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BOOK REVIEW

Handbook of clinical neurology

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This is a very good book and a very important one. The list of authors (107) reads like the 'Who's Who' of spinal cord medicine. The volume is much more than an update of previous volumes of the 'Handbook', which also dealt with this topic and were published in 1976 and 1992. New developments have produced important and exciting changes that have altered the subject almost beyond recognition. This statement is true as regards the clinical achievments including diagnosis, prognosis and rehabilitation, but not quite so accurate as regards pre-clinical research.

The 38 chapters form five sections. The first section, on development and anatomical perspectives, deals with the growth and maturation of the spinal cord. A good overview of the embryology, both cellular and molecular, is followed by a description of maldevelopment and the implications of molecular and genetic defects. The anatomy and biomechanisms are dealt with in terms of fundamental principles applied to the spinal column and spinal cord, and lead on to spinal cord injury. This is a good base for the following chapters that form the second section and which deal with the diagnosis, prognosis and monitoring of spinal cord trauma. Hopefully, in the future, there will be clinical trials of therapeutic interventions (but more of that later), and this will require accurate and quantitative measurement. The standard and recognized method is the ASIA scale, but this has limitations, and the best potential lies with neurophysiology and with advanced high-resolution neuroimaging techniques.This is dealt with in two excellent and comprehensive chapters.

The majority of spinal cord injury outcome measures are understandably related to the younger population. However, the increasingly ageing population in most countries has to be addressed. This is a problem in the entire field of medicine. Specifically, in spinal cord injury, the average age of injury has increased and is still increasing. A short but notable chapter deals with the pathophysiology of the ageing nervous system, the aetiology and clinical presentation, complications and mortality and outcome.

The third section deals with acute spinal cord injury: medical and surgical treatment, management and rehabilitation. These are useful straightforward reviews but are also good accounts of exciting developments. It is pointed out, and it cannot be over-emphasized, that spinal cord injury, although interrupting motor and sensory long tracts, still leaves neuronal networks intact below the site of the lesion. This is potentially a much more fruitful area of study than the conventional, and so far fruitless, pursuit of axonal repair. Chapter 20, on the changing field of rehabilitation, gives a brief account of how neural activity has a role in central nervous system (CNS) development and plasticity, but this important subject could have been improved to a great extent.

A chapter on spinal cord stimulation (SCS) should have given more prominence to Cook, who, in the early 1970s, was the first to demonstrate improvement in neurological deficit with SCS. He was carrying out this procedure for pain on a young sufferer with multiple sclerosis when to his great surprise he saw a marked improvement in spasticity with consequent improvement in ambulation. The speed of change suggested that this was almost certainly due to an increase in inhibition. Cook took his observations to the neurologists in his hospital and later to the neurological societies in New York. They refused to even investigate this. Subsequent studies (elsewhere) demonstrated recordable and reproducible neurophysiologcal changes at spinal and brain-stem levels and eventually led to the formation of the International Neuromodulation Society. What Cook had observed was no more than that reported by Frohlich and Sherrington in 1902: after decerebration in cat, dog and Macaque, stimulation of the lower thoracic and lumbar region of the spinal cord showed '..an effect...constant and regular...evoked marked inhibition of the rigidity..'. Cook deserves much greater recognition.

Section 4 is concerned with chronic-stage rehabilitation, and overlaps with the previous section. In fact, it is difficult to see why the two sections were separated. 'Rehabilitation strategies that optimize spontaneous repair and promote neurological recovery are becoming mainstream'. Is this perhaps rather optimistic? 'Spontaneous repair' and 'neurological recovery' risks undue raising of hopes. This is based on a single case report about 11 years ago. Nevertheless, this is an interesting section that, in this chapter, deals with the effect of activity including electrical stimulation on synapses. Although the field is not exactly comprehensively covered, a good trenchant point is made: that conventional rehabilitation of spinal cord disease ignores the beneficial effects of afferent feedback and stimulation, which is aninteresting and potentially exciting concept that brings into focus the undamaged, but altered, central nervous system.

The final section, section 5, deals with preclinical research 'bridging the gap between bench and bedside.' This is the longest section in 15 chapters and approximately one-third of the total volume.The first chapter in this section sets out the goals for therapy, discusses protocols and gives an algorithm for discovery through to clinical use. The authors point out that *no clinical trial so far has been shown to be effective* (reviewer's emphasis). An outstanding and thoughtful chapter follows, again emphasizing the improvement in animals and man with appropriate afferent input, and discusses the challenges to be met. However, there is some inconsistency among the contributors, which, though understandable, is somewhat confusing. Chapter 25 states that 'basic research in spinal cord repair is promising'. A more realistic description might state the opposite. Further chapters point out that there are no satisfactory solutions. Indeed, chapter 33 begins with 'so far, there is no clinical procedure for inducing severed nerve fibres to regenerate'. Further on, the authors state that 'the grandfather of the transplantation strategies was espoused by Santiago Ramon y Cajal in the 19th century'.

Presumably, this is meant to indicate that Cajal was the grandfather of CNS regeneration. However, what Cajal said was '....imposed on the neurones two great lacunae; proliferative inability and irreversability 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', and 100 years or more later that statement still holds true. 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.

There are some confusing historical timescales: chapter 35 states that 'over the last 3 decades considerable progress has been made in understanding mechanisms that limit axonal regeneration in the injured mammalian CNS'. Really? There is then a list including inhibitory molecules, glial scar, lack of growth substrates, lack of suitable stimuli and so on. Most, if not all, of these causes are descriptions rather than explanations, and have been discussed for considerably longer than 3 decades (they were the subject of discussion in J Z Young's anatomy department when I was a medical student in the 1950s). Three decades takes us back to the 1980s. Windle in his 1980 book, 'The Spinal Cord and its Reaction to Traumatic Injury' talks of the advances over the past two decades: 'in a historical sense the findings of the past 2 decades have reinforced the hypothesis that functional regeneration of the damaged spinal cord can become a reality', so that takes us back to the 1950s. So for over 50 years talk has been of the advances made and the actual situation is of no advance.

Throughout this long and important section, the failure of CNS regeneration is mentioned but hardly recognized. One can but admire the dedication and perseverence of researchers attacking the site of the lesion in order to repair the damaged CNS. Repair the damaged circuit and all will be well, ignoring how the undamaged CNS has reacted to the lesion. One almost feels that one is reading an ode to the triumph of hope over experience.

Chapter 31 is a thought-provoking discussion on why the mammalian CNS has apparently evolved mechanisms that appear to actively block or inhibit regeneration. Sadly, there is no answer. However, could it be that the inhibitory environment at the lesion site is secondary or a consequence of feedback from the target area, that is, the area affected by the lesion?

For this, one has to look at the target area and the effect of a partial lesion on the CNS (all lesions to the CNS are partial. Even complete transection of the spinal cord leaves the distal cord with afferent and efferent fibres and internuncial networks. The only complete lesion is death). In addition, for the target area, one has to look at the synapse. In the 1950s, JZ Young and colleagues demonstrated the extraordinary complexity of the neurone surface, and the term 'synaptic zone' was coined. Even in the 1960s, Eccles in his book 'The Physiology of Synapses' (1964) says 'there are multiple endings on any one nerve cell, even many hundreds' and disregards dendrites more than 300 μm from the cell body despite the fact that dendrites form about 80% of the neurone-receptive area. Ranson's book 'The Anatomy of the Nervous System' is a text book used in probably every medical school in the world; the depiction of the nerve cell surface shows a few synapses and is unchanged from the time of Cajal. Young and associates demonstrated that the number of synapses on a nerve cell was of the order of tens of thousands rather than a few hundred. The anterior horn cell in the cat spinal cord has up to 30 000 synapses on its surface, occupying at least 70% of the cell, and the dendrite surface is covered with synapses up to 1000 μm from the nerve cell body. This was a remarkable change of several orders of magnitude. If a paradigm shift is a fundamental change in underlying assumptions, then JZ Young and colleagues' work on the nerve cell surface deserves such an accolade. This completely altered the ideas of the complexity of the nerve cell surface and moved the emphasis from the nerve fibre to the cell surface—the area of discontinuity. The area of discontinuity is the synapse and is the unique feature of the CNS—the only part of the nervous system where information from one unit is accessible to another unit. It is the basis of both the reflex activity and the 'higher' behaviour of the animal.

This area is the synaptic zone. Although the complexity is relatively recent, the concept certainly dates back to Sherrington: '….the portion of the synaptic system which is termed 'central' …..it is known as the spinal cord and brain...not merely a meeting place where afferent paths conjoin with efferent but an organ of reflex reinforcements and interferences, and of refractory phases...an organ of co-ordination..the synaptic system.....'(1906)

Of course, as witnessed by this section, the demonstration of neurone surface complexity has not shifted the emphasis from pathways to the synatic zone; it has been completely ignored. Why is it so important? Simply put, it is because of collateral sprouting and unmasking following a lesion in the CNS. Incidentally, unmasking is not even mentioned in the index. Following a lesion in the central nervous system, new connections are formed as a result of sprouting, and the final result is that the target neurone surface is indistinguishable from that existing before the injury. Following a lesion, there may be a sudden change, as in spinal shock, followed by a gradual alteration as the CNS alters as a result of sprouting and unmasking. The receptor area, the synaptic zones, will be 'restored' in an altered form. Even if regeneration of axons occurred, where would these regenerated fibres end? Studies on sprouting after a partial lesion show that the target area beomes indistinguishable from the normal. The nerve cell surface regains the mosaic-like appearance of synapses covering the cell surface intermixed, or as it were, embedded with glial cells and their processes. The CNS has altered and there is altered physiology. Can this be signalled back to the site of the lesion? Retrograde axoplasmic transport exists and is capable of altering the synthesis of proteins, the transport of vesicles and mitochondria and other organelles. Conventional experimental work on CNS regeneration appears to have no theoretical recognized framework only a belief that because nerve tracts have been disrupted there should be a way of repairing them in the same way that one would attempt a repair of an electrical wiring system. Conversely, changes in the undamaged CNS take place within a rigorous theoretical and experimental structure.

Chapter 31 states that anatomical reorganization is restricted to lesions occurring in postnatal life.However, structural and functional changes have been reported in experimental and environmental stimulation since at least 1950, and many of these reports were in adult animals.Collateral sprouting of new connections following partial damage to the nervous system has been demonstrated in the periheral, central and autonomic nervous systems, and, again, many of these reports concerned adult animals.

In this section, a review of brain-machine interfaces raises future therapeutic possibilities (and some eyebrows).

The final chapter ends with the hope that the future '...will lead to the discovery and implementation of the right combination therapy'.

This is a substantial, comprehensive and a very important book that should undoubtedly be in the library of every medical school and spinal unit. It could, however, have been much better if there had been some sense of history to give depth, some understanding of the nature of a lesion in the CNS and the nature of recovery and a stronger emphasis on the undamaged central nervous system and the central pattern generator: an approach that has shown great potential as demonstrated by Dietz and colleagues and Dimitrijevic and colleagues.

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