix of patients. In the large study conducted by Jennett and colleagues (International Data Bank) published in 1977, the mortality rate varied from 49% to 52% among four participating centers. In the same year, Becker, et al., reported a mortality rate of only 32%, but it was not clear that the criteria for admission to their series were equivalent to those of the International Data Bank. Bruce, et al., described a mortality rate of only 6% in a small series of children with an average age of 7 years. This remains far and away the most encouraging report, but it has been known for a long time that children with head injuries fare better than adults, and the unanswered question posed by this study is whether age alone could account for such a low mortality rate.

In a report published in 1978, a plea was made to standardize the definition of a serious head injury and, therefore, the criteria for admission to patient studies. Also, the suggestions were made that the Glasgow Coma Scale (GCS) be used for assessment of the seriousness of injury, at least for a period of a few years; that the criteria employed by the International Data Bank (a total score on the GCS of 8 or less for 6 hours) be used to set the boundaries of the study group; and that the Glasgow Outcome Scale be used, at a specified time from the injury, as the initial end point for measuring morbidity and mortality.

Since that time, a number of additional observations on the outcome from head injury have been reported. In Table 1, data are presented from four studies of serious head injury for the years 1980 and 1981. The mortality rates varied from 34% to 49%. Once again, however, the criteria for inclusion...
and evaluation of the patients are not entirely uniform. The importance of this point is evident on comparing the outcome in the Richmond patients who met the International Data Bank criteria for study and those who did not. The total series of 225 patients was reduced to an International Data Bank-compatible group of 158 patients. The mortality rate in the latter cases was 40% compared to 34% in the group as a whole, and there was a comparable inverse shift in the good recovery/moderate disability category.

Although the principal criteria for defining the study group (the seriousness of the injury measured by the GCS, the length of coma required to admit a patient to the study group, and the time from injury to measurement of outcome) are important variables, there are others of equal importance. The age distribution of the patients is one, and the pathology of the injury and the overall length of coma are also important considerations. Recently we described a new classification of serious head injury in which the patients are divided into a group of focal injuries (extradural hematoma, subdural hematoma, other focal lesions) and a group of diffuse injuries that are further subdivided into patients who are comatose (GCS score of 8 or less) for less than 24 hours and patients who are comatose for more than 24 hours.

In turn, each subdivision in the focal and diffuse categories is divided into two further categories, patients with a GCS score of 3 to 5, and patients with a GCS score of 6 to 8. Because of the large number of subdivisions, it was clear that many patients would be required to provide enough numbers for statistically valid comparisons among the subdivisions. We then asked several of our colleagues with a major interest in head injury to enter their patients into the classification retrospectively. A total of 1107 patients were accumulated from seven centers. The results are presented in detail in the following paper.

The main reason for addressing the study here is to note that the nature of the pathology was found to be as important a determinant of outcome as the patient's neurological status measured on the GCS. The mortality rates among the centers varied from 34% to 52%. Since the International Data Bank criteria for inclusion in the study were rigidly observed by all participants, one might conclude that the center with the lowest mortality rates managed their patients considerably better than the center with the highest mortality. Although this might be true, further analysis of the data tended not to support that conclusion, because when mortality rates were corrected for the incidence of subdural hematoma, the major killer among all of the series, the rates were nearly equal.

This is the best example we have encountered of the need to examine the influence of each one of a substantial number of variables on the outcome from head injury before concluding that any one of them is more important than the others. Table 2 lists the most important variables as we understand them today. Very large numbers of patients who are collected and evaluated with clearly defined criteria will be required to assess the contribution of each one of these variables to outcome. Without this kind of data base to categorize patients and measure morbidity and mortality by category, it will be most difficult to prove that any therapeutic intervention in fact improves the outcome from head injury.

Building a Data Base

In order to improve the outcome from head injury, one must identify a diagnostic or therapeutic intervention that appears likely to influence outcome, then compare the results in a group of patients submitted to the intervention and a matched group of patients with head injury who did not receive the intervention. The first requirement, then, is to establish a large data base. The landmark cooperative effort in building a head-injury data bank was made by the three-nation program organized by Jennett in Glasgow. Another major effort, the Traumatic Coma Data Bank, is now underway, sponsored by the National Institute of Neurological and Communicative Disorders and Stroke.
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There are several purposes for creating a traumatic coma data bank. The first purpose is to permit a prediction of outcome in the individual patient as soon as possible following admission by comparing certain characteristics of the patient with the same characteristics in a population of patients in the data bank for whom the outcome is known. For example, using information on two-thirds of the patients in the International Data Bank to assess the other third, Jennett, et al., were able to predict outcome in 44% of the patients with a probability of 0.97. Braakman, et al., have determined that a powerful prediction of outcome can be made using combinations of age, depth and duration of coma, pupil reactivity to light, and spontaneous and reflex eye movements.

A second purpose of the data bank is to make comparisons among neurosurgical centers in both the characteristics of the patient population and the outcomes so that a distinction can be made between differences in outcome based on patient mix and differences in outcome based on patient management. Suppose for example that Center A has a mortality rate 20% better than Center B. If the patients in Center A were younger, and if their average score on the GCS was higher, and if one knew from the information contained in a large data bank that in this particular example each of these factors contributed 10% to the difference in mortality, then one could say with a probability defined by the data bank that differences in the management of the two groups of patients did not account for the difference in mortality.

The third purpose of a data bank is to provide the information base for prospective studies of therapeutic interventions designed to improve outcome. Even under the best of circumstances the use of a data bank for this purpose is subject to criticism, because comparisons are made across different time epochs. A more acceptable method for evaluating therapy is the randomized clinical trial wherein, in the simplest form, even-numbered patients serve as a controls for odd-numbered patients who receive the therapy to be evaluated. Admirable as it is in concept, a randomized trial is very difficult to conduct in head-injured patients who are so ill that the neurosurgeon often must use every means available as quickly as possible to attempt to save their lives.

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TABLE 2
Variables in determining the outcome from head injury

<table>
<thead>
<tr>
<th>Variables</th>
<th>Outcome from head injury</th>
</tr>
</thead>
<tbody>
<tr>
<td>age</td>
<td></td>
</tr>
<tr>
<td>level of consciousness (Glasgow Coma Scale)</td>
<td></td>
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<tr>
<td>duration of unconsciousness</td>
<td></td>
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<tr>
<td>pupil reactivity to light</td>
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<tr>
<td>spontaneous and reflex eye movements</td>
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<tr>
<td>specific diagnosis (computerized tomography and surgery)</td>
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<tr>
<td>intracranial pressure</td>
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<tr>
<td>extracranial complications</td>
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<tr>
<td>patient management</td>
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FIG. 1. The Glasgow Coma Scale.

Minor and Moderate Head Injury

Nearly all of the attention of neurosurgeons has been directed to patients with serious head injuries. Figure 1 illustrates the Glasgow Coma Scale. Although a GCS score of 8 or less clearly constitutes a serious head injury, a patient who opens his eyes only on command, does not localize painful stimuli, and is able to utter only inappropriate words (a score of 10) also has suffered significant brain damage if he remains in that state for very long. More than 400,000 patients with head injuries are admitted to hospitals in the United States each year, and probably one-quarter of those patients have GCS scores of 8 or less. The time has come to assess the outcome in the other three-quarters. This has become a particularly urgent need because of the recent report by Rimel, et al., demonstrating a high degree of morbidity in patients with minor head injury (defined as a period of unconsciousness of 20 minutes or less, a GCS score of 13 to 15, and a period of hospitalization of 48 hours or less). At 3 months, one-third of the patients had not returned to work, the majority complained of headache and memory problems, and a large number of a subset of these patients showed a variety of neuropsychological dysfunctions on formal testing. Considering the additional fact that the number of patients in the United States who are rendered unconscious or suffer posttraumatic amnesia has been estimated at 1.9 million per annum, it is apparent that head injury is a major public health problem, much larger than we had been led to believe in the past. Clearly, the full range of the problem should command the attention...
Ways to Improve Outcome

There are four mechanisms that appear to be the major cause of brain damage in head-injured patients. They are: 1) mechanical injury, particularly to axons; 2) hemorrhage into the brain parenchyma; 3) edema that develops around a contusion or hematoma; and 4) ischemia produced by an expanding mass or brain swelling. Systemic complications of the injury, especially in patients with multiple trauma, also may contribute to brain damage through systemic hypoxemia, hypotension, hypercarbia, and acidosis. There has been discussion of the possible role of neurotransmitters dysfunction in head injury, but to date there is no clear evidence that this is a significant pathological process.

Mechanical Injury

In acceleration-deceleration injuries of the head, large shearing forces are applied to the brain tissue resulting in stretching and tearing of the neural elements, particularly axons. In particular, when shearing strains are very large, there is extensive destruction of axons in the white matter in the cerebral hemispheres and brain stem accompanied by prolonged coma. These pathological alterations of the white matter were first described in detail by Strich, and are called Strich lesions or diffuse white-matter shearing injury. Lesser degrees of shearing injury almost surely occur in patients with less severe neurological deficits. In fact, Jane, et al., have found degeneration of axons in the white matter of monkeys submitted to a quite minor head injury.

In a broad sense, regeneration of neurons in the central nervous system (CNS) consists of two separate phenomena; first, the growth of damaged or severed axons toward their target cells by axoplasmic outgrowth from damaged terminals; and second, sprouting of adjacent, intact neuronal processes that make functional, synaptic contacts with denervated target cells. For many years, central regeneration was studied largely in the spinal cord. Reattachment of the cut ends of severed cords accompanied by a variety of mechanical and chemical interventions to enhance axonal growth has demonstrated that central regeneration in these circumstances is quite limited. It is important to note that, in regeneration studies in the CNS, either the cell bodies are destroyed or the processes of the neurons under study are physically divided. In the latter circumstance not only must the axon regrow, it must also find its way to its distal axis cylinder, or it must make a new pathway through the substance of the nervous tissue to reach its target cell. Although retraction balls, which are the histological remnants of severed axons, represent one of the most characteristic signs of mechanical damage to neurons in patients with head injury, it is likely that, with a given injury, much larger numbers of axons are damaged and rendered nonfunctional but are not severed. The degenerating axons demonstrated by Jane, et al., in the brain stem of monkeys with minor head injuries probably are in this category. This raises the possibility that the limits of regeneration of damaged neurons in head injury may extend much beyond our ordinary concepts of central regeneration. If an axon degenerates but is physically intact, clearly the opportunity for regeneration is much greater than if the axon is physically torn and its ends are separated.

In fact, the term “regeneration” in its ordinary sense may not be applicable to this situation. The axons might suffer different types of mechanical lesions, each type with its own time constant for both structural and functional recovery. Some possibilities come to mind. Axoplasmic transport is a well known phenomenon wherein proteins are transported both anterograde and retrograde within the axons. The presence of actin and myosin in neurons suggests that axoplasmic transport may be produced by contractile mechanisms similar to those found in muscle. Perhaps mechanical injury of the axon results in irreversible damage of the axoplasm, and restoration of function is dependent on the delivery of undamaged or newly formed axoplasm from the cell body through the region of injury to the axon terminal. Some components of the axoplasm flow at very fast rates, as high as 280 mm/day, whereas others are transported at rates as slow as 1.5 mm/day. This factor alone could account for large differences in recovery rates among axons, depending on the nature and the severity of the injury to the individual axon. There is evidence from studies of the giant axon of the squid that macromolecules are synthesized in the investing glia and pass through plasma membranes into the axoplasm. This is another time-dependent phenomenon that could contribute to restoration of structure and function in damaged axons.

The other mechanism that might contribute to structural and functional recovery of the brain following head injury is sprouting. In the original observations of Liu and Chambers, axonal sprouts from an intact dorsal root were capable of growing through the spinal cord over several lumbar segments to innervate cells in the dorsal horn that had been denervated by sectioning dorsal roots above and below the intact root. Since that time, sprouting has been demonstrated in a variety of pathways in the brain and spinal cord; however, of equal importance, there has been failure to demonstrate sprouting in many systems and, depending on the nature of the lesions, difficulty is often encountered in determining whether recovery of function is due to sprouting or to regeneration of damaged neurons.

Within the field of nervous system trauma, the biology of nerve regeneration has been the special
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province of neurosurgical investigators interested in peripheral nerve and spinal cord injuries. The growing evidence that the primary lesion in head injury is mechanical damage to neurons, resulting in axonal degeneration, puts head injury alongside spinal cord and peripheral nerve trauma as a target area for the study of regeneration.

Ischemia

Most of the pathological consequences of head injury other than mechanical damage have as their common denominator an insufficient supply of oxygen to brain cells, and the most common and important problems are brain ischemia caused by compression from an extracerebral or intracerebral hematoma and uncontrollable intracranial hypertension from brain swelling. Edema per se appears not to disturb brain function, but edema surrounding a hematoma contributes to the mass effect and the consequent ischemia. Therefore, the two most effective ways of preventing or controlling cerebral ischemia are 1) evacuation of intracranial hematomas before they become large enough to produce irreversible ischemic damage, and 2) medical management of the brain swelling that causes severe intracranial hypertension.

In early reports in which the timing of surgery for subdural hematomas was correlated with the clinical outcome, the mortality rate was about the same in patients operated on during the first 24 hours and those undergoing surgery beyond 24 hours after injury, suggesting that early surgery does not improve the outcome. However, Seelig and colleagues have recently described a striking reduction in mortality and improvement in functional recovery in patients with acute subdural hematomas operated on less than 4 hours after injury as compared to patients who were operated on later. Indeed, in patients operated on before 6 hours, the mortality rate was less than 30% compared to approximately 95% in patients operated on after 6 hours from the injury. We noted earlier in this report that it is dangerous to attribute an improvement in outcome to a single variable in a condition with as many important variables as serious head injury. Nevertheless, the differences in outcome in this series of patients were so large that the evidence in support of the authors' conclusion is compelling. If their observations can be confirmed by other investigators, they will explain the failure of other studies to demonstrate an influence of the timing of surgery on outcome, namely that the ischemic damage produced by the hematoma has already become irreversible at 24 hours, and, therefore, it can be prevented only by the earliest possible surgery.

Brain swelling and intracranial hypertension are the other common causes of irreversible cerebral ischemia in head-injured patients. In a review of the literature on intracranial hypertension in head injury published several years ago, some degree of increased intracranial pressure (ICP) was found in more than 90% of 288 patients. Intracranial pressure was over 50 torr in 17% of the patients, and the mortality rate was clearly related to the presence and degree of increased ICP. These experiences have been confirmed in more recent publications, and treatment is now being instituted at lower levels of pressure than was true in the past. In the early days of ICP monitoring, pressures of 20 to 40 torr were considered to be of little importance, because perfusion pressure was still sufficient to maintain adequate cerebral blood flow, even in the face of defective autoregulation. More experience has taught that although these levels of pressure may not compromise brain function at the time, there is a correlation between the level of pressure and its response to treatment. In the ongoing studies by Bruce at the Childrens Hospital of Philadelphia, there have been 15 deaths among 140 children with serious head injury, a mortality rate of 11%. In these 15 cases the mean initial ICP on insertion of a monitor was 61 torr, and none of the children had an ICP of less than 40 torr. The ultimate cause of death in all of the children, despite the most vigorous therapy, was uncontrollable, increased ICP. In contrast, in those patients with an initial pressure below 40 torr, none died from intracranial hypertension.

These latest observations on increased ICP in head-injured patients are intriguing, because not only do they demonstrate again the importance of intracranial hypertension, they suggest that at a point in the course of brain swelling in the individual patient the swelling becomes irreversible, and that point of irreversibility correlates at least roughly with the level of ICP. By the time the pressure reaches the 25 to 30 torr range, it is more difficult to control than when it is less than 20 torr; over 40 torr the most vigorous therapy is required to control it, and with limited success; and when the opening pressure is over 60 torr, death is nearly inevitable. What, then, is the sequence of events that leads from brain swelling that is readily controlled by hyperventilation and intermittent mannitol, to a greater degree of brain swelling that requires more vigorous therapy and may be responsive only to barbiturates, and finally to massive swelling that is unresponsive to all available forms of therapy? Space does not permit a detailed review of the etiology and treatment of brain swelling. Vascular factors appear to be most important in the early stages, and the onset of vasomotor paralysis may be the turning point between reversible and irreversible swelling. In the latter stages of brain swelling, however, it is likely that the brain parenchyma is also involved by either extracellular or intracellular edema. In any event, we now have more evidence than ever of the importance of brain swelling in head-injured patients and of the need to better understand the nature of the swelling and its management if we are to improve the outcome in this group of patients.
General Management

It is difficult to assess the potential effect of better general management of head-injured patients on outcome. It is not surprising that outcome is adversely affected by systemic hypoxemia or arterial hypotension and hypercarbia. A major goal in the management of head-injured patients in the intensive care unit and afterward is the prevention of sepsis of various kinds in order to give those patients who might recover from their brain injury an opportunity to do so. The importance of preventing systemic complications was emphasized in one large series of patients with prolonged unconsciousness. Although the mortality rate among patients who remained unconscious for more than 2 weeks was very high, 31% had made a satisfactory recovery 1 year following injury.

On the other hand, there is evidence that nearly 70% of all patients who die following their head injury do so during the first 48 hours, before general management of the patient (other than treatment of the immediate pulmonary and cardiovascular complications of the injury) becomes a factor. The latter statistic emphasizes once again that large improvements in the mortality from head injury must come from rapid diagnosis and as rapid as possible intervention, particularly in those patients with mass lesion or diffuse cerebral swelling that can cause irreversible ischemia within minutes to hours.

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