

REVIEW

Central nervous system regeneration does not occur

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Study design: Review.

Objectives: To examine the state of research in central nervous system (CNS) regeneration and to suggest an alternative to the sterile research at the lesion site.

Setting: Worldwide.

Methods: A search of publications using 'PubMed' and a search of the historical literature relevant to CNS regeneration, biological models, the neurone theory, collateral sprouting, spinal shock and the central pattern generator.

Results: There is no evidence for CNS regeneration.

Conclusion: A century of research focussed on the lesion site has been unproductive. An alternative field of research must be developed and the best candidate is the undamaged CNS.

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INTRODUCTION

The central nervous system (CNS) is the only tissue in the body that does not regenerate. Other organs may regenerate by the multiplication of intact cells but this is compensatory hyperplasia and not true regeneration. Theories of failure (see ref. 1) include:

1. The CNS is inherently incapable of regeneration. This is a description not an explanation.
2. There is a non-permissive environment. This is another description.
3. The failure of growth factors. Although growth factors have been identified, no meaningful regeneration has been demonstrated. That is, no regeneration which has significantly altered structure or function.
4. The presence of inhibitory factors; the identification of these factors has not resulted in meaningful regeneration.
5. The presence of a glial scar. This has been the subject of animal experiments involving chondroitinase, peripheral axon grafts and cellular matrices but this has not resulted in meaningful regeneration.

The failure of CNS regeneration is not due to want of trying. Google 'CNS regeneration' and there are more than one and a half million results; few, if any, show any evidence of significant regeneration. Significance in this context means regeneration which is important, noteworthy or of some consequence to the organism. Ever since the time of Cajal (1852–1934) there have been countless attempts at demonstrating regeneration in the CNS; all have failed. There are some interesting exceptions.

Tsai *et al.*² in a series of complicated experiments in rats involving complete cord transection, repair with peripheral nerves, fibroblast growth factor, fibrin glue and spinal fixation reported regeneration of the cortico-spinal tract. In their words, 'For the first time ...'. Interestingly enough, Liu *et al.* (2010), see below, point out that successful regeneration 'beyond a spinal lesion has never been achieved'.

Kadoya *et al.*³ reported axonal bridging of spinal cord injury. This work was on rats with a C3 dorsal column lesion. The rats were treated with a combination of bilateral sciatic nerve crush, bone marrow mixed with NT-3 protein instilled into the established C3 cystic lesion cavity and the injection of Lentivirus into the dorsal column white matter. The authors reported 'Axonal bridging beyond the lesion site' with an average of 1.4 mm at 3 months post-injury when treated 6 weeks after injury, and an average of 0.65 mm 16.5 months post-injury when treatment was initiated 15 months after the original injury.

Regeneration of cut axons from retinal ganglion cells (RGCs) has been demonstrated but only through peripheral nerve grafts⁴ and even then only some of the contacts showed synaptic membrane specialisations. RGCs are derived from the inner neuroblastic layer, which is itself derived from the optic cup. The optic cup is derived from the optic vesicles, which are diverticulae from the fore brain. RGCs are, therefore, part of the CNS but only by an anatomical stretch of the imagination does regeneration of RGCs represent significant regeneration in the CNS.

PTEN, a protein encoded by the *PTEN* gene, is a negative regulator of mTOR, which is a protein kinase that regulates cell growth. Liu *et al.*⁵ point out that successful regeneration 'beyond a spinal cord lesion has never been achieved'. However, mTOR activation promotes regeneration in RGCs. The authors used *PTEN* mutant mice and demonstrated 'a robust regenerative response never seen before in the mammalian spinal cord'. Nevertheless, the authors also state that 'despite robust regenerative growth of cortico-spinal tract axons ... *many robustly growing axons fail to penetrate ... the lesion site*' (my emphasis). The authors state that 'significant numbers of ... axons regenerated past the lesion site' and this was by two routes: either circumventing the injury site by the spared white matter or growing through the lesion site. In T8 crush experiments the axons extended for 'up to' 3 mm (my emphasis). As regards forming synaptic contacts, the authors state 'we found many structures with characteristics of synapses, with pre-synaptic vesicles (*partially obscured by the reaction products in the labelled terminal*) (my emphasis).

Liu's paper is unusual to say the least. It was published online on 8 August 2010. In Annual Reviews of Neuroscience 2011⁶ a paper by K Liu *et al* (same address) entitled 'Neuronal Intrinsic Mechanisms of Axon Regeneration' makes no mention, in the abstract, of this startling and unique regeneration but discusses possible strategies for stimulating axon regeneration.

There is, therefore, some evidence of CNS regeneration, but the evidence is of doubtful neurological significance.

There is not a single example of experimental work translating into a therapeutic effect. This should not be confused with the very real advances in the management and symptomatic treatment of lesions in the CNS.

It would be difficult to find any other branch of science with over a century of such sterile endeavour. In effect there has been repetition of the same idea, albeit with different techniques, that is, looking at the lesion site. Are we sentenced to repeating the same experiments in the hope of expecting a different result?

Fawcett¹ summed up the endeavour: 'no patient has yet benefited from a regeneration therapy'.

But was he saying any more than Cajal nearly 100 years earlier?

'...Imposed on the neurones two great lacunae; proliferative inability and irreversibility of intraprotoplasmic differentiation. It is for this reason that, once the development was ended, the founts of growth and regeneration of the axons and dendrites dried up irrevocably.' (cited by Stahnisch and Nitsch⁷).

Wang and Sun⁸ discuss general aspects of neural plasticity, including sprouting in a comprehensive and illuminating review (though their historical attributions are not entirely accurate), and point out that structural repair of the CNS has not materialised.

A search of the relevant research literature using 'PubMed' and a search of the historical literature was carried out. The overwhelming majority of research papers refer to work carried out at the site of the lesion and confirm the view of Cajal, Fawcett and Wang and Sun that none of the published work focussing on the site of the lesion shows any promise of a therapeutic effect.

Why does CNS regeneration not occur? What should be the alternative approach? An apparently diverse group of subjects: a simple 'thought' experiment, examination of biological models, the neurone theory, the phenomena of spinal shock and the central pattern generator (CPG) perhaps indicates the answer.

A 'THOUGHT' EXPERIMENT

Consider two large cities connected by a complex telephone network via a multitude of sub-stations. There is, in addition, a major connection that becomes irretrievably broken and the terminals of this pathway destroyed, thus leaving space for new terminals to make contact from other undamaged connections. This would be carried out from various sub-stations. If the 'target' of the major connection is able to signal that all spaces have now been filled then clearly there would be no attempt to repair the interrupted pathway. What would be the point? This pre-supposes that there is a means of signalling from the target area back to the parent city that there is no means of making a functional contact, even if the line connection were to be repaired.

How does this translate into the CNS?

Axoplasmic transport occurs in both anterograde (towards the synapse) and retrograde (towards the cell body). It is responsible for the movement of proteins, lipids and others, and also messenger ribonucleic acid. Fast (up to 400 mm per day) and slow (less than 8 mm per day) transport has been described. Retrograde transport is capable of altering the synthesis of proteins, the transport of vesicles

and mitochondria and other organelles. A method of signalling therefore exists.

Collateral sprouting (see below) is recognised as a widespread phenomenon and has been demonstrated in peripheral and autonomic systems as well as in the CNS. If a proportion of terminals degenerate due to axonal injury then the uninjured axons sprout to fill the local sites available and consequently expand the synaptic field of the uninjured axon. This has implications in terms of altered physiology as the relative contributions of afferent axons (that is, those axons afferent to the relevant synaptic zones) are now altered.

Plasticity does not necessarily mean a change in structure as with sprouting. An important field of plasticity was opened up by PD Wall *et al.*⁹ when they described unmasking of synapses: when nerve cells lose their normal input, they begin to respond to new inputs that, in the intact animal, produce no response.

Conclusion: no repair is possible if connection with the target cannot be made. Signalling back to the parent cell may take place from axons at the lesion site and from undamaged axons. Changes at the target synaptic zones from sprouting or unmasking produce an altered CNS and altered physiology.

If research at the site of the lesion is sterile, and that is clearly the case, where do we look for the potential of recovery? The answer lies at the area most neglected: the intact nervous system, which has altered as a result of a partial lesion. In effect, all lesions of the CNS are partial. Even a complete transection of the spinal cord leaves the distal cord with internuncial fibres, propriospinal fibres and nerve roots.

The unique features of the CNS are the discontinuity and plasticity, both of which were studied and discussed by Cajal. Biological models and the neurone theory point to the target areas as the real source of the solution to the problem and not the site of the lesion. Examining spinal shock is an example of how the intact nervous system is a more fruitful area than looking at the site of interruption of pathways.

BIOLOGICAL MODELS

It is helpful when considering how the CNS reacts to a lesion and the importance this may have in terms of recovery to consider biological models of nervous integration. There are two main types of such models: those with a random or diffuse structure and those with a well-localised or specific structure. The rapid association of sensory information from widely different sources and of different modalities obviously requires a richly cross-connected network and this confers flexibility. If highly specific inborn circuits were present in the CNS then this would imply the genetic determination of synaptic connections and would reduce to a minor role the effect of use and disuse on connectivity, and this is contrary to known facts. However, complete randomness of connections is also contrary to known anatomical facts. Assuming the property of synaptic facilitation, such a structure could be altered as a result of the sensory input and made to perform a variety of learned tasks. Some specificity would be established as a result of repetitive stimulation as the effect of such stimulation is to produce a demonstrable structural change in appropriate synapses.¹⁰

In addition, unmasking may be seen not only after degeneration but also when there is a change in afferent bombardment without any central degeneration and therefore no sprouting to establish new connections. The fact that altering peripheral stimulation may alter the receptive fields in the CNS has major implications for research in recovery in humans.

The random-specific mode throws into prominence the synaptic zone (see below) that is, the areas of discontinuity.

In the simplest view there are three main bodies of opinion regarding the nature of recovery: Von Monakow's concept of

'diaschisis',¹¹ sprouting and unmasking of nerve terminals, that is, structural and physiological changes and alteration of synaptic effectiveness. The three groups are not mutually exclusive. Von Monakov suggested that if a part of the CNS is destroyed a distant part with which it was in neuronal contact might stop functioning. After a period of time the 'depressed' area recovers its ability to function.

Conclusion: the synaptic zone is the most likely area where reorganisation of the CNS is likely to occur and where a degree of recovery may be expected. The synaptic zone is in effect the target area of all lesions in the CNS. It is the site of sprouting and unmasking and is susceptible to the effects of repetitive stimulation or afferent bombardment.

DISCONTINUITY: THE NEURONE THEORY, PLASTICITY AND SPROUTING

Cajal is perhaps best known for his championship of the independence of neuronal units, which would eventually become the neurone doctrine.

In fact it is possible that Sigmund Freud¹² helped to pave the way for the concept of the neurone theory. In the 1880's he was working on Petromyzon (lamprey) and Crayfish and he demonstrated continuity of neurofibrils between the nerve cell body and its axon. He regarded the cell and its processes as a single unit. A nervous system built up of such units implies discontinuity between its constituent parts. He presented his findings to the Verein für Psychiatrie, Vienna in 1882 or 1883 and published in that society's journal in 1884. Freud, however, was less imaginative in his histological deductions than in his later psycho-analytical studies and the obvious conclusions of his work were not drawn.

The site of discontinuity is the synaptic zone.¹³ The synaptic zone consists of boutons terminaux, post-synaptic thickenings and glial cells and their processes. It is the only part of the nervous system where information from one unit is accessible to another unit, and the only place where one part of the nervous system can influence another part. It is the basis of both the reflex activity and the 'higher' behaviour of the animal.

Cajal explicitly used the term 'plasticity' (circa 1913) in reference to the CNS not just the peripheral nervous system. In fact he adopted the term from the Romanian scientist Ioan Minea who was a pupil of Marinesco. As early as 1894 Cajal was thinking about collateral sprouting and demonstrated synaptic replacement in the dentate gyrus after a unilateral entero-rhinocortical lesion. This was the first demonstration of neuronal plasticity. The term plasticity was regarded as controversial since most neuroscientists at that time regarded the sprouting process as pathological, and it took many years to become acceptable.¹⁴

The complexity of the motor neuron was not appreciated until the paper by Wyckoff and Young.¹⁵ Eccles in his book on synapses¹⁶ says, 'there are multiple endings on any one nerve cell, even many hundreds', and disregards dendrites that are more than 300 μ m from the cell body despite the fact that dendrites form about 80% of the neuron receptive area and are covered with synapses up to 1000 μ m from the cell body.¹⁷ The first demonstration that the number of boutons terminaux was of the order of tens of thousands rather than hundreds was by Armstrong *et al.*¹⁷ using a modified silver technique, which actually stained synaptic vesicles.¹⁸ A large motor cell, such as the anterior horn cell in the cat, has 15 000–30 000 boutons terminaux on its surface.^{19,20} Sprouting must, of course, be seen in the light of this complexity.

Without discontinuity, sprouting cannot of course occur. 'Regenerative' sprouting refers to sprouting replacing a lost axon. Distant

uninjured branches of a damaged axon may react by 'compensatory' sprouting. 'Collateral' or 'reactive' sprouting occurs when intact axons produce new connections in response to injury of neighbouring axons. As indicated above, collateral sprouting has a long history. The first demonstration of collateral sprouting was by Cajal and is largely ignored. Liu and Chambers²¹ demonstrated sprouting in the cat spinal cord in 1958 after section of posterior roots. In 1966, examining the effect of tri-ortho-cresyl phosphate on the synaptic zones in the cat there was a suggestion of the long-term reorganisation of the synaptic zone possibly consequent upon reinnervation.²² Raisman²³ demonstrated collateral reinnervation in septal nuclei. Electron microscopy, though producing ever more important facts of synaptic morphology, is limited by the difficulties of orientation and quantitative work. Armstrong *et al.*'s new silver stain, using light microscopy with its wide range though limited definition, opened the way for a working idea of the motor neurone surface using statistical techniques. In a series of papers in *Brain*,^{20,24–26} the motoneuron surface and the reaction to partial de-nerivation were studied, and demonstrated a sequence of changes, which could only be ascribed to collateral sprouting.

Conclusion: collateral sprouting is an indication of plasticity in the CNS and the target area is the most fruitful site of study.

SPINAL SHOCK

Can spinal shock tell us anything about the effect of a lesion in the CNS? It is a good example of how studying the intact CNS (in this case below the transection of the spinal cord) actually provides an answer. The term 'spinal shock' was introduced by Marshall Hall in 1850, though the actual phenomena were described earlier, by Whytt in 1750 (quoted by Sherrington²⁷). The term is used to signify the effect of sudden injury or transection of the spinal cord. It is characterised by sensory and motor paralysis and then, later, gradual recovery of the reflexes in altered form. Until the intact CNS below the lesion was studied nobody had ever given a convincing explanation of the recovery of reflexes following their complete abolition.^{13,28}

Sherrington²⁷ came to the conclusion that the phenomena were due to '...a defect of transmission at the synapse'. Various theories of dysfunction have been put forward, all involving the long tracts; facilitatory, inhibitory, release of function, interruption of control normally exerted by forebrain structures.²⁹ The final result is a defect of transmission at the synapse and the explanation (actually a description) remains unchanged since the time of Sherrington. There are two further features, which are of particular interest. First, it has been commonly assumed that the effects of transection occur in a caudal direction only. This is not the case, as rostral of the transection there is a change in the reflex response.³⁰ Second, there are the experiments of Teasdell and Stavray³¹ in which one limb of a cat was de-afferented by section of posterior roots. Electrical stimulation of the basis pedunculi produced no response in the corresponding limb, but 5–47 days later responses were evoked more readily in the de-nerivated than in the normal limb. This is a similar, but reversed, state of affairs to that pertaining in spinal shock and has particular reference to some of the work to be described.

Twenty-four hours after partial de-nerivation a profound change is seen in the synaptic zones of the target area. There appears to be a widespread disorganisation of the boutons terminaux on the nerve cells and the dendrites.^{13,24} The mosaic appearance so characteristic of the normal is lost. This appearance is far more widespread than could be accounted for by the actual site of termination of the fibres severed and is present equally on nerve cell and dendrite. This disorganisation is transient and is followed by the appearance of degeneration and then by glial cell replacement of areas, which had become bare of

synaptic contact. Glial cell replacement was first described by Gray and Hamlyn in 1962.³² This is followed by reinnervation of the bare areas from intact fibres and the synaptic zones are indistinguishable from the normal.¹³ Independently, Raisman noted 'new connections are formed by adjacent nerve fibres restoring exactly the original number of connections that existed before the injury'.³³

Sprouting can neither account for the early phenomena of spinal shock nor for the defect of synaptic transmission. The period of temporary absence of reflexes in spinal shock, and the period during which Teasdell and Stavraky failed to evoke a response in a de-afferented limb by stimulation of the basis pedunculi coincides with the phase of widespread anatomical disruption of the synaptic zone, and function returns as the synaptic zone reverts to a more or less stable equilibrium. Reflexes return in an altered form because the synaptic zone is altered by sprouting and unmasking with consequent changes in the relative importance of pathways. Spinal shock is not a static phenomenon with a beginning and an end. There is a dramatic beginning but the return of function is an evolving process.

Non-synaptic or extra-synaptic also called volume transmission is a mechanism for neurotransmission by means of the diffusion of neurotransmitters and ions via extra-cellular fluid with the resulting activation of synaptic and extra-synaptic receptors on the cell surface. This has been put forward as a possible mechanism for spinal shock.³⁴ This, again, is an indication of the importance of the undamaged CNS in understanding the effect of a lesion in the CNS.

The early phenomena may also be due to an alteration of transmission in an extra-synaptic way.³⁴

Conclusion: examination of the undamaged CNS indicates a marked propensity for reorganisation even after a dramatic lesion.

CENTRAL PATTERN GENERATOR

It is clear that the intact CNS has the potential for reorganisation, but can this be translated into function? One strong contender for such a translation is the CPG.

Below a spinal lesion, even with complete transection, there exists a spinal cord which, although altered as a result of sprouting and unmasking, is potentially capable of central processing of signals with a 'normal' distal apparatus of segmental nerve roots, internuncial fibres, propriospinal fibres, peripheral nerves, muscles, ligaments and limbs that are simply cut off from higher influences. The anatomical and physiological properties, which form the connections contributing to the control of walking, exist, but the programming remains poorly understood.

After spinal transection lower vertebrates can perform stepping movements indicating the integrity of neural mechanisms capable of co-ordinating muscle activity over several segments. The groups of nerve cells responsible for this integrated activity are called the CPG, first proposed in 1914 but later refined³⁵ to involve only three types of neuron. In the cat, the CPG can act soon after injury and stepping becomes progressively stronger and may eventually lead to weight bearing. This stepping may be enhanced by electrical stimulation^{36,37} and injection of noradrenergic agonists or precursors.^{38,39}

The presence of the CPG in the human can be inferred by the occurrence of locomotion-like movements in the anencephalic infant. In normal infants, holding the child with the feet touching the floor will elicit walking movements of the legs.

Wernig and Muller in 1992⁴⁰ reported improved locomotion in persons with severe spinal cord injuries with body weight support. Dietz *et al.*,⁴¹ in what may become a landmark paper, demonstrated locomotor activity in spinal man. They studied five patients with complete paraplegia, four with incomplete paraplegia and five age-

matched controls. None of the patients could make stepping movements on a stationary surface. Four to five weeks after the injury they were subjected to training using a treadmill and body weight support. Coordinated stepping movements and muscle activity could be induced by these methods without the use of drugs. Dimitrijevic *et al.*⁴² demonstrated step-like activity in subjects with long-standing spinal cord injury by the use of non-patterned epidural spinal stimulation—a method suggested in 1992.⁴³

It is correct to say that incorporating the results from animal experiments has already led to the development of rehabilitation techniques in humans.

Conclusion: the intact CNS is capable of functioning even after a severe lesion. The necessary steps include (1) the unequivocal demonstration of the existence of the CPG in man, which has probably now been achieved as indicated above, and (2) the possibility of activating the CPG by some sort of external stimulation, which would mean that the subject would have control and, with the techniques of control engineering, sensory feedback would be provided.

CONCLUSIONS

The long history of research in regeneration in the CNS centred on the site of the lesion has proved to be sterile. After a century of such research the focus should move away from the site of the lesion to the intact CNS where there is real promise of improvement of function.

CONFLICT OF INTEREST

The author declares no conflict of interest.

- 1 Fawcett J. Repair of spinal cord injuries: where are we, where are we going? *Spinal Cord* 2002; **40**: 615–623.
- 2 Tsai EC, Krassioukov AV, Tator CH. Corticospinal regeneration into lumbar grey matter correlates with locomotor recovery after complete spinal cord transection and repair with peripheral nerve grafts, fibroblast growth factor 1, fibrin glue and spinal fusion. *J Neuropathol Ex Neuro* 2005; **64**: 230–244.
- 3 Kadoya K, Tsukada S, Lu P, Coppola G, Geschwind D, Filbin M *et al.* Combined intrinsic and extrinsic neuronal mechanisms facilitate bridging axonal regeneration one year after spinal cord injury. *Neuron* 2009; **64**: 165–172.
- 4 Vidal-Sanz M, Bray GM, Villegas-Perez MP, Thanos S, Aguayo AJ. Axonal regeneration and synapse formation in the superior colliculus by retinal ganglion cells in the adult rat. *J Neurosci* 1987; **7**: 2894–2909.
- 5 Lui K, Lu Y, Lee JK, Samara R, Willenberg R, Sears-Kraxberger I *et al.* PTEN depletion enhances the regenerative ability of adult corticospinal neurons. *Nat Neurosci* 2010; **13**: 1075–1081.
- 6 Liu K, Tedeschi A, Park KK, He Z. Neuronal intrinsic mechanisms of axon regeneration. *Ann Rev Neurosci* 2011; **34**: 131–152.
- 7 Stahnisch FW, Nitsch R, Santiago Ramon y Cajal's concept of neurological plasticity. *Trends Neurosci* 2002; **25**: 589–591.
- 8 Wang D, Sun T. Neural plasticity and functional recovery of human central nervous system with special reference to spinal cord injury. *Spinal Cord* 2011; **49**: 486–492.
- 9 Merrill EG, Wall PD. Plasticity of connections in the adult nervous system. In: Cotman CW (ed). *Neuronal Plasticity* 1978. Raven Press: New York, 97–111.
- 10 Illis LS. Enlargement of spinal cord synapses after repetitive stimulation. *Nature* 1969; **223**: 76–77.
- 11 von Monakow C. *Der Grosshirn und die Abbaufunktion durch kortikale* 1914. Bergman. Herde: Wiesbaden.
- 12 Freud S. Quoted by E Jones in 'The Life and Work of Sigmund Freud'. 1953. Basic Books Inc.: New York.
- 13 Illis LS. The motor neuron surface and spinal shock. In: Williams D (ed). *Modern Trends in Neurology*, vol. 4. 1967. Butterworths: London, pp 53–68.
- 14 Young JZ. Growth and plasticity in the nervous system. *Proc Roy Soc* 1951; **B139**: 18–37.
- 15 Wyckoff RWG, Young JZ. The motoneuron surface. *Proc Roy Soc* 1956; **B144**: 440–450.
- 16 Eccles JC. *The Physiology of Synapses* 1964. Springer-Verlag: Berlin.
- 17 Armstrong J, Richardson KC, Young JZ. Staining neural end feet and mitochondria after post-chroming and carbox embedding. *Stain Technol* 1956; **31**: 263–270.
- 18 Fitzsimons JTR, Illis LS, Mitchell J. Silver deposition in synaptic vesicles using the Armstrong-Stephens stain. *Brain Res* 1974; **72**: 277–281.
- 19 Aitken JT, Bridger JE. Neuron size and neuron population density in the lumbosacral region of the cat's spinal cord. *J Anat* 1961; **95**: 38–53.

- 20 Illis LS. Spinal cord synapses in the cat. The normal appearances by the light microscope. *Brain* 1964; **87**: 543–554.
- 21 Liu Cnchambers WW. Intrasprouting of dorsal root axons Arch. *Neurol Psychiat* 1958; **79**: 46–61.
- 22 Illis LS, Patangia GN, Cavanagh JB. Boutons termineaux and tri-ortho-cresyl phosphate toxicity. *Exp Neurol* 1966; **14**: 160–174.
- 23 Raisman G. Neuronal plasticity in the septal nuclei of the adult rat. *Brain Res* 1969; **14**: 25–48.
- 24 Illis LS. Spinal cord synapses in the cat: the reaction of boutons termineaux at the motoneuron surface to experimental denervation. *Brain* 1964; **87**: 55–572.
- 25 Illis LS. Experimental model of regeneration in the CNS. I *Synaptic Changes Brain* 1973; **96**: 47–60.
- 26 Illis LS. Experimental model of regeneration in the CNS. II. The reaction of glia. *Brain* 1973; **96**: 61–68.
- 27 Sherrington CS. *The Integrative Action of the Nervous System*. Cambridge University Press: Cambridge, 1947 p 245.
- 28 Illis LS. Changes in spinal cord synapses and possible explanation for spinal shock. *Exp Neurol* 1963; **8**: 328–335.
- 29 Ruch TC. *Medical Physiology and Biophysics*. Saunders: Philadelphia, 1960.
- 30 Creed RS, Denny-Brown D, Eccles JC, Liddell EGT, Sherrington CS. *Reflex Activity of the Spinal Cord*. Oxford University Press: Oxford, 1932.
- 31 Teasdale RD, Stavratsky GW. Responses of the de-afferented spinal neurones to cortico-spinal impulses. *J Neurophysiol* 1953; **16**: 367–375.
- 32 Gray EG, Hamlyn LH. Election microscopy of experimental degeneration in the avian optic tectum. *J Anat* 1962; **96**: 309–316.
- 33 Raisman G. A promising therapeutic approach to spinal cord repair. *J R Soc Med* 2003; **96**: 259–261.
- 34 Bach-Y-Rita P, Illis LS. Spinal shock: possible role of receptor plasticity and non-synaptic transmission. *Paraplegia* 1993; **31**: 82–87.
- 35 Miller S Scott PD. The spinal locomotor generator. *Exp Brain Res* 1977; **30**: 387–403.
- 36 Shik ML, Orlovski GN, Severin FV. Locomotion in the mesencephalic cat elicited by stimulation of the pyramids. *Biophysics* 1968; **13**: 143–152.
- 37 Shefchyk SJ, Jordan LM. Excitatory and inhibitory postsynaptic potentials in alpha motoneurons produced during fictive locomotion by stimulation of the mesencephalic locomotor region. *J Neurophysiol* 1958; **53**: 1345–1355.
- 38 Fossberg H, Grillner S. The locomotion of the acute spinal cat injected with clonidine I. *V Brain Res* 1973; **50**: 184–186.
- 39 Barbeau H, Chan C, Rossignol S. Noradrenergic agonists and locomotor training effect locomotor recovery after cord transection in adult cats. *Brain Res Bull* 1993; **30**: 387–393.
- 40 Wernig A, Muller S. Laufband locomotion with body weight support improved walking in persons with severe spinal cord injuries. *Paraplegia* 1992; **30**: 229–238.
- 41 Dietz V, Colombo G, Jensen L. Locomotor activity in spinal man. *Lancet* 1994; **344**: 1260–1263.
- 42 Dimitrijevic MR, Gerasimenko Y, Pinter MM. Evidence for a spinal central pattern generator in humans. *Ann N Y Acad Sci* 1998; **16**: 360–376.
- 43 Illis LS. Recovery in the CNS and the experimental background of central functional simulation in spinal cord dysfunction. In: Illis LS (ed). *Chapter 1 in Spinal Cord Dysfunction*. Oxford University Press: Oxford, 1992, 9–37.