RESTORATIVE NEUROLOGY. ADVANCES IN PHARMACOTHERAPY FOR RECOVERY AFTER STROKE.
Edited by Larry B. Goldstein.

Until 30 years ago, the acupuncturist or reflexologist knew more about neural plasticity than most clinical neuroscientists, who were taught that the adult central nervous system was hard-wired and the consequences of damage immutable. However, over the last 15 years an increasingly extensive literature has described activity-dependent remodelling of CNS pathways, particularly in cortex but also in other parts of the brain and spinal cord, and has paved the way for a clinical interest in recovery of neural function. Although these descriptions of neural plasticity have considerably influenced therapy techniques, they have yet to result in effective pharmacological facilitation of neural recovery, as Goldstein’s book illustrates.

Rehabilitation programmes aim in general to increase functional activity and participation in social roles, and to improve quality of life. In recent years there has been particular focus, driven by a need to demonstrate effectiveness in the market place, on the study of outcome at these levels, and ‘whether’ rather than ‘how’ rehabilitation works. As class 1 studies confirm that organized care is better than unorganized care, study of how treatments ameliorate the effects of loss of physiological or psychological function, or anatomical structure, collectively known as impairments, after neurological damage becomes crucial to advances in rehabilitation. This is restorative neurology, and it is an area in which the clinical neurosciences can make a unique contribution.

Recovery after neurological damage is complex, particularly when it is complicated by ongoing disease processes, and the arrest of ongoing cellular damage must be the treatment and research priority.

The interested reader could start with http://www.unm.edu/feeney/index.html, the internet address of a short video which illustrates Feeney’s second chapter in this volume. It shows how, in the rat, after unilateral sensory-motor cortex ablation, recovery of beam walking occurs with D-amphetamine (2 mg/kg intraperitoneally) plus exposure to beam walking, as physiotherapy, during the period of drug action. Drug alone, without exposure to beam walking, only works during the first 24 h after ablation; thereafter beam walking during the period of drug action is required to produce the effect. This appears to be the result of alpha 1-noradrenergic, rather than dopaminergic, stimulation in the contralateral cerebellum. Thus, a recovered hemiparesis can be reinstated in the rat by the alpha 1-noradrenergic antagonists prazocin or phenoxybenzamine, and infusion of noradrenalin into the contralateral but not ipsilateral cerebellum produces the same effect on locomotor recovery as intraperitoneal amphetamines. Noradrenalin thus appears to reduce remote functional depression (diaschisis), in this case crossed cerebellar. Amphetamine also restores binocular depth perception, which is otherwise permanently lost, after visual cortex ablation in the cat. This effect is not seen if the animals are kept in darkness for 8 h after each drug administration. Again, reversal of cerebellar diaschisis, which is as yet unexplored, may underlie this use-dependent reversal of deficit with amphetamine. Chapter 11, by Goldstein, reviews the surprisingly scanty data in man that reflects these findings in animal experiments. These comprise two studies showing worse outcome after stroke in groups incidentally prescribed medications theoretically detrimental to neural recovery, and three prospective randomized studies after stroke, two of which show, in only 8 and 10 patients, better motor recovery with physiotherapy in patients randomized to D-amphetamine versus placebo when drug prescription was linked to the timing of physiotherapy. Facilitation of skill learning, using an alpha 1-adrenergic agonist plus repetitive training during the period of drug action, in the context of a variety of physical and cognitive disorders seen after brain injury, is thus a potentially exciting area requiring more extensive investigation.

Stein’s first chapter reviews theories of recovery after brain injury, which he has observed in the laboratory in the same way that one sees it in a rehabilitation unit, as he remarks when discussing redundancy, equipotentiality, and parallel processing: ‘those of us who have had the patience to do extensive behavioural testing in bilaterally brain-damaged laboratory rats know that with enough time, and despite massive injuries to almost any part of the cerebral mantle, the animals will attain criterion on the tasks employed’. He emphasizes that studies of topographical and morphological reorganization resulting from unmasking, sprouting and synaptogenesis, and dependent on training and experience to
shape function in the damaged brain, are unhelpful unless they include behavioural as well as cellular outcomes. Unmasking remote functional depression (diaschisis), by inhibiting normal brain, remains a manoeuvre to be explored, made tantalizing by the Sprague effect in cats where surgical damage of the superior colliculus contralateral to a previously lesioned visual cortex reverses the initial hemianopia, but not by the observation in man that crossed cerebellar diachisis after middle cerebral artery infarction remains unchanged at 3 months post-stroke, despite neurological improvement.

Chapters 3, 4 and 5, on acetylcholine, GABAergic drugs and glutamate antagonists, particularly MK-801, distinguish between acute neuroprotective effects and late effects on neural recovery. Early administration of scopolamine and GABAergic agonists, including benzodiazepines, in general improves outcome after brain injury in animal models, whilst later administration of these drugs impairs recovery, which appears to be improved by treatment with the GABAergic receptor antagonist pentylenetetrazol, even at convulsant doses. There is disappointing brevity in the description in Chapter 6, not only of ways in which trophic factors regulate activity-dependent synaptic plasticity, but also in speculating how these factors and neural stem cells might be manipulated or modified in vivo either by sensory experience and motor activity or by pharmacological means. Chapter 9, which might more logically be Chapter 2, describes relatively briefly the contribution of PET and functional MRI to the description of plastic changes during recovery, but omits mention of other functional imaging techniques including electrophysiological studies and particularly transcranial magnetic stimulation. Chapter 10, a useful summary of functional outcome measures after stroke, serves to emphasize the hope that pharmacological manipulation of plasticity will achieve clinical usefulness, whilst Chapters 12 and 13 demonstrate the paucity of data confirming benefit in man in relation to drug treatment of aphasia and depression after stroke.

Much of the material focuses on neuroprotection, preventing cell death, rather than restorative neurology, promotion of neural recovery. Chapters 7, 8 and 14 describing treatment of stroke with ganglioside and CDP-choline, treatments aimed at protecting neuronal membranes, would be more appropriately allied to other methods of acute and early neuroprotection, including thrombolysis, rather than restorative pharmacotherapy. Expanding the latter, possibly by including data relating to neural recovery after other types of brain injury, and excluding trials of neuroprotection, might have resulted in a more integrated volume and a better understanding of whether restorative pharmacotherapy will translate into clinical usefulness or merely remain a website curio.

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