Textbook of Neural Repair and Rehabilitation

Volume I – Neural Repair and Plasticity

Second Edition

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Preface

Neurorehabilitation is a medical specialty that is growing rapidly because medical advances have extended life expectancy and saved the lives of persons who previously would not have survived neurological injury. It is now urgent to develop a rigorous scientific basis for the field. The basic science relevant to functional recovery from neural injury is perhaps the most exciting and compelling of all the medical sciences. It encompasses areas of plasticity, regeneration, and transplantation in the nervous system that individually have been the subjects of many monographs. With the *Textbook of Neural Repair and Rehabilitation*, these areas are integrated with each other and with the clinical topics to which they apply.

The *Textbook of Neural Repair and Rehabilitation* is organized into two volumes. Volume I: *Neural Repair and Plasticity* can stand alone as a textbook for graduate- or advanced undergraduate-level courses on recovery from neural injury. Following an injury to the nervous system, most patients partially regain function, but this is very incomplete. Volume I is subdivided into seven sections covering areas of physiological and anatomical plasticity in the normal and injured nervous system, the determinants of regeneration and therapeutic approaches to restore connectivity and function after neural injury. Chapters cover the anatomical and physiologic responses of neurons to injury, mechanisms of learning and memory, and plasticity in specific areas of the nervous system consequent to intense use, disuse and injury. Ultimately, interventions aimed at repairing the damaged neural circuitry will be required if full function is to be restored. Thus chapters also cover topics on neuronal death, trophic factors, axonal regeneration and the molecules that inhibit it, stem cell biology, and cell transplantation. Compared with the first edition, greater emphasis has been placed on gene and cell based therapies and on intracellular signalling. Section 7 is devoted to translational research applied to human neural injury.

Volume II: *Medical Neurorehabilitation* can stand alone as a clinical handbook for physicians, therapists, rehabilitation nurses, and other neurorehabilitation professionals. It too is organized into seven sections. The first two cover the diagnostic and therapeutic technology of neurorehabilitation and constitute a direct transition from Volume I, emphasizing the applications of basic scientific principles to the practice of neurorehabilitation. Included are new chapters on the design of clinical trials in neurorehabilitation, requirements for valid clinical trials in regenerative therapies, expanded coverage of gene, cell transplantation, and brain stimulation therapies, as well as functional imaging, motor control, gait and balance assessment, electrodiagnosis, virtual reality, and bioengineering and robotic applications to prosthetics and orthotics. The second section includes chapters on the organization of neurorehabilitation services, including a new chapter on rehabilitation during the acute phase of injury. Sections 4–6 cover symptom-specific approaches to neurorehabilitation, including sensory, motor, autonomic, vegetative, and cognitive functions. This includes a new chapter on disorders of consciousness. Section 7 includes 9 chapters on comprehensive approaches to the rehabilitation of persons suffering from the major categories of disabling neurologic disorders, such as spinal cord injury, multiple sclerosis, stroke, and neurodegenerative diseases.

Wherever possible, the chapters in this book refer the reader back to chapters that deal with relevant material at a different level. However, in the second edition, the level of truly interactive content between basic laboratory and clinical science is vastly increased compared to the first edition. It is hoped that, by stressing the integration of clinical and basic scientific knowledge, this book is helping to advance the quality and scientific rigor of neurorehabilitation.

Introduction to *Neural Repair and Rehabilitation*

The first edition of this textbook was published in 2006. At that time, we expressed concern that, among medical specialties, rehabilitation had been one of the slowest to develop a basic science framework and to establish evidence-based practices as its norms. The reasons for the lag in developing a scientific framework for rehabilitation medicine relate in part to the urgent need for clinical service and to the dearth of experienced practitioners in the field during its formative years. Over the last 30 years, interest in understanding the mechanisms underlying recovery of function has increased. An expression of this interest has been the substantial increment in basic science and translational studies geared toward characterizing the extent to which the central nervous system can reorganize to sustain clinical rehabilitation. In the past 6 years, there has been substantial progress in rehabilitation medicine in general, and in neurorehabilitation in particular. The perception among medical professionals that rehabilitation medicine lacks a scientific basis has been reversed to a considerable degree, although not completely, and rehabilitation medicine has yet to achieve its full academic recognition or to fulfill its great potential for relieving human suffering. The goal of this book remains to place the practice of neurorehabilitation in a rigorous scientific framework. Precisely because the need and the potential are so great, the editors have devoted equal space and emphasis to the clinical practice of neurorehabilitation and to its basic science underpinnings. In particular, two areas of basic science are highlighted: neuroplasticity and neural repair. In this respect, the book differs from most clinical textbooks. The professional neurorehabilitation community has been especially supportive of this direction and has taken very active steps to further the development of a basic scientific underpinning for its field. Similarly, the field of rehabilitation medicine, and in particular neurorehabilitation, has made great strides in the development of evidence-based medical practices (Ifejika-Jones and Barrett, 2011; Ottenbacher and Maas, 1999; Practice, 2001; Veerbeek et al., 2014; Winstein et al., 2003). Although much of the rehabilitation literature continues to rely on relatively weak observational methods (chart review, case series, single-group designs, *etc.*)(Komaroff and DeLisa, 2009), and large numbers of underpowered studies with high rates of false-negative results cloud meta-analyses and inhibit the establishment of evidence-based practice guidelines (Ottenbacher and Maas, 1999; Veerbeek et al., 2014), this could be argued concerning most fields in medicine, and neurorehabilitation is now on a par with most of medicine. In this respect, the field has undergone a revolution since the first edition. The chapters in the clinical sections of the book stress those therapies for which evidence exists, based on controlled clinical trials.

1. Definitions

Neurorehabilitation

Neurorehabilitation is the clinical subspecialty that is devoted to the restoration and maximization of functions that have been lost due to impairments caused by injury or disease of the nervous system. According to the social model of disability adopted by the World Health Organization (WHO), "'impairment' refers to an individual's biological condition. . .," whereas ". . . disability" denotes the collective economic, political, cultural, and social disadvantage encountered by people with impairments." (Barnes, 2001) These definitions have collapsed older distinctions of the WHO's 1980 International Classification of Impairments, Disabilities and Handicap (ICIDH) (Langhorne et al., 2011; Thuriaux, 1995). In that classification, "impairment" referred to a biological condition, e.g., spinal cord injury; "disability" referred to the loss of a specific function, e.g., loss of locomotor ability consequent to the impairment; and "handicap" referred to the loss of functioning in society, e.g., inability to work as a postman, consequent to the disability. In order to improve health care data reporting by the nations of the world, the WHO replaced ICIDH with an International Classification of Functioning, Disability and Health (ICF) in 2001. ICF has two *parts*, each with two *components:*

Part 1. Functioning and Disability

(*a*) Body Functions and Structures
(*b*) Activities and Participation

Part 2. Contextual Factors

(*c*) Environmental Factors
(*d*) Personal Factors

It is not possible to review the entire classification here, but because of its widespread use, including some of the chapters in this book, a brief summary is presented in Volume II, Chapter 25. The complete version can be found at http://www3.who.int/icf/icftemplate.cfm. By focusing on components of health, ICF can be used to describe both healthy and disabled populations, whereas the ICIDH focused on consequences of disease and thus had a narrower usefulness. However, the older classification is more useful in understanding the level of interventions and research performed by the rehabilitation community. Traditionally, rehabilitation medicine has concerned itself with disabilities and handicaps but very little with the level of impairment and even less with the molecular and cellular mechanisms that underlie impairments. This state of affairs has changed as rehabilitation professionals recognize the continuity that exists from molecular pathophysiology to impairments, to disabilities, to handicaps. "Neurorehabilitation" now represents the application of this continuum to neurologically impaired individuals.

In recent years, interest in understanding the mechanisms underlying recovery of function has increased dramatically. An expression of this interest has been the substantial increment in basic science and translational studies geared to characterize the extent to which the central nervous system (CNS) can reorganize to sustain clinical rehabilitation.

Neuroplasticity

The term "neuroplasticity" is used to describe the ability of neurons and neuron aggregates to adjust their activity and even their morphology to alterations in their environment or patterns of use. The term encompasses diverse processes, as from learning and memory in the execution of normal activities of life, to dendritic pruning and axonal sprouting in response to injury. Once considered overused and trite, the term "neuroplasticity" has regained currency in the neurorehabilitation community as a concise way to refer to hypothetical mechanisms that may underlie spontaneous or coaxed functional recovery after neural injury, and can now be studied in humans through such techniques as functional imaging (including positron-emission tomography (PET) and functional magnetic resonance imaging (fMRI)), electrical and magnetic event-related potentials (including electroencephalogram (EEG), evoked potentials (EPs), and magneto-encephalography (MEG)) and noninvasive brain stimulation in the form of transcranial magnetic or electrical stimulation (TMS and trancranial direct current stimulation, tDCS). Anatomical tract tracing can be studied by diffusion tensor imaging (DTI), and the physiological connectivity subsumed by these anatomical connections can be demonstrated by resting state functional connectivity BOLD magnetic resonance imaging (resting state fcMRI), in which BOLD MRI signal concordance is used to infer functional connection between brain locations in health and disease, and thus to better define functional networks (Baldassarre et al., 2012; Carter et al., 2012).

Neural repair

The term "neural repair" has been introduced over the past two decades to describe the range of interventions by which the function of neuronal circuits lost to injury or disease can be restored. Included in this term are means to enhance axonal regeneration, the transplantation of a variety of tissues and cells to replace lost neurons and glial cells, and the use of prosthetic neuronal circuits to bridge parts of the nervous system that have become functionally separated by injury or disease. Although there is overlap with aspects of "neuroplasticity," the term "neural repair" generally refers to processes that do not occur spontaneously in humans to a degree sufficient to result in functional recovery. Thus therapeutic intervention is necessary to promote repair. The term is useful as part of the basic science of neurorehabilitation because it encompasses more than "regeneration" or "transplantation" alone. In recent years, concepts of neural plasticity have been accepted as important elements in the scientific understanding of functional recovery. The rehabilitation community has been slower to embrace repair as a relevant therapeutic goal. "Neural repair" is used in the title of this textbook in order to convey the breadth of subject matter that it covers and is now considered relevant to neurorehabilitation.

2. History of neurorehabilitation as a medical subspecialty

Origins of rehabilitation medicine

In late 19th century America, interest developed in the possibility that then exotic forms of energy, i.e., electricity, could help to heal patients with diseases and disabilities. In particular, high frequency electrical stimuli were applied to generate deep heat in tissues (diathermy) and some physicians adopted this treatment modality as a specialty. In the early days, X-ray treatments and radiology were closely linked to electrotherapy (Nelson, 1973) and, in 1923, an organization, the American College of Radiology and Physiotherapy was formed, changing its name to the American Congress of Physical Therapy in 1925. This organization merged with the American Physical Therapy Association in 1933, and in 1945 it adopted the name American Congress of Physical Medicine, then American Congress of Physical Medicine and Rehabilitation, and finally, in 1966, the American Congress of Rehabilitation Medicine (ACRM). This is a multidisciplinary organization with membership open to physicians from many specialties and to nonphysician rehabilitation specialists. With the large number of injuries to soldiers in World War I, the need for therapists to attend to their retraining and reintroduction to productive life created a new specialty that was based on physical modalities of treatment, including physical and occupational therapy, diathermy, electrostimulation, heat, and massage. These modalities were expanded during World War II. Training programs for physical therapy technicians were started in the 1920s and an AMA Council on Physical Therapy (later the

Council on Physical Medicine) was started in 1926. By 1938, a medical specialty organization, the American Academy of Physical Medicine and Rehabilitation (AAPM&R) was formed and, in 1947, the Academy sponsored a specialty board with a residency requirement and qualifying examination (Krusen, 1969). Gradually, the focus of rehabilitation has broadened to include the social and psychological adjustment to disability, treatment of medical complications such as bed sores, autonomic instability and urinary tract infections, management of pain syndromes, and other medical aspects of the treatment of chronically ill patients. As with the name of the ACRM, the term "Rehabilitation Medicine" has replaced "Physical Medicine and Rehabilitation" in the naming of some hospital and university departments, since the latter term is associated with limitations to specific therapeutic modalities, such as physical therapy, rather than to a target patient population or therapeutic goal, i.e., restoration of function. With variations, parallel developments have occurred in many countries throughout the world.

Establishment of societies of neurorehabilitation

A concomitant of the broadening of the focus of rehabilitation has been a trend toward specialization, including organ system-specific specialization. Previously, the tendency was to approach disabilities generically, based on their symptoms (e.g., gait disorder) and signs (e.g., spasticity), regardless of the cause. But with a growing conviction that the rehabilitation of patients requires knowledge of the pathophysiological basis of their disorders, and with the dramatic increase in knowledge about that pathophysiology, medical specialists outside of PM&R became more interested in the rehabilitation of patients whom they might have treated during the acute phase of their illness. This was especially true among neurologists. The American Academy of Neurology formed a section on rehabilitation and, in 1990, members of that section formed the American Society for Neurorehabilitation, which has expanded its membership to include both physicians and nonphysicians, including basic scientists, with an interest in restoring function to persons with neurological disabilities. National societies of neurorehabilitation were also formed in Europe and more recently in other parts of the world. In 2003, these national societies confederated officially as the World Federation for NeuroRehabilitation (WFNR), designating *Neurorehabilitation and Neural Repair* as its official journal. As of 2012, there were 32 national and regional societies of neurorehabilitation in the WFNR, representing the majority of the world's population.

Epidemiology of neurological disabilities

For many years, and especially during the two world wars, the practice of rehabilitation medicine was dominated by orthopedic problems, such as bone fractures and limb amputations. More recently, progress in keeping severely neurologically injured patients alive has shifted the emphasis toward rehabilitation of patients with developmental neurological disorders, stroke, traumatic injuries of the brain and spinal cord, and other chronic disabling diseases. The World Health Organization estimates that more than 300 million people worldwide are physically disabled, of whom over 70% live in developing countries. It is estimated that in the USA, 22% of the adult population have some form of disability. The five conditions most frequently listed as the cause of disability are: arthritis (19%), back problems (17%), heart disease (7%); respiratory disorders (5%); and mental disorders (5%) ((CDC), 2009). However, when the burden of disability was measured in disability-adjusted life years (DALYs), the categories of conditions causing the most disability in the USA, in % of total DALYs were: neuropsychiatric disorders (28.5), cardiovascular disease (13.9), malignant neoplasms (13.6), unintentional injuries (6.7), sense organ disorders (6.6), respiratory diseases (6.6), musculoskeletal diseases (3.8), and digestive diseases (3.3). A review of specific diagnoses listed by the World Health Organization (WHO) in a 2009 report for 2004 data revealed that neuropsychiatric disorders accounted for at least 40% of the DALYs in the USA. In the USA, approximately 300,000 people are admitted to inpatient rehabilitation facilities each year. In one survey, orthopedic conditions (hip and limb fractures, amputations, hip replacements) accounted for 20% of rehabilitation admissions, while neurological conditions (stroke, traumatic brain injury, spinal cord injury, polyneuropathy, and other neurological conditions) accounted for 80% (Deutsch et al., 2000). The survey excluded Guillain Barré syndrome, so that the prevalence of neurological disabilities may have been underestimated. Thus disorders of the nervous system are those most often requiring intensive rehabilitation interventions.

3. Outcomes measurement in rehabilitation medicine

The complex medical, emotional, and social problems of the medically disabled patient population, and the complexity of the treatment regimens has made assessing outcomes difficult. As practiced in most countries, rehabilitation is a multidisciplinary process, involving combinations of treatment modalities administered by multiple therapists. Moreover, the most important outcome of the rehabilitation process is the degree of reintegration of the patient in society, in terms of roles in work, family, and community. This also was difficult to assess with the limited instruments available only one generation ago. In order to catch up to other fields in the practice of evidence-based medicine, the rehabilitation field has been forced to become extremely resourceful in designing outcomes measures to evaluate the efficacy of its treatments (Stineman, 2001; Stineman et al., 2003). An especially vexing problem is the extension of outcomes measurements to the recovery of persons with varying baseline levels of neurological function. No single instrument can be equally sensitive to progress at all levels unless a great deal of time is spent establishing the

baseline level and then administering an appropriate test. A great advance has been the use of computer adaptive testing to the population of neurologically impaired subjects in which item selection is tailored to the individual patient (Haley et al., 2006). This has even been applied to rehabilitation of children, whose variation in developmental levels, added to their physical or cognitive impairments, makes them an especially difficult moving target (Dumas et al., 2010; Montpetit et al., 2011; Mulcahey et al., 2008). The resulting sophistication of outcomes measurement has had an important impact on all of medicine, which now routinely considers quality of life in the evaluation of effectiveness in clinical trials.

4. Impact of evidence-based medicine on neurorehabilitation

While outcomes measurement has begun to have an important impact on the evaluation of systems of rehabilitation, and on complex aspects of rehabilitation outcomes, the evaluation of outcomes for specific physical therapy treatments has lagged. A consensus conference was held in 2002, which developed a structured and rigorous methodology to improve formulation of evidence-based clinical practice guidelines (EBCPGs) (Practice, 2001). This was used to develop EBCPGs, based on the literature for selected rehabilitation interventions for the management of low back, neck, knee, and shoulder pain, and to make recommendations for randomized clinical trials. Remarkably, the first two large-scale, prospective, multicenter, randomized clinical trials to test specific physical therapy treatments were published in 2006. These were the trial of body weight supported treadmill training for spinal cord injury (Dobkin et al., 2006) and the trial of constraint-induced movement therapy for upper extremity dysfunction after stroke (Wolf et al., 2006). Based on evidence that amphetamines combined with physical therapy can enhance recovery in animal models of stroke and traumatic brain injury, several small-scale randomized clinical trials gave inconsistent results and, in total, they have not supported this therapy in human stroke patients (Martinsson et al., 2007). Since then, several similarly randomized trials have been published, including studies of robotic-assisted physical therapy. An entire chapter of this second edition is devoted to the design of clinical trials in neurorehabilitation (Volume 2, Chapter 1). According to a recent systematic review, between 2003 and 2011, the number of randomized clinical trials quadrupled from 153 to 476 (Veerbeek et al., 2014). In addition, the methodological quality of these trials improved significantly, suggesting that studies have more closely followed the CONSORT (CONsolidated Standards of Reporting Trials) guidelines to reduce bias in reporting outcomes (http://www.consort-statement.org/consort-statement/).

Impact of the revolution in the science of neuroplasticity and regeneration on neurorehabilitation

Between 1980 and 1986, there was a relatively constant annual publication rate in the field of rehabilitation medicine (350 journal articles/yr $\pm$ 55 SD). Then the rate increased dramatically, rising to 4765 in 2010, a 14-fold increase in as many years. A Medline search using the terms "neuroplasticity" or "nerve regeneration" showed a steady or slightly accelerating 12-fold increase during the same time, from 303 to 3761 (Figure 1). However, the combination of "rehabilitation" and either "neuroplasticity" or "regeneration" did not appear until after the term "neurorehabilitation" became current.

As indicated in Figure 2, the term "neurorehabilitation" was used less than ten times/year in medline-indexed articles until 1994. From then until 2010, the number of articles referring to "neurorehabilitation" increased 30-fold. During that same period, the number of articles on "rehabilitation" and "neuroplasticity" or "nerve regeneration" increased 17-fold, from 11 to 192 articles/yr. Similarly, the terms "rehabilitation" and "evidence-based medicine" did not appear in the same article until 1995. From then until 2010, their coincidence increased to more than 300 articles/yr. Thus there appears to be a correlation between the use of the term "neurorehabilitation" and acceleration in the application of

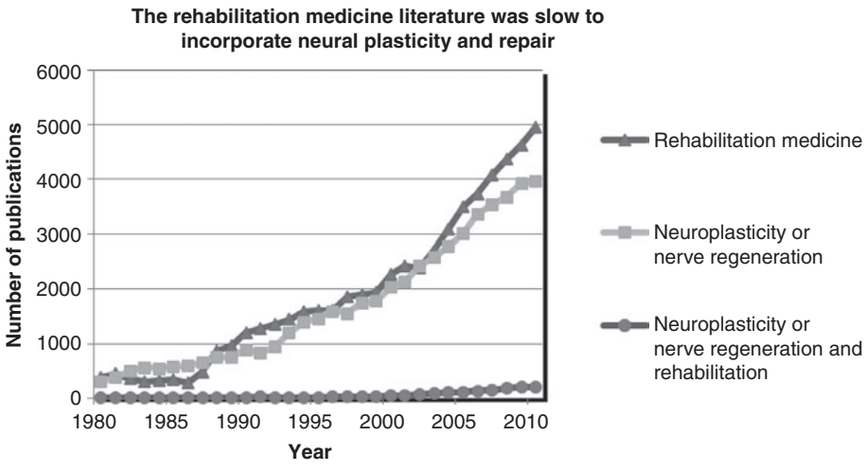

Figure 1. Relatively small impact of research in neuroplasticity and regeneration on the rehabilitation medicine literature.

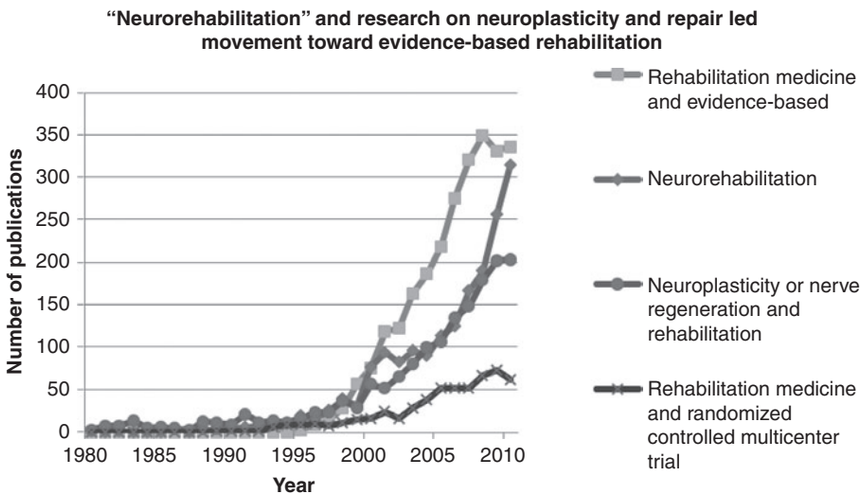

Figure 2. The field of neurorehabilitation has fostered the application of research in neuroplasticity and regeneration to rehabilitation.

basic science and evidence-based medicine to rehabilitation research. This can be ascribed to the accelerated interest in organ-specific rehabilitation, and in particular to interest in rehabilitation of patients disabled by neurological disorders. Note that the term "rehabilitation" can be ambiguous when used in isolation. The object could be drug abuse, alcoholism, dilapidated houses, etc. Therefore, in performing Medline searches, it was necessary to restrict the term to "rehabilitation medicine," "medical rehabilitation," or "physical rehabilitation," each of which has slightly different meanings and gave somewhat different numbers, although they were similar. We used "rehabilitation medicine" because it incorporated the concept of a medical specialty, was not restricted to physical modalities of therapy, and gave data that were intermediate between the other two terms. However, the general conclusions described above were the same, regardless of which term was used. On the other hand, in searching for combinations of terms, such as "regeneration" and "rehabilitation," we used "rehabilitation" rather than "rehabilitation medicine" because the context was already restricted and we were not limiting the search to a formal medical specialty.

Purpose and organization of this book

If most severely disabling disorders are neurological anyway, why write a separate textbook of neurorehabilitation rather than incorporating the rest of rehabilitation medicine into a general rehabilitation textbook? The editors believe that rehabilitation medicine must go beyond optimizing function based on what is left to the body after an injury or illness. Rather, the goal should be full restoration of function by any means necessary, including actual repair of the injured tissues and organs. By focusing on the nervous system, we can present a cogent and intellectually rigorous approach to restoration of function, based on principles and professional interactions that have a deep vertical penetration. This requires two additions to the traditional rehabilitation approach, which considered disabilities and handicaps in the abstract, apart from the specific disease processes that underlie them. First, there is a need to understand the pathophysiological bases of disabling neurological disorders. Second, there is a need to apply basic scientific knowledge about the plastic properties of the nervous system in order to effect anatomical repair and physiological restoration of lost functions.

As in the first edition, this book is presented in two volumes, designed to be used either separately or as an integrated whole. Volume I, *Neural Plasticity and Repair*, explores the basic science underpinnings of neurorehabilitation and can be used as a textbook for graduate level courses in recovery of function after neural injury. It is divided into two sections. *Section 1, Neural Plasticity*, includes chapters on the morphological and physiological plasticity of neurons that underlie the ability of the nervous system to learn, accommodate to altered patterns of use, and adapt to injury. *Section 2, Neural Repair*, includes chapters on the neuronal responses to injury, stem cells and neurogenesis in the adult CNS, the molecular mechanisms inhibiting and promoting axon regeneration in the CNS and PNS, strategies to promote cell replacement and axon regeneration after injury, the design of prosthetic neural circuitry, and translational research, applying animal experimental results to human patients. Volume II, *Medical Neurorehabilitation*, will be of greatest interest to clinical rehabilitation specialists, but will be useful to basic scientists who need to understand the clinical implications of their work. The volume is divided into three sections. *Section 3, Technology of Neurorehabilitation*, contains chapters on outcomes measurement, diagnostic techniques such as functional imaging and clinical electrophysiology, rehabilitation engineering and prosthetics design, and special therapeutic techniques. *Section 4, Symptom-Specific Rehabilitation*, considers rehabilitation approaches to neurological symptoms that are common to many types of neurological disorders, e.g., spasticity and other motor dysfunctions, autonomic and sexual dysfunctions, sensory disturbances including chronic pain,

and cognitive dysfunctions. *Section 5, Disease-Specific Neurorehabilitation Systems*, considers the integrated approaches that have been developed to address the rehabilitation of patients with specific diseases and disease categories; i.e., multiple sclerosis, stroke, traumatic brain injury, neurodegenerative diseases, etc.. Throughout the two volumes, efforts have been made to relate the basic science to the clinical material. But, whereas in the first edition, this integration was achieved primarily through extensive cross-referencing between the two volumes, in the second edition, the rapid pace of scientific advance has meant that the integration is far more substantive. Thus many chapters in Volume 1 are far more translational than before, and many chapters in Volume 2 incorporate substantial basic science content.

Major advances in neurorehabilitation since the first edition

Every chapter in Volume 1 of this 2nd edition reflects tremendous expansion of our knowledge of the mechanisms underlying response to neural injury, and is rich in implications for potential therapeutic intervention. The past few years have seen an enormous increase in emphasis on the neuron-intrinsic determinants of axonal regeneration and several chapters in Volume 1, e.g., Chapters 1 and 30, discuss the centrality of mTOR and several interlocking signaling pathways in the readiness of neurons to regenerate their axons. However, a great deal of progress has also been made in defining the role of matrix molecules, such as the chondroitin sulfate proteoglycans, in restricting axon growth, and in particular, in sculpting the short-range anatomical plasticity observed in response to CNS injury, e.g., Chapters 12 and 27. Indeed, there has been a greater appreciation of the mechanistic differences between collateral sprouting of spared axons and regeneration of their injured neighbors. Perhaps these differences explain why, after so much progress in discovering the mechanisms of growth inhibition, the degree of functional recovery induced by regenerative therapies remains limited. This and the enormous redundancy of growth-inhibiting pathways has resulted in emphasis being placed on the need to combine therapies (Lu and Tuszynski, 2008; Wang et al., 2012), as described in Volume 2, Chapter 22. The news is not all bad, though. A great deal of progress has been made in understanding the mechanisms of cell death after injury, and of the role of basic metabolic pathways such as ER stress (Chapter 18), presenting many possibilities for pharmacological and molecular interventions. Moreover, recent evidence suggests that, after axotomy, some neurons that were thought to have died had only undergone atrophy, which could be reversed by administration of trophic factors (Chapter 1). The degree to which these neurons could become functional again is not yet established.

The power of basic neuroscience to contribute to our understanding of the response of the nervous system to injury and disease is reflected by an increased representation of the pathobiology and even therapy of specific human neurological disorders in Volume 1, e.g., stroke (Chapter 14, 17), cerebral palsy (Chapter 15), and cognitive disorders (Chapter 16), peripheral neuropathies (Chapter 19), and multiple sclerosis (Chapter 32). There also is expanded coverage of neural prostheses and brain–machine interfaces (Chapters 37–40).

In Volume 2, the section on technology of neurorehabilitation covers a very rapidly growing field, incorporating basic laboratory discoveries in neuroplasticity, motor learning, mechanisms of recovery, genetics, and innovative interventions and technologies. This section reflects the increased emphasis on filling the gaps of the translational research pipeline in this field. Several major roadblocks remain, such as the slow pace of transferring preclinical knowledge into Phase I and II clinical trials, let alone large-scale Phase III and IV trials. Therefore, we have incorporated chapters specifically addressing the design of clinical trials for physical therapeutic modalities, including the development of national and foundation-based programs to enhance inter-institutional links and increase patient recruitment (Chapter 1), and regenerative therapies (Chapter 21). Indeed, the field has advanced to such an extent that a great deal of basic science explanation must be incorporated into the chapters of Volume 2, particularly in the Section on therapeutic technology, e.g., Chapter 3, Genetics in neurorehabilitation, and Chapter 22, Spinal cord injury: mechanisms, molecular therapies, and human translation. On a practical level, this edition also enhances the discussion of critical paths in neurorehabilitation, e.g., Chapter 7, and the evidence in favor of beginning neurorehabilitation in the acute phase of illness.

However, it has become clear that the effects of almost all evidenced-based therapies in neurorehabilitation are heavily dependent on appropriate selection of patients. This requires better insight into the mechanisms of neural recovery and the factors that predict successful functional outcomes. In particular, the precise nature of what is learned or changed neurologically when patients show post-therapy improvement in abilities such as gait and reaching is poorly understood. Chapter 2, on the mechanisms of stroke recovery, addresses this deficit. The chapter assesses whether the amount of true neurological recovery goes beyond the spontaneous recovery post-stroke, and how the time course of improvement correlates with those of observed dynamics in cortical plasticity. This new chapter is a direct link between Volume 2 and the chapters on neural plasticity in Volume 1, particularly the chapters on mechanisms of plasticity after injury to the spinal cord (Chapter 13) and brain (Chapter 14).

Ten new chapters have been added to the Section on technology of neurorehabilitation. Clinical application of scientific advances in neurorehabilitation can seem frustratingly slow, but one is impressed that, even in the sections on symptom- and disease-specific neurorehabilitation, a great deal of scientific progress has been made, for example in the areas of functional imaging, functional brain mapping, and electrodiagnostic approaches (Chapter 26 on chronic pain, Chapter 27 on loss of somatic sensation). A theme that has been

emerging increasingly since the first edition is the importance of intensity of training in promoting functional recovery, as opposed to the specific modality of training. Thus much of the interest in the several evolving forms of robotic assistance has focused on their potential to increase the intensity of training, possibly by home use, or at least by expanding the capabilities of institution-based therapists. But there is also an emerging interest in the role of exercise in enhancing cognitive functions, possibly by BDNF-activated stem cell proliferation in the hippocampus (Chapter 32). Evidence is also accumulating that release of BDNF and other trophic factors and cytokines plays an important role in promoting plasticity in the injured brain, for example after stroke, has become a recurring theme in Volume 2 (Chapters 2, 3, 14, 22, 32, 46, and 47). At present, these insights provide rationales for current rehabilitation therapies, but in the future, may be recruited into more cell-based and molecular therapeutic approaches.

We hope that this effort to provide basic and clinical science chapters that have in mind the common purpose of functional recovery will stimulate the development of basic scientists with a biological understanding of the clinical relevance of their work and of physicians, therapists, and other clinical practitioners and clinician-scientists in the various fields of rehabilitative medicine with curiosity and understanding of the mechanisms underlying their practice.

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