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Review Article

The applied neuropathology of human spinal cord injury

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Introduction

The timeliness of a review of the neuropathology of human spinal cord injury (SCI) centres on the increasing interest in central axonal regeneration in the search for a 'cure' of spinal paralysis. Neuropathology contributes to this end by describing the nature of the disorder to be cured. More broadly a knowledge of the neuropathology underlying SCI is essential also for the clinician responsible for management of the patient as well as the neuroscientist working on SCI. There has been spectacular progress in neurobiology in recent years with CNS repair and regeneration now reported by many centres. However, in order for these discoveries to be applied to human SCI an appreciation of the neuropathology is required. The neurobiologist must be aware of the nature of the condition to be cured for the research to be relevant. Furthermore, before the experimental findings may be applied to the patient it must be shown that the reactions to injury are comparable in each. An outline of recent advances in the neurobiology of experimental SCI is therefore included in this review in order to bridge the gap between human SCI and the experimental models. Most importantly the insight provided by the complexity of the problem of finding a cure serves to inform those waiting for this to occur to be realistic in their expectations.

Historical review

There are several excellent reviews of the neuropathology of human SCI. Ancient texts which refer to spinal injury such as the Edwin Smith Surgical Papyrus C3000-2500 BC and the writings of Hippocrates, Celsus, Ambrose Pare, Paulus of Aegina and Galen are quoted by J Trevor Hughes[1] in his monograph on spinal cord pathology. He and others provide excellent summaries of the 19th and 20th century literature.[2–6] A few of the highlights follow.

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Wolman[3] observed that SCI was a modern disease related to industrialisation with the advent of the railways and motor transport. Many of his observations hold true today including the rarity of compressive effects attributable to epidural, subdural and subarachnoid haemorrhages. The lack of equivalence between experimental injuries which are precise and human SCI lesions which are diffuse remains topical. He points out that human SCI has multiple morphologies; contusions, lacerations, haemorrhages, maceration, extensive cone-shaped necroses and cysts are all described. Of special interest, because of our own studies, is his observation that the spinal column may be injured with the spinal cord remaining intact and the reverse. The distinction between blunt and penetrating injuries is to the point. He describes the susceptibility of the cervical spine to injury when affected by degenerative osteoarthrosis which is also a prevailing theme even today. He summarises the literature concerned with nerve root regenerations as a late phenomenon these being derived mainly from the posterior horns and root ganglia. The reader is referred to these articles for a fuller account of his studies.[3–5]

Of the several aspects of human SCI which remain controversial, the mechanism of injury requires discussion especially in view of recent observations concerning 'discomplete' cases and the phenomenon of 'secondary' or continuing damage. Braakman and Penning[7] correctly point out that mechanical compression due to displacement of the vertebrae which may be momentary is the principal cause of spinal cord damage. They also emphasise that radiographic examination may be normal in 50% of cases with cervical cord lesions. The rarity of extradural or intramedullary haematomas which would require surgical decompression is also documented and they question the value of decompressive laminectomy. Sir Ludwig Guttmann[6] in his monumental work also subscribes to the view that the cord is damaged immediately by acute compression with the destruction of nervous tissue elements and their blood supply at the time of impact. Sir Ludwig was also one of the

first to consider the natural history of SCI with acute, intermediate and late stages recognised. He noted that late deterioration requires a pathological explanation.

In addition to his excellent synopsis of the early literature, Jellinger[2] draws on his own extensive experience of SCI in his review of SCI. His approach is classic, dealing with open and closed injuries separately thus underlining the distinction between penetrating (war) injuries and the industrial and motor vehicle accidents of civil life. Concerning the mechanism of injury these are grouped conventionally into; (1) flexion and (2) deflexion, ie hyperextension or dorsiflexion injuries, (3) vertical compression, (4) rotation, (5) injuries with combined mechanisms. He was also one of the first to describe the different effects of each type of injury on the anterior and posterior longitudinal ligaments and recognises primary damage of the spinal roots and nerve root regenerations in the chronic lesions. He also draws attention to the modern concept of primary and secondary damage and agrees that compressive or space-taking effects of haemorrhages, epidural or subdural which may require surgical decompression are rare. Late sequelae and complications are discussed including local and remote effects in the cord. However, he does not clearly distinguish between residual cysts and syringomyelia, a matter which has recently been considered in relationship to spinal stenosis.[8]

In his account of the mechanism of injury, Trevor Hughes[1] considers that malalignment following injury narrows the spinal canal so that the spinal cord is pinched between the lower vertebral body and the neural arch of the vertebra above. He also refers to the absence of radiological evidence of injury in many cases especially in 'rotation and flexion' injury.

Among the more recent publications of human SCI pathology, one of the most important is that of Bunge *et al*.[9] These authors give details of 22 cases of spinal cord injury with MRI and pathological correlation. The patients were aged 16–80 years with survival 3 h to 22 years. Sixteen of the 22 cases were cervical. They were classified into four groups:

(1) *Contusion cyst*
Five of their 22 cases showed this type of injury. The authors considered this lesion to be comparable to the experimental animal models.

(2) *Cord maceration*
Seven of their 22 cases showed massive compression after closed injury, the cord being lacerated and severley distorted. In three of these, fragments of remaining CNS parenchyma was found suggesting that a small number of central nerve fibres may occasionally maintain their continuity.

(3) *Cord laceration*
Six of 22 patients showed this type of lesion which were due to gunshot wounds.

(4) *Solid cord injury*
Four cases fell into this group. One of these showed chronic compression. These four patients were clinically incomplete and neurological examination showed the central cord syndrome of Schneider *et al*.[10] These patients had no grey matter changes at autopsy but axonal disruption was present in the surrounding white matter especially in the lateral columns. These authors conclude that 'these findings suggest that in a subset of human cord injury the cord lesion present is primarily a focal damage to axon-myelin units, largely confined to white matter regions of the cord. This may be considered a focal axonal loss from white matter damage and may be similar, except in distribution, to the disseminated axonal loss seen in head injury'.[9] These patients were mostly elderly and had relatively minor injuries which were aggravated by the presence of advanced degenerative arthritis of the cervical spine. Martin *et al*[11] also reported a case of central cord syndrome at C3-4 with similar white matter changes demonstrated by pre and post-mortem MRI as well as histopathologically. In their patient recent necrosis was present in the right anterior horn at C4-5.

Leditschke *et al*[12] described 100 fatal SCI cases involving motor vehicles. Sixty showed damage to the cervical spine, involving bony or disc damage in 31 and focal haemorrhages in another 29. In eight cases, pre-mortem radiology failed to detect lesions which were found by postmortem radiology and pathological examination. The initial radiological examination 'missed' many laterally placed fractures and small chip fractures.

There is considerable interest in spinal cord injuries in Japan. Kinoshita[13] published autopsies on 31 patients performed between 1957 and 1987. Nine of his patients were elderly with rigid spines. The susceptibility of older people to hyperextension injuries is further described in a later report.[14] Cross sections showed total absence of cord parenchyma at the level of injury. Haemorrhagic necrosis is demonstrated in others.[13] Ito *et al*[15] describe eight patients who died following SCI. In one of these, neurological deterioration continued for 43 h following injury. At autopsy an unusually extensive longitudinal spreading pencil lesion was found to extend from the medulla to T5.

Taylor[16] has made an extensive study of vertebral fractures by a delicate dissection technique in which the cervical spine is sectioned vertically at 2 mm intervals in the coronal plane. He has also shown that in a large number of patients, small 'tear drop' fractures of the vertebral body and small fractures of the zygapophyseal (facet) joints are not visible in X-rays. He emphasises the frequency of pulposus haemorrhages and tears of the annulus.[17] Taylor's observations are of great medico-legal importance especially in litigation concerning 'whiplash' injuries of the neck in patients in whom the radiological examination of the spine is reported as normal.

Turning briefly to alterations in the paralysed muscles, Burnham *et al*[18] sampled 19 vastus lateralis muscle biopsy specimens from 12 spinal cord injury patients from 2 weeks to 219 months post-injury. The fibre typing was assessed by immunohistochemistry for fast and slow myosin heavy chain (MHC) isoform distribution. Their results indicated that between 1 and 20 months post-SCI there was a progressive drop in the proportion of slow MHC isoform fibres and a rise in the population of co-expressed both fast and slow MHC isoform. By 17 months a steady state was reached where the muscle consisted almost exclusively of the fast MHC isoform. Their results demonstrate that in SCI muscle fibre transformation toward histochemical type 2 occurs in stages.

The West Australian contribution

In Western Australia, interest in the neuropathology of human SCI began with the establishment of the Spinal Unit by the late Sir George Bedbrook in the early 1950's.[19] In particular, Sir George, an orthopaedist, was much against routinely treating acute injuries by decompressive laminectomy because this was shown to be of no value in his abundant personal experience. From his postmortem studies Sir George concluded that in most cases of human SCI there is no intrusion into the spinal canal of bony debris, disc material or space taking haematomas which would benefit from surgical drainage. It was also apparent that the additional stress caused by the surgery and the exposure of the cord which interfered with blood flow was neurologically detrimental. Laminectomy also caused vertebral instability and late complications. Operative reduction was shown to be unnecessary as re-alignment occurred almost immediately in extension injuries and more gradually in flexion injuries with the patient at rest. Surgical fixation was confined to unstable injuries and 'locked facets'.

Sir George's main concern in his postmortem examinations was to determine whether or not there was any aspect of the spinal injury which was amenable to surgical treatment. His conclusion was emphatically in the negative. In the pioneer rehabilitation management system known as 'total care' he showed conclusively that the conservative approach gave better results with reduced morbidity and improved rehabilitation.[19] Earlier a similar conservative management regime was developed independently by Sir Ludwig Guttman at the Stoke Mandeville Hospital and for the same reasons.[6] Sir Ludwig was a trained neurosurgeon, which gives weight to his conservative views.

Sir George was assiduous in gaining permission for autopsy examination in all SCI deaths. Because of my developing special interest in neuropathology in the late 1950's he enlisted my aid in these investigations. From these beginnings, the collection of spinal injuries held at the Royal Perth Hospital has grown so that it now consists of 1815 spinal cords, 566 of which are traumatic. Of the 566 cases of trauma, 354 are hyperacute, ie where the victim of SCI is dead on arrival at hospital, 125 are of acute survivors of less than 6 months and 87 chronic cases of SCI who survived 6 months or more. With the advent of computerisation the materials were organised into a clinicopathological database and tissue bank which is a priceless resource in the worldwide fight against spinal injuries.[20]

The neuropathology of human spinal cord injury

Preamble

In order to fully appreciate the neuropathology of SCI it must be kept in mind that living tissues, in contrast to inanimate machines respond to injury over a period of time changing continuously and undergoing a sequence of structural alterations as time passes. The fact that tissue reactions require time to develop is also of great medico-legal importance. The courts must understand that visible effects of injury take time to develop and that symptoms do become worse in parallel. The key to improvement of the neurological outcome of SCI is to discover how and why such a continuum of changes occurs, aiming at the molecular level for proper elucidation. This work is performed in the hope that the tissue alterations may be arrested or modified and the pristine state of the cord preserved. This philosophy has been the driving force behind much of the experimental work on acute lesions which is considered in more detail below.

The following description of the neuropathology of human SCI is an aggregate of the general features derived from our study of a large number of cases.[21,22] However, it should be understood that every human SCI patient is unique. This contrasts sharply with the stereotyped nature of injury of animal experiments. For scientific purposes, standardisation is necessary, however this does limit the applicability of the results obtained to the human. This description of the neuropathology of SCI refers only to closed injuries resulting from road trauma, industrial and sporting accidents and not to gunshot wounds or other open wounds, adequate details of which may be found elsewhere.[2,3]

Neuropathological features

The neuropathological reactions which follow SCI are similar to those of the CNS in general. The primary mechanism of injury is usually direct mechanical compression of the cord parenchyma resulting from the displacement of the fractured vertebrae and/or discs intruding into the spinal canal. Extradural, subdural and subarachnoid haemorrhages are common but do not cause compression of the cord. Haematomyelia is rare. At first the cord is swollen, bruised and soft. The injury typically extends over several segments and is usually associated with central

haemorrhagic necrosis which may involve the surrounding white matter tracts to a variable degree. Microscopically there is hyperaemia with many free red cells within the disrupted tissues. A variable number of polymorphs appearing at first are followed by macrophages over several days. These mononuclear cells gradually remove the dead tissue. Axonal damage can be detected within hours of injury by immunocytochemical methods using antibodies prepared against the βA4 moiety of the amyloid precursor protein (APP). Astrocytes appear in 5 or 6 days after injury and glial scar formation ensues. Typically, at the level of injury a proportion of white matter mainly at the periphery of the cord is preserved in many SCI cases.[23,24]

The natural history of the lesions in human SCI is conveniently divided into early, intermediate and late stages. Immediately following injury there is complete disruption of a proportion of nerve fibres and partial injury of others. This consists of permanently damaged central axons and others with possibly reversible damage. βA4 immunocytochemistry reveals axonal damage to be of two types, irregular varicosities and axonal spheroids.[23,24] The varicosities indicate a failure of rapid axonal anterograde transport and appear within 30 min of injury. Whether such irregular swellings continue to total 'axotomy' with spheroid formation ('retraction bulbs') or if a number recover is not known. The spheroids only become apparent 24 h after injury which suggests a progression of changes. These spheroids are the equivalent of embryonal 'growth cones' and are the source of (abortive) regeneration. Similar axonal changes are found in the central cord syndrome of the 'solid cord injury'.[9]

Traumatic demyelination is also observed within a few hours after injury. Remyelination of spinal cord axons is found in many longterm survivors in our studies of human SCI but not of the central oligodendrocytic type, but consisting of peripheral myelin produced by Schwann cells. Peripheral myelin is clearly demonstrated by a method developed many years ago for paraffin embedded tissues in multiple sclerosis research.[25] Such remyelination of central axons by Schwann cells is a common feature of the established lesion being present in 16 of 27 patients who lived for 6 months or more. Whether this remyelination also supports spontaneous central regeneration is at present conjectural.

As the lesion progresses debris is removed continuously by macrophages and 'healing' takes place. Scar tissue in the form of astrogliosis, heteromorphic at the level of the lesion and isomorphic above and below the injured segments in association with tract degeneration follows. There may also be collagenous fibrosis present to a variable degree particularly near the leptomeninges which are always fibrotic. The central area of haemorrhagic necrosis is usually replaced by a multilocular cyst traversed by glial-vascular bundles during the healing process. Occasionally a solid collagenous scar admixed with gliosis completely replaces the destroyed central grey matter. Thus, the intermediate stage is characterised by reactive changes with removal of debris, leaving gliotic cavities at the level of the lesion.

The cellular and tissue changes continue until the 'end stage' is reached. The lesion is now composed of glial lined, multilocular cysts, nerve root regenerations and a variable degree of preserved central white matter usually at the periphery. Wallerian degeneration of the afferent and efferent pathways is continuous.

At present there is no information concerning plastic changes which may occur below the level of injury as a result of altered afferent inputs, reflex changes and transmitter neurochemistry. However, by morphological counting methods, transsynaptic degeneration does not seem to occur.[26,27] Late complications such as post-traumatic syringomyelia, spinal stenosis due to osteoarthrosis or ischaemic changes secondary to atherosclerosis are the cause of clinical deterioration many years after the initial injury.

The concept of discomplete

It is evident that despite its delicate consistency the human spinal cord is relatively resistant to the initial injury. Of 354 cases in the database with vertebral injuries who were dead at the scene of the accident, the spinal cord was found to be intact at the level of the lesion in 139. Of the 125 patients with vertebral column injuries who survived for a day or more, the spinal cord was transfected in only 17. Of 87 chronic patients who survived for at least 6 months, 24 were neurologically incomplete, 31 were discomplete showing anatomical continuity across the injured segments and 22 were anatomically complete. The status of the remaining ten was unknown.

The term 'discomplete' was first introduced by Dimitrijevic *et al*[28,29] to explain their finding of electrophysiological transmission of signals across the lesion in patients who were clinically complete having lost all sensation and voluntary motor functions below the level of the lesion. We have examined neuropathologically many patients who were clinically complete but in whom a variable number of intact nerve fibres traverse the lesion. These patients may be regarded as being 'anatomically discomplete'. The finding that a large proportion of patients show some anatomical continuity of the spinal cord white matter across the lesion in clinically incomplete and 'discomplete' patients, emphasises the relative sparing of CNS tracts even in the most severe cases of SCI. This observation underlines the importance of protecting the cord against further injury and gives hope that a significant proportion of such fibres may be salvaged by interventional methods currently being developed (see below).

In their report of 22 spinal injury postmortems, Bunge *et al*[9] observe that 'although it has been said that 90% of SCI cases show tissue continuity across the maximum lesion level', there was a complete lack

of continuity of CNS parenchyma in eight of their 22 cases (38%). Conversely, 62% of their postmortems did show some continuity of CNS tissue across the lesion. This figure is not different to our findings in the SCI survivors. The roadside deaths data are given in a different context. In those cases who show intact spinal cords in the presence of severe vertebral injuries there is no way of determining their clinical neurological status since in the majority death occurred within minutes. The importance of the roadside death experience is to highlight the fact that the spinal cord may escape visible injury even in very severe injuries of the vertebrae.

Quantification

Quantification of the residual white matter with clinicopathological correlation has been undertaken in a number of our complete, incomplete and discomplete SCI. Of interest is the finding that in one complete patient with retained motor function of the ankle there was only 1.17 mm of retained white matter at the level of the lesion whereas in complete SCI patients there may be as much as 3.89 mm^2 spared. Clearly there is no direct correlation with function, which is not unexpected as the site and quality of preserved white matter would be quite variable. Similarly, an attempt was made to quantify the minimum number of fibres associated with retained motor and sensory functions. In six clinically incomplete cervical injuries the descending axonal fibres in the corticospinal tracts of lateral columns were counted at T4. The lowest number of axons found in an incomplete patient with minimal motor function below the level of the lesion was 3175 (normal control 41 472). This patient had retained plantar flexion of the right foot. The lowest number of fibres counted in the posterior columns in a sensory incomplete patients was 117 359 (normal control 452 480).[23,26] The white matter preservation in many complete SCI lesions provides a substrate for the restorative neurologist to work upon in order to improve physiological functions in incomplete SCI patients and to amplify residual subclinical activity in the discomplete group.

The road to cure

Preamble

In considering the neuropathology of human SCI in the present climate of hope it is relevant to discuss how close or distant a 'cure' is likely to be especially since there is a great deal of anticipation by lay parties and even many scientists that this time may be close. Regeneration of CNS is now consistently obtained experimentally and many Conferences and Symposia have been held on the topic in recent years. However, in each of these laboratories, regeneration is achieved under differing experimental conditions. This difference may be a reflection of the research grant funding system which calls for original research or simply because of the complexity of the problem. However, standardisation of methodology and independent confirmation will be necessary before the methods are applied to the human. The end point of much of this experimental work is the morphological demonstration of regeneration of central axons without any reference to functional correlation. In the few studies in which functional assessment has been made, moderate improvement is reported. When demonstrated by video, convincing improvement may be observed especially with pharmacological supplementation.[30] On the other hand there is no doubt that with the power of modern molecular genetics the stage is being set for real neurological recovery.

There are two quite diverse aspects to any consideration of how SCI may be controlled or cured. Broadly these are clinical and neurobiological.

Role of the clinician

The paraplegist has a major role in all of the approaches which seek to overcome the problem of SCI. The clinician should be the leader in primary, secondary and tertiary prevention. The paraplegist is also the person who will apply new discoveries at the bedside directing clinical trials of new treatments as they come forward. Competence for these responsibilities depends upon a sound knowledge of the pathology of SCI. It is also the spinal clinician who must guide the roadside attendants and in the emergency departments of the hospitals in order to avoid further damage to the spinal cord. Clear evidence of aggravation of the SCI has been documented in eight of our cases. Most of these patients had a vertebral injury with no neurological complications at the time of admission. They later became tetraplegic or paraplegic because of poor handling, the attendant not realising the danger. These untoward events occurred in transfer while in the emergency department, during physiotherapy for respiratory complications, when positioning the patient for radiological examination and also during intubation for anaesthesia; all dangerous situations.

Each patient's rehabilitative potential is governed by a combination of neurological and non-neurological factors. One of the most important determinants of the rehabilitative potential of any patient is the level of injury and whether it is partial or complete. There is also a critical difference created by just one higher cervical level, eg a C4-5 lesion is far more disabling than a C5-6 lesion. Broadly approached, the neurological disability in SCI is due to a combination of loss or dysfunction of the motor, sensory and autonomic systems. Each must be corrected in seeking a cure. This contrasts with the simplistic view that all that is required for a 'cure' is independent ambulation. However, paralysis is only one aspect of the disability in SCI and possibly not the most crucial. For instance, there is an enormous difference in the degree of overall

disability between a post-polio patient with intact sensory and autonomic functions compared with a spinal injured patient who also suffers profound sensory and autonomic deficits in addition to loss of voluntary motor control. The non-neurological factors are medical, psychological, social and spiritual, important topics which will not be discussed here.

Restorative neurology

Restorative neurology is a clinical speciality which seeks to improve residual neurological functions of the spinal cord below the injured segments whereas conventional rehabilitation tends to concentrate upon the uninjured parts. Dimitrijevic was one of the first to devote his efforts to this most important specialty which fortunately in recent years has gained wider acceptance.[31] Evaluation of retained functions in SCI is the first step in restorative neurology in order to identify elements which may be enhanced and unwanted reflexes suppressed. Fertile ground is improved for the restorative neurologist by the 'discomplete' cases mentioned above. Using a variety of techniques it may be possible to improve the neurological functions of the residual CNS below the level of the SCI lesion so that clinical benefit is derived. The effects may be obtained by physical, electronic, neurophysiological, pharmacological or biological methods. Neurophysiological methods consist of epidural stimulation, functional electrical stimulation (FES) and computer modelling[32] among others.

In animal experiments a number of measures have been directed toward improving the 'salvage rate' of partially injured but not axotomized nerve fibres in the acute injury. Methylprednisolone and 4-aminopyridine which are now used clinically are examples of the benefits of this approach.[33,34] There is no doubt that with a complete understanding of the tissue reactions, especially at the molecular level, much more will be gained in this way. Neuropathological studies show us that there is a gradient in the severity of SCI from the epicentre of the injury to the periphery. The 'penumbra' of partially injured fibres are those which may be saved. Much interest has been shown in this possibility by several neurobiologists.[35–37]

There is also the property of CNS plasticity to be considered. The importance of this concept is that simple reconnection by CNS regeneration may not restore normal function because the isolated segments of the spinal cord are subject to abnormal inputs and thus physiologically disordered.

Role of the neurobiologist

A vast amount of experimental work has been undertaken in recent years by neurobiologists concerned with SCI. Broadly viewed, these experiments may be divided into two groups. Firstly, some refer to the immediate effects of injury hoping to arrest the continuing or secondary damage of the injured spinal cord. Secondly there are those who are mainly concerned with central axonal regeneration, the re-establishment of anatomicophysiological pathways and the return of normal CNS functions. A variety of approaches are utilised by these researchers. The most basic are those which investigate the developing CNS of mammals. Some study regeneration in primitive species such as fish and amphibia.[38] Another group employs techniques of grafting and transplantation for the reconstruction of the injured segments of spinal cord. These aspects will now be considered in more detail.

The acute phase of injury

The immediate changes following SCI are the disruption of tissues, oedema, inflammation, vascular alterations and the effects of injury on intact axons and myelin. Initially the most obvious abnormality is the mechanical disruption of spinal cord tissue. Oedema appears within a few minutes and becomes well developed within an hour or two after the injury. Petechial haemorrhages in association with disrupted parenchyma are mainly present in the central grey matter. The endothelium of intact capillaries swells so that perfusion through the injured segment is reduced causing ischaemia.[36] Metabolic products accumulate and cytokines are released from injured and reactive cells. These generate an inflammatory response which is responsible for some of the continuing damage.[36,39,40] Polymorphs and monocytes migrate through the vessel walls into the damaged parenchyma. Here the monocytes are converted to macrophages which 'present antigens' to lymphocytes which then continue the assault.

Experimentalists are already able to introduce pharmacological interventions in the acute phase, an example being methylprednisolone[41] and the ganglioside GM-1[42] treatment in order to reduce the severity of the injury.[43] There is no doubt that with improved understanding of each element of the reactive process involved in the continuing lesion methods will be developed in the future which will be of benefit. The severity of the lesion may thus be reduced and the quantity of necrotic parenchyma minimised and partially damaged axis cylinders preserved. Inhibition of the inflammatory reaction and vascular changes holds great promise in this regard. Analysis of the trophic factors, cytokines and other molecular events will also provide opportunities for further interventions.[44,45]

The acute lesion is characterised by traumatic demyelination and by changes in the axis cylinders which have escaped total disruption. These changes are in the form of 'varicose' irregularities and swellings of the axons and are best demonstrated experimentally by use of antibodies against the βA4 moiety of the amyloid precursor protein (βA4 APP). Apoptosis and the role of Bcl-2 expression has also been investigated in the early stage.[46–48]

Free radical damage to membranes is also implicated in the secondary process of continuing damage allowing the entry of excess calcium into the cytosol. Calcium ions activate proteases which autodigest the damaged tissues as part of the necrobiotic consequences of injury. This opens the way for exploration of the effect of antioxidants.[49] Nitric oxide synthetase (NOS) is upregulated following injury and NOS antiserum has been shown to have a protective effect.[39]

In the early phase following injury, changes in neurotransmitters such as substance P and acetyl choline have been identified and the expression of trophic factors such as B-50 (GAP-43) studied.[50,51] The early gene c-*jun* is transiently expressed and c-*fos* continuously in the experimental model. These and other phenomena including spontaneous longitudinal orientation of regenerating axons within a Schwann cell framework are described.[52]

Excitotoxic shock is also believed to play a role in the continuing lesion.[53,54] For this reason GABA (γ aminobutyric acid) inhibitors such as riluzole or gabapentin may be useful in limiting the damage.

The continuing lesion

The next phase in the natural history of SCI is represented by a continuation of the inflammatory reaction. Within the 72 h macrophages ingest tissue breakdown products converting the complex lipids to neutral fat. Astrocytic nuclei swell in 24 h and by 72 h are in increased numbers. Glial fibres are produced within 5–7 days. Considerable work has been devoted to the study of the role of the glia in repair and regeneration[55,56] and inhibitors of CNS regeneration.[57] In the subacute stage, oligodendrocytes and central myelin products such as proteoglycans inhibit regeneration.[58,59] Astrocytes appear to be neutral.

Martin *et al*[60] have transplanted cultured Schwann cells at various intervals into a spinal cord contusion injury model at the low thoracic level in adult female rats. The Schwann cells were derived from adult syngeneic animals. They report that the transplants are well tolerated and invade the injured spinal cord. Better results were obtained 10 days after injury rather than at 3 or 4 days. Microcavities which develop following experimental spinal cord lesions are greatly reduced as a result of the grafts. Astrogliosis is also reduced but only in those animals grafted immediately after the injury. In their experiments the Schwann cell transplanted area is invaded by numerous regenerating axons the majority of which originate from dorsal root ganglia. No regeneration of corticospinal tract as assessed by anterograde tracing or descending aminergic fibres could be demonstrated by these workers.

Wallerian degeneration occurs distal to the level of injury in the descending spinal pathways and proximally in the ascending systems following injury. Wallerian degeneration is characterised by the breakdown of axis cylinders due to failure of the neuronal transport systems. The breakdown of the axis cylinder is followed by degeneration of myelin the products of which are ingested by macrophages. Wallerian degeneration is more rapid in experimental animals than in the human. In the experimental models, target nuclei such as the red nucleus above and Clarke's nucleus below, express oncogenes particularly c-*jun* as a consequence.[51,52] No studies of this type have yet been undertaken in man.

From the outset physiological changes begin above and below the level of the spinal cord lesion due to altered sensory inputs and changes in neurotransmitters. For example, alterations in substance P are reported with a significant increase being found at the level of injury in 1 to 2 h with a reduction occurring at 5 h.[40] Such alterations are more prominent in the isolated segments of the cord below the level of the lesion than in the nuclei above. However, it is now known that there is continuous reorganisation of cortical representation of motor and sensory modalities as a result of the afferent inputs, a plastic process which occurs throughout the CNS. The functional aspects of experimental SCI have received little attention but are an implicitly serious matter when considering a cure.

Below the level of injury, the isolated segments show altered physiological activity in human SCI.[29] Changing the synaptic inputs from above leads to disinhibition of motor neurons with increased levels of glutamates and diminished levels of acetyl choline responsible for altered reflexes. It is now accepted that a central pattern generator[61] in the lumbar cord exists and becomes isolated following injury. Activated by afferent inputs from the paralysed limbs, paroxysmal reflex contractions occur. This is the origin of the 'spasms' which are a common problem in management of SCI patients which may be controlled by intrathecal baclofen.

The end-stage lesion

At about 6 months after injury and sooner in experimental animals the definitive end-stage morphology becomes established. The final lesion consists of multilocular cysts created by the removal of debris by macrophages and astrogliosis forming gliovascular trabeculae traversing the cysts. A variable degree of collagenous fibrosis arises from adventia of blood vessels and meninges. The greater the initial haemorrhage the more collagen is formed. In many patients there is also a variable amount of preserved white matter mainly at the periphery of the spinal cord at the level of injury. In human SCI, nerve root regenerations are also prominent. These grow mainly from the posterior root ganglia but also from the anterior horn cells which have escaped injury. Nerve root regenerations are observed in almost all patients who have survived 12 months or more. To the present no

functional correlation has been associated with nerve root regeneration.

Regeneration of the CNS axons is the prime objective in addressing the end-stage lesions. In this regard grafting, transplantation and other methods which allow central regeneration hold promise.[55] Trophic factors introduced transgenically have also led to success.[55] Peripheral nerve grafts developed by Aguayo *et al*[62,63] have been shown to allow CNS regeneration, a property conferred on the regenerating axons by Schwann cells. This methodology continues to be improved.[64–67] Others seek to reproduce the conditions which apply to the developing nervous system in the mammalian foetus or the regenerating nervous system of fish and amphibia.[38] Other techniques involve the transplantation of embryonic tissues or Schwann cells.[68,69] Falci *et al*[70] have gone one step further by introducing human foetal spinal cord tissue into the post-traumatic cysts in the human SCI patient. However, they state that the intention is not to obtain regeneration but to prevent the development of post-traumatic syringomyelia for which some success has been achieved. Although there have been many encouraging experimental models for CNS regeneration, these have all been specifically addressed to axonal regrowth and not to much to physiological restoration of function.

Conclusion

There are many diverse factors to be considered in seeking a 'cure' for SCI which requires restoration of normal spinal cord function. It should be kept well in mind that there are three principal neurophysiological spinal cord systems. These are motor (pyramidal and extrapyramidal), sensory and autonomic, all of which require to be restored if a true cure is to be achieved. Up to now the voluntary motor system has received most attention. However, anaesthesia often aggravated by symptoms such as burning and phantom pains and distortion of body image is responsible for morbidity in SCI. Similarly, autonomic dysfunction causes bladder, bowel, reproductive and cardiovascular abnormalities all of which limit wellbeing as well as rehabilitation.

The established injury requires a better appreciation of the altered neurophysiology which will be a determining factor in the restoration of functions consequent to the achievement of central regeneration by whatever means. What has been said for the isolated segments below the level of the lesion in this regard also applies to the re-establishment of functional sensory connections above the level of the lesion.

It would be misleading to believe that a 'cure' for SCI is 'just around the corner'. Unrealistic expectations should be discouraged as they will be followed by disillusionment and depression. Certainly the momentum and enthusiasm should be maintained but with more objectivity in assessing progress. It is also a truism that the time it will take to find a cure is directly proportional to the resources applied to the problem. It is now clear that the necessary theoretical knowledge is becoming available and the relevant technology considerably enhanced especially by the advent of modern molecular genetic methods. The means required to complete the task may now be considered available.

Given that regeneration is achieved in the experimental animals it remains to be shown that similar methods will lead to successful regeneration in human SCI. In this respect a most important matter is to determine whether the reactions of human spinal cord are equivalent to the animal models. That is, to show that the molecular processes and their products, neurotrophins, early genes, cytokines and other factors are similar in man and animal both in their nature, quantity and temporal sequence of expression and in their action. In addressing this topic it becomes immediately apparent that much more is known of experimental SCI in animals than in man a situation which deserves immediate attention.

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