Improving outcome after traumatic brain injury – progress and challenges

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This article describes the rapid advances in the head injury field which have taken place within the professional lifetime of many doctors in practice today. These have led to a better understanding of what happens in the injured brain and how these events might be manipulated to achieve better outcomes.

Clinical tools we now take for granted, like the CT scanner and the Glasgow Coma Scale, were new developments 25 years ago. They provided a foundation on which clinicians and basic scientists could build what we now know: what to assess in the patient, how to respond to certain findings, what imaging to do, how to plan treatment rationally, how to minimise brain damage at different stages after injury, how to predict and measure outcome, what disabled survivors need, and how to organise the service to do the greatest good for the most people. Some of these topics raise as many questions as answers.

The head injury field may be broad but it has essential unity. At one extreme, some patients have a life-threatening illness where the acts and omissions of the clinical team can powerfully influence not only survival but its quality. Later the drama of the acute phase gives way to the ‘hidden disabilities’ of the long-term deficits which so many survivors have. At the other end of the severity spectrum is the relatively vast number of people who suffer an apparently mild head injury, a few of whom deteriorate and need urgent treatment, and many of whom have unspectacular but, nevertheless, disabling problems. The article attempts to address this broad canvas.

Clinicians, neuroscientists, policy makers, and service users must work together to address the major scientific, individual, and population challenges posed by head injury. Much has already been achieved, but much remains to be done, especially in translating ‘what we know’ into ‘what we do’.

Throughout history, patients and their doctors have had good reason to fear head injury. We are fortunate to practise in an era when rapid scientific and clinical advance has enabled us to deliver outcomes which were well out of reach only a generation ago. However, much remains to be discovered about the best way to treat the many ways in which head injury presents, and the organisation and funding of services have lagged behind scientific and clinical knowledge. This article explores the
changes of the last 30 years, looks at why the outcome of severe head injury has improved, discusses key issues in current research, and suggests what could be done better with our existing knowledge.

The proverb ‘everyone’s business is no-one’s business’ sums up the organisation of head injury care in the UK. The problem is that no medical specialty has ownership of the problem or a monopoly of expertise, and the inevitable result is the collision of different and often antagonistic agendas.

The science of neurotrauma in the last 30 years has tended to focus on the first hours, when life and death decisions are made and clinicians of several specialties come together to manage what is often multisystem trauma. Dramatic improvements have been seen in this phase, and there is a good story to tell of improved outcomes\textsuperscript{1-5}. However, once the patient has been ‘snatched from the jaws of death’ there are more gaps in what we know and especially in what we do. Many of the consequences of brain damage remain or emerge at that stage, but rehabilitation has attracted comparatively little attention and funding, at least in the UK. This is now changing in response to rising expectations of patients and their families, and as our growing understanding of cellular and molecular mechanisms of injury and repair allow the formulation of a more strategic approach to head injury management\textsuperscript{6}. How to restore function, independence, and quality of life to the brain injured patient is now a major area of scientific endeavour, and clinical practice is becoming underpinned by a steadily growing evidence base\textsuperscript{7-11}.

Managing the acutely head injured patient before 1970

A generation ago, the only tools most doctors had for assessing head injured patients were their clinical skills and plain skull films. Invasive tests such as air encephalography and angiography were available in neurosurgical centres, but could show only the more gross pathological changes. Management decisions had to be made with only a fraction of the information which is routinely available nowadays, and usually it was only possible to react to neurological deterioration, not to predict or prevent it. The biological basis for this deterioration was poorly understood.

There were other problems too. Few epidemiological data had ever been collected, and there was no widely accepted way to classify head injury or measure its severity. In the UK at least, services for head injured patients were fragmented and poorly co-ordinated, resources for research and for improving clinical care were inadequate, and no specialty had taken a leadership role.

In this discouraging climate, the outcome from serious head injury was often dismal. To take only one example, extradural haematoma in the
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Glasgow neurosurgical unit during the period 1963–73 carried a mortality of 36%. By 1988 it had fallen to 9% (Teasdale, personal communication), and this was mirrored elsewhere. What had changed?

The march of science

The anatomy of injury – imaging the injured brain

By far the most important single advance was the introduction of cross-sectional imaging of the head in the 1970s. This let the clinician see into the brain, identify normal and abnormal structures, and plan treatment with confidence. Although early CT scans were crude by modern standards, this was a quantum leap forward and revolutionised head injury management from the very start. Magnetic resonance imaging (MRI) has so far had less impact because of the practical difficulties of getting MR images in an acutely injured patient, but it can provide more detail about structural brain damage. This may become useful for predicting specific residual deficits on which rehabilitative efforts can be targeted. Functional imaging, e.g. by PET scanning and SPECT scanning, has proved a valuable tool in neuroscience research, and may soon have a clinical pay-off in the assessment of areas of physiological rather than anatomical disruption after brain injury.

The physiology of injury – measuring neurological disturbance

Clinicians need a reliable way to quantify disturbed neurological function after head injury, and to monitor its progress. Many local systems were used until the 1970s, inevitably unfamiliar to outsiders, and either too crude to detect early deterioration or too complex for general use. The Glasgow Coma Scale (GCS) overcame these failings, and its world-wide adoption over the last 20 years underlines its usefulness in clinical practice. Like anything else, it only works well if those who use it are properly trained in its use and understand its limitations.

The pathology of injury – understanding events in the injured brain

Concepts of ‘primary’ and ‘secondary’ brain damage have been helpful in clinical practice for over 20 years, but it is now clear that the distinction is not an absolute one. Electron microscopy after experimental head injury has shown that the ultrastructural changes of diffuse axonal injury are not always immediately apparent, and secondary brain damage can
be the end result of biochemical and pharmacological cascades which begin in the brain at the moment of injury\textsuperscript{22,23}.

The anatomical basis of primary brain damage is mechanical disruption of neurones and the cerebral micro-circulation at the time of injury, on a severity spectrum which ranges from simple concussion to overwhelming – and often fatal – diffuse axonal injury\textsuperscript{24}. Little can be done to mitigate its direct effects, and this is perhaps why it has attracted less interest from clinicians than from the forensic community. Prevention has far more to offer than treatment.

Neuropathological work on fatal cases of head injury has shown how often traumatic brain damage is the result of events which occur after the time of injury and which may, therefore, be preventable\textsuperscript{24}. Secondary brain damage – the ‘second insult’ – has commanded much attention over the last 25 years. Jennett’s group described head injured patients who ‘talked and died’, whose death was due to causes other than overwhelming primary brain damage\textsuperscript{25}. They turned the spotlight on to raised intracranial pressure (ICP) from haematoma or brain swelling, and identified ‘avoidable factors’ which had caused or contributed to the death of these patients: delay in evacuating haematomas; uncontrolled intracranial infection or epilepsy; and failure to correct systemic hypoxia, hypercarbia, and shock\textsuperscript{26-28}. Other groups have since reinforced these findings in different geographical settings and patient groups\textsuperscript{29-33}.

The aim is to define what should and should not be done in the early hours and days after injury in order to optimise outcome. It is now well understood that the final common pathway for secondary brain damage is an inadequate oxygen supply to the injured brain, often associated with reduced cerebral blood flow and a rise in ICP\textsuperscript{34}. Mechanically injured neurones are highly susceptible to hypoxic-ischaemic damage, and the depth and duration of the insult determine the extent and reversibility of this damage\textsuperscript{35,36}. Technical advances in monitoring techniques have only served to underline the fundamental role of a failing oxygen supply in causing neuronal loss after trauma\textsuperscript{37-39}.

\textit{The biochemistry of injury – analysing the chemical environment}

The last decade has seen an explosion in our understanding of the biochemical cascades which follow brain injury. Injured neurones can be further compromised by the action of molecules and ions in their immediate environment. Depolarisation by excitotoxic neurotransmitters, degradation of phospholipid membranes, inflammatory tissue changes, and disruption of the regulatory mechanisms for trans-membrane sodium and calcium ion transport can all deliver the \textit{coup de grace} to injured neurones and worsen clinical outcome\textsuperscript{22,23,40,41}. 

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More positively, a better understanding of these processes has led to a vigorous search for ‘neuro-protective’ drugs to prevent or limit this type of secondary brain damage at the cellular level. Unfortunately, promising results in animal studies and preliminary clinical studies have been followed by disappointing results from almost all clinical trials carried out so far. There is some good news: the calcium channel blocker nimodipine (used for over a decade in aneurysmal subarachnoid haemorrhage) benefits patients with traumatic subarachnoid haemorrhage too, and encouraging results have also been obtained from the use of gangliosides and steroids in spinal cord injury. Perhaps head injury is too heterogeneous a condition to be much affected by drugs with a single mechanism under the conditions of a randomised controlled trial.

The cell biology and molecular biology of injury – how the brain repairs itself

Animal experiments, tissue culture techniques, and electron microscopy have taught us much about the mechanisms of structural repair in the injured brain and their functional significance. We are also starting to glimpse how these might be manipulated. For example, grafting peripheral nerves into the brain can alter the cellular micro-environment in a way which favours axonal regrowth and new synapse formation. Neurotrophins can stimulate neuronal and glial activity, up-regulate the production of antioxidant enzymes, and attenuate cell death in experimental models of cerebral ischaemia. Difficulties of delivering the drug to the brain may eventually be overcome by chemically linking it to polyethylene glycol and a monoclonal antibody to promote receptor-mediated transport across the blood-brain barrier. Unfortunately the value of some potential treatments (e.g. antibodies to cytokines such as interleukin) may be undermined by their interference with beneficial as well as harmful effects.

Translating scientific progress into clinical practice – how far have we got?

The common thread from all clinical and pathological studies of head injury over the last 30 years is that secondary brain damage is common and usually preventable by clinical or organisational means. Often it can be traced to delay in the evacuation of a significant intracranial haematoma, or failure to correct systemic cardio-respiratory compromise. How to minimise these ‘second insults’ to the brain through optimal organisation of services and care of individuals is the main clinical challenge in head injury.
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Finding and treating intracranial lesions

The advent of CT scanning revolutionised head injury practice by allowing treatable lesions—especially haematomas—to be diagnosed before cascades of intracranial events cause physiological ‘meltdown’. One consequence was that many patients were found to be harbouring clinically silent lesions which caused delayed deterioration, with only a small window of opportunity to prevent this becoming a point of no return. Good practice now demands that decisions about where to care for a patient are informed by early knowledge of what structural pathology is present in the brain.

Less than 0.5% of head injured hospital attenders need a neurosurgical operation, usually for haematoma, but it is essential to have a triage tool which reliably identifies them. In both adults and children, an abnormal conscious level and a skull fracture are powerful and additive predictors of haematoma, and define a high risk group needing urgent CT scan. At first, the scarcity of scanners meant that a decision to do a scan was usually the same as referral to a neurosurgeon, and led to a great increase in the number of high risk patients transferred urgently to neurosurgical units for a scan. The consequences for the safety of transfer are considered later.

Nowadays almost every accident and emergency department in the UK has easy access to a scanner, at least during working hours, and the information from these can aid the decision-making process. Patients no longer need to travel to a neurosurgical unit simply for diagnosis, but if transfer is indicated on clinical grounds anyway it may be quicker and more convenient to do the scan on arrival at the neurosurgical unit.

Imaging mildly head-injured patients – are some lesions incidental?

Many patients with less severe head injuries (as judged by early physiological and neurological disturbance) nevertheless go on to develop residual physical and especially neuropsychological deficits which affect their health and function in the longer term. There is growing interest in how these patients can be identified, and in the possible benefits of follow-up and rehabilitation.

The history of imaging after head trauma shows that ever more lesions are diagnosed as better resources and growing demand progressively lower the threshold for CT scan. A few patients certainly deteriorate as the result of intracranial complications after apparently minor head injury. In healthcare systems with high public expectations and intolerance of clinical misjudgement this becomes an important driver of clinical policy.

There are of course well-known traps for the unwary in the management of mild head injury: drunks, children, and the elderly. Beyond
these categories the traditional tools of clinical assessment and plain skull radiology have found a new lease of life in the triage of mildly head injured patients to select those who merit a CT scan\textsuperscript{83-85}.

Standard UK practice is now rapidly evolving to the point where any persistent alteration of conscious level (or other neurological symptom or sign) warrants a CT scan in a general hospital, even if it is likely that no surgically significant lesion will be found. This has already become widespread practice in North America and much of continental Europe\textsuperscript{75,84-89}. There is also growing interest in holistic approaches to assessing and managing the head injury workload of a region\textsuperscript{83,91}.

An obvious question is whether some types of intracranial pathology can safely be ignored. Discovering a small haematoma or contusion may not alter clinical management in the acute stage, but finding a lesion should increase the care with which the patient is monitored, and raise the index of suspicion for any changes in their clinical condition. Given the scarcity and uneven distribution of rehabilitation services in the UK finding a lesion may also alter decisions about follow-up assessment to detect and treat residual deficits. MR imaging detects far more lesions than CT scanning\textsuperscript{14,15,92}, and if it becomes more widely used in the acute (or post-acute) investigation of minor head injury this will have implications for the number of such patients referred to head injury clinics and rehabilitation services.

**Monitoring the patient with a serious brain injury**

Another dilemma has been how to decide whether a particular haematoma needs to be evacuated. Monitoring ICP can identify those at risk of neurological deterioration and allow pre-emptive intervention\textsuperscript{93}. Fluid-phase monitoring using a ventricular catheter is cheap but prone to malfunction, and single use high fidelity solid state transducers are now available (at a price). Despite much enthusiasm for ICP monitoring over the years there is no evidence that lowering ICP by pharmacological or other means improves outcome after head injury. Perhaps high ICP is just an epiphenomenon, and to focus on lowering it is to miss the pathophysiological point.

ICP monitoring seems to be of greatest use when linked to other physiological data to derive variables such as cerebral perfusion pressure and cerebral oxygen extraction\textsuperscript{94}. Technical advances now allow the automated collection and integration of data in neurosurgical ITUs, which through servo systems can be used to regulate ventilatory parameters or drug infusion as a form of artificial homeostasis\textsuperscript{37}. The rationale is that on-line correction of physiological abnormalities can prevent or limit secondary brain damage and improve outcome,
especially in an unstable patient, although this has yet to be proved. Such systems require a high level of clinical and technical support, and more work needs to be done to establish their place in clinical practice.

**Resuscitation and transfer**

Hypoxaemia, hypercarbia, and hypovolaemic shock are potent causes of avoidable death and disability after injury, independent of the patient’s conscious level and the CT scan findings\(^4,32,33,95\).

Some complications of head injury carry a high risk of hypoxaemia and hypercarbia: uncontrolled seizures, inadequate breathing, and obstruction of the airway by vomit, blood, or dentures\(^28\). The risk to the airway is closely related to the patient’s conscious level, and it is now widely accepted that the only effective way to protect the airway in a patient who is unconscious (or nearly so) is endotracheal intubation and ventilation using sedative or paralysing drugs.

In patients with a seriously altered conscious level the airway can become obstructed at any time – accident scene, ambulance, accident and emergency department, ward, or neurosurgical unit. Oxygenation must be guaranteed at every stage. Bringing the doctor or paramedic to the scene of the accident can secure the airway early on, but it is now generally accepted that a severely injured patient cannot be fully stabilised in the field. Military experience has taught valuable lessons; in all recent wars a seriously injured soldier’s interests have been best served by rapid evacuation to a field hospital after life-saving interventions\(^96,97\) and in civilian practice the same principle holds true. The US and Germany have developed trauma systems based on networks of designated trauma centres and fast transport\(^98-101\), whereas the UK system is still based on local hospitals – most with no neurosurgical unit on site. However, recent controversial data suggest that the ‘macro-organisation’ of the trauma service may matter less than the quality of care at the ‘micro-level’ – the individual clinician and team\(^102\).

Seriously head injured patients remain liable to airway obstruction and hypoxaemia after arrival at hospital, especially when moved between departments or taken to another hospital for CT scanning or specialist treatment\(^103\). Complications often follow sub-optimal management of the airway before and during transfer to the neurosurgical unit\(^4\), and recognition of this has led to improved airway care and arrangements for transfer, and improved outcomes, although shortcomings persist\(^104,105\).

Victims of high velocity injuries such as road accidents and falls from a height often suffer serious blood loss from major extracranial injuries. These can be surprisingly hard to detect in the head injured patient, especially if unconscious and unable to complain of pain\(^106,107\).
or underestimate these injuries puts the patient at substantial risk of hypovolaemic shock and secondary brain damage.

A pro-active and systematic approach to assessment is needed – clinical examination of every part of the body by an experienced doctor, focused use of radiography and other investigations, and a high index of suspicion when seeking injuries (especially with ongoing cardiovascular instability). To underestimate a serious extracranial injury can be as serious as to miss it, and undue haste in sending an unconscious patient to the neurosurgical unit or the CT scanner can result in inadequate fluid resuscitation or a failure to stop bleeding before transfer. The surgical control of thoracic or abdominal haemorrhage can be a higher priority than the head injury itself.

The introduction of Advanced Trauma Life Support (ATLS) courses in the US in 1980 and the UK eight years later systematised organisation and early management. ATLS promotes a uniform method of assessment, a clear order of priorities in resuscitation, the principle of ‘do no further harm’, and an emphasis on the benefits of early surgical involvement in trauma care. The lack of randomised controlled trials makes it hard to show scientifically conclusive evidence that ATLS has improved outcomes. However, in the UK the ‘early’ peak in the trimodal distribution of deaths after trauma has been largely eliminated, suggesting that the quality of early care has improved. Victims of injury now die either at once (perhaps inevitably) or else later in the ITU from multi-organ failure, suggesting that new educational practices have had positive clinical results.

Guidelines in head injury practice

The ‘guidelines movement’ in medicine has recently emerged as part of a drive for evidence-based practice. Guidelines are not rigid protocols and do not replace clinical judgement, but provide a framework within which it can be exercised safely. Guidelines for managing seriously head injured patients were first formalised in the UK in the 1980s, and were based on evidence that timely transfer to neurosurgery would reduce the number of haematoma patients who deteriorated into coma before surgery, and would lower mortality and morbidity. New or updated guidelines are emerging from the UK, Scotland, Europe, and North America, to take account of new scientific and clinical knowledge and changes in facilities and in expectations.

Different groups tend to focus on different problems and their recommendations can seem confusingly different. One solution is a multispecialty or multi-professional approach to the development of guidelines, based on the best possible evidence available from the literature or from
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Those who have been through this process are well aware how few rigorous scientific studies exist in the head injury field, partly because of practical difficulties in devising such studies. Recommendations then have to be made on the basis of less robust evidence such as observational studies and expert opinion. There are also concerns about whether guidelines are actually put into practice. The challenge over the next few years will be not just to devise guidelines but to make them pragmatic and acceptable to those who have to adapt them to everyday clinical practice within their local circumstances.

**Epidemiology and organisation of head injury care in the UK**

Head injury is extremely common, whether isolated or as part of multi-system trauma. Epidemiological studies 20 years ago suggested that about a million people attend UK hospitals each year after a head injury, and there seems no reason to believe that this has changed. Most have had a minor head injury and can go home after first aid, but we need to be able to identify the 10–15% who have (or may have had) a brain injury and who must be admitted to hospital for observation or treatment.

Where they should go? In the UK as a whole only around 1% of hospital attenders are transferred to a neurosurgical unit, and widely different bed-population ratios provide indirect support to the anecdotal belief that practice varies around the country. Clearly everyone should be transferred whose injury may need a neurosurgical operation, but that is perhaps only 3% of those admitted to hospital. This raises important questions about the management of the others. Should an unconscious patient with a proven diffuse brain injury be admitted to a general ITU which has limited facilities for intracranial monitoring, or to a neurosurgical unit despite the absence of need for operative intervention? Is it reasonable to admit someone with a moderately altered conscious level and scattered contusions to a general surgical or orthopaedic ward for clinical ‘observation’? What is observation anyway?

Where head injured patients should be taken, when and how they should get there, and what staff and facilities should be awaiting them, are still live issues. The recent report on the organisation of head injury care from The Royal College of Surgeons of England is unlikely to be the last word on a subject which inevitably affects a number of specialties. Its recommendation that more head injured patients should be cared for in accident and emergency medicine and neurosurgery, and fewer in general and orthopaedic surgery, is proving predictably controversial. This would require the re-allocation of existing resources and would have major implications for training and manpower.
Rehabilitation

Earlier in this chapter evidence was presented to support the concept that brains which have sustained sub-lethal doses of injury have some capacity to restore neuronal connections and function if the subsequent microenvironment is supportive rather than hostile. Mechanisms include neuronal plasticity, unmasking of latent pathways, differentiation of stem cells into neurones and glia, support of injured neurones by glia, and up-regulation of antioxidant enzymes and neurotrophins. Therapeutic trials have generally sought to mimic the action of endogenous compounds using drugs or implants: neurotrophins, gangliosides, or neurotransmitters. Promising results from the laboratory and from early clinical studies offer a biological rationale for providing maximum care to support the severely injured brain until the acutely disturbed physiology starts to stabilise, then embarking on a rehabilitation programme aimed at restoring maximum function and independence.

In an ideal world, rehabilitation would be a concept or process which permeated all therapeutic endeavours after head injury, not a medical specialty or an activity done at a particular place. Practical considerations dictate that specialist units are necessary to concentrate scarce expertise and to provide an appropriate therapeutic environment. There are far too few brain injury rehabilitation services in the UK, and access to them is variable and can appear to reflect 'postcode medicine'. Evidence suggests that most British head injured patients have no access to any organised rehabilitation process, such as accurate information about head injury, a multi-professional assessment of their needs, or specialist therapists or clinical neuropsychologists. This is despite clear evidence from different types of study that the neuropsychological and psychosocial sequelae of traumatic brain injury are extremely common, have pervasive and persistent adverse effects (even after a 'good' neurological recovery), and need skilled intervention.

Data from several countries, including the UK, have shown as conclusively as will ever be possible that organised rehabilitation programmes are beneficial to the seriously brain injured patient. Insurance funders in the US are prepared to spend money up front in order to save money later, and one study has suggested that their outlay is recouped within 3 years through reduced care bills. Recent evidence suggests that systematic follow-up after head injury reduces social morbidity and the severity of post-concussional symptoms. There are many models for brain injury rehabilitation, the details of which are beyond the scope of this article. Most are based on goal setting and achievement and use an interdisciplinary approach. Unfortunately, resource and specialist staffing are major limiting factors for the sorely needed expansion of rehabilitation facilities in the UK.
Auditing process and outcome

As clinical innovation has matured into respectable clinical practice the emphasis has begun to shift towards auditing process and outcome. Perhaps the aim is to reassure ourselves and others that we are doing our best, but audit can also demonstrate the local variability in the quality of trauma care. Greater governmental and public scrutiny of hospital services in the coming years is likely to yield interesting findings about variations in the organisation and quality of trauma care.

The future

Preventing secondary brain damage after head injury poses organisational and scientific challenges. The treatment of seriously injured patients in the accident and emergency department is no longer routinely left to the least experienced doctors without supervision — a professional response to better data and to rising public expectations of the standard of care. However, given the fast turnover of junior medical staff, the education of those who treat the injured must be a constant propaganda exercise. Guidelines can help doctors and nurses know what to do in a given set of circumstances.

The head-injured patient presents a multi-speciality and multi-professional problem. There is an urgent need for more consultants in neurosurgery and general surgery to take an interest in trauma, and for more therapists and clinical psychologists to work in neurotrauma rehabilitation. The UK National Health Service culture of recent years has unwittingly contributed to a tendency to regard trauma patients as a nuisance and an obstacle to the proper business of treating elective patients. Some head injured patients, notably those with a severe diffuse injury and those with mild or moderate injuries, continue to have a particularly raw deal. The limited resources for developing trauma care and for research also tend to dampen professional enthusiasm for innovation and improvement.

The quest for the holy grail of a neuro-protective drug against secondary brain damage has so far proved as fruitless as the Arthurian original, but perhaps the journey is as important as the arrival. What we learn from these studies informs us greatly about processes which take place in the injured brain. Our challenge is to match our treatments to these processes, and it is probably safe to predict that in the next 20 years many exciting developments will further improve outcome after brain injury.
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