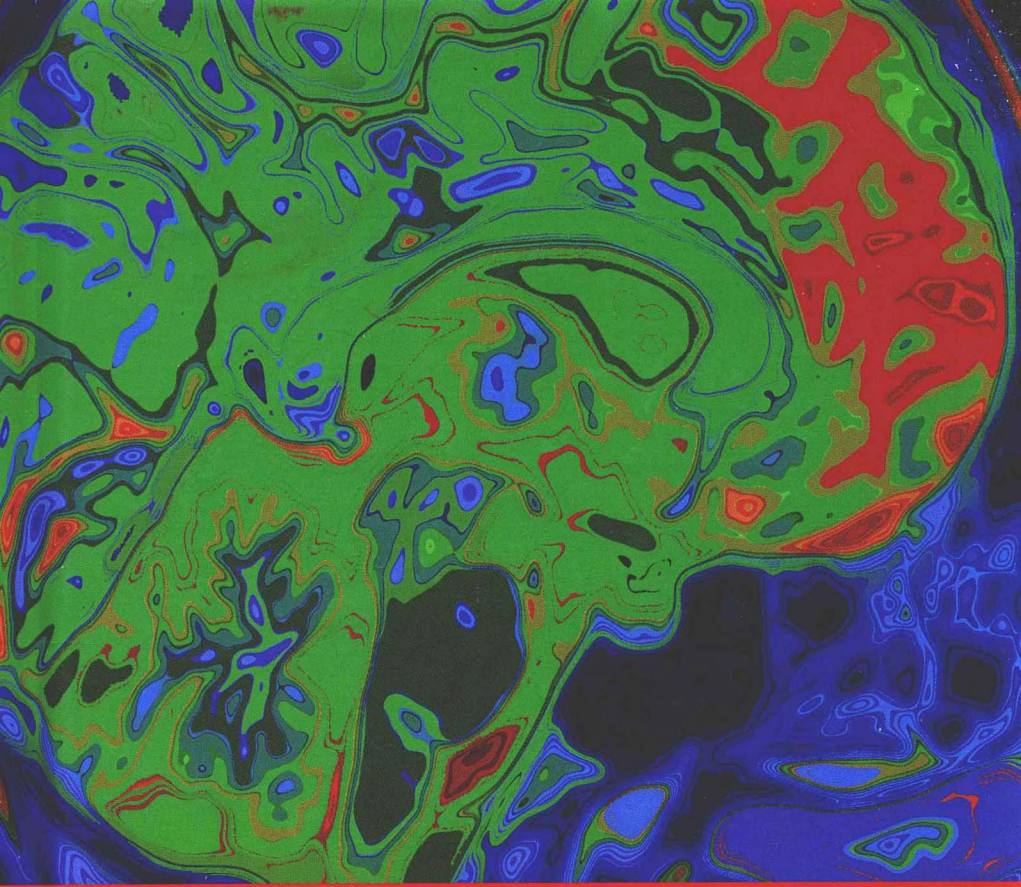
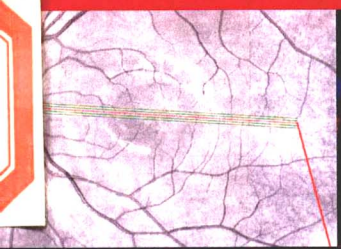
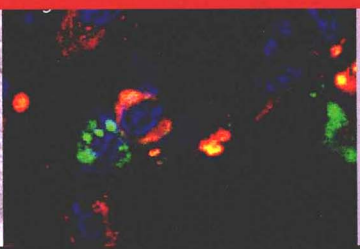
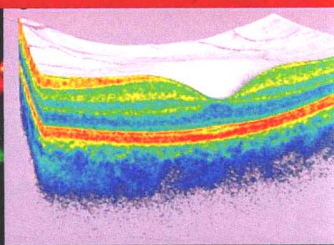


MULTIPLE SCLEROSIS

A Mechanistic View







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MULTIPLE SCLEROSIS

A MECHANISTIC VIEW

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Preface

Multiple sclerosis (MS) is presumably an immune-mediated and neurodegenerative disease of the human central nervous system (CNS), which generally causes irreversible neurologic disability in young adults. As an incurable disease, MS imposes significant medical and financial burdens on patients, their family members, and society, which often leads to devastating outcomes. Despite major leaps in our understanding of the pathophysiology of MS since the 1980s, it remains largely unknown as to why individuals initially develop MS. Such lack of insight into the exact cause of MS translates into our inability to cure MS and, at best, we can only offer certain treatments to slow down disease progression and postpone the beginning the inevitable disability that such a rapidly progressive neurologic ailment creates.

Numerous textbooks and monographs about MS have been published, and the majority of these publications are clinically oriented and target, mainly, clinicians. Few textbooks exist to discuss the fundamental mechanisms involved in MS pathophysiology. The present textbook differs from other traditional books in the sense that it addresses what we know up to now about mechanisms of disease formation and progression in MS. Except for one chapter which briefly addresses the clinical manifestations of MS, the rest of this textbook focuses on pathophysiologic mechanisms involved in MS. The editor and contributors of this unique textbook have intentionally and significantly eliminated the clinical and therapeutic aspects of MS and have concentrated on molecular pathophysiology of this complex and fascinating disease. A panel of brilliant, well-published, and internationally known authors have kindly contributed their magnificent chapters on various aspects of MS pathophysiology. Each chapter addresses a different component of MS pathophysiology and discusses the latest achievements and findings in that field. I am eternally grateful and indebted to these phenomenal neurologists, neuroimagers, neuropathologists, and neuroscientists who made this book a reality.

During the course of preparation of this textbook, we lost a great neurologist and neuroscientist, Dr Istvan Pirko. Dr Pirko was a brilliant neuroimmunologist from the Mayo Clinic, Rochester, MN, USA, whose area of research was imaging of the animal models of MS. After a courageous battle against cancer, he eventually succumbed to this devastating disease. However, during his short life, he achieved much and improved our understanding of MS pathophysiology. I dedicate this book to his

name and memory. To a man who devoted his life to a great cause and for years after his untimely death, the scientific world will benefit from his achievements.

I would like to acknowledge Mrs April Farr, Mr Timothy Bennette, and their production team at Elsevier, Inc. for their dedication, hard work, time, and energy which they spent on this book. Thank you for all of your efforts.

At the end, the editor and the contributors to this interesting book wish that our effort will stimulate the scientific curiosity of other younger colleagues to continue the research on the pathophysiology of MS and find a cure for this progressive disease.

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CHAPTER

1

Clinical Manifestations of Multiple Sclerosis: An Overview

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INTRODUCTION

Multiple sclerosis (MS) is a presumably immune-mediated, demyelinating, and neurodegenerative disease of the human central nervous system, which usually affects young adults and causes significant irreversible neurological disability. Up to 85% of newly diagnosed MS patients have relapsing–remitting (RR) disease which is characterized by periods of development of new or worsening of older neurological deficits followed by complete or partial improvement. In most cases, MS manifests between the ages of 20 and 40, with a peak age of 29 and females being predominantly affected, at least in the most common form of MS. MS lesions develop in various areas of the brain and spinal cord which, in turn, lead to the development of a wide array of clinical manifestations. In many cases the neurologic manifestations of MS present episodically and then advance to a progressive phase with steady accumulation of neurologic deficits. In many patients the severity and complexity of clinical manifestations of MS are severe and devastating and significantly compromise the patient's quality of life. The present chapter presents an overview of MS clinical features.

MOTOR AND SENSORY MANIFESTATIONS

Weakness is a common finding in MS patients and significantly stems from the involvement of corticospinal tract. Patients describe their weakness as heaviness, stiffness, or giving way under their weight of their

Multiple Sclerosis
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extremities. The lower extremities are more commonly and usually earlier affected than the upper extremities. Weakness begins in one lower extremity; however, both lower extremities eventually are affected. The weakness is usually associated with hyperactive reflexes and increased tone in the lower extremities, and many patients present with spastic paraparesis. Clonus is present at the ankle, and examination of these patients also reveals extensor plantar responses. Spasticity of the upper, lower, or four extremities is also a significant finding and may interfere with the patient's gait and other physical activities.

Sensory symptoms, including numbness, pins and needles sensation, dysesthetic pain, tingling, and burning, are among the most common complaints of MS patients and often present early in its clinical course. These sensory presentations may be more indicative of the demyelination of the posterior columns than spinothalamic tracts. Neurologic examination of these patients may reveal impairment and decrease in feeling of the vibration and abnormalities in fine touch and joint position senses. Pinprick and temperature sensations are less commonly affected over the course of MS. An interesting sensory symptom of MS is Lhermitte's sign wherein the patient experiences an acute feeling of electric shock sensation which travels down the spine and the extremities. This event occurs when the individual bends the neck forward. A number of painful sensory experiences in MS patients include persistent and painful dysesthesia, burning pain, and painful cramps and spasms of the muscles, particularly in the lower extremities.

FATIGUE

Mental and physical fatigue constitutes the most common problem voiced by MS patients. Many report an increase of their fatigue prior to and during the clinical exacerbation. During pathophysiology of MS, the demyelination of the axons leads to tardy and desynchronized transmission of nervous impulses to the point that the impulse conduction may completely cease. Interestingly, exposure to heat intensifies the fatigue in MS patients. They describe fatigue as an unusual and overwhelming feeling of mental and physical exhaustion, which is worse with heat exposure and may slightly improve with rest and sleep. Fatigue significantly restricts patients' mental and physical activity and adversely affects their performance on neuropsychological evaluations. Fatigue is worse during relapses of MS and does not show any meaningful correlations with brain magnetic resonance imaging (MRI) parameters such as gadolinium-enhancing lesions, lesion load, or any known inflammatory biomarkers. Primary mechanisms for fatigue in MS include pro-inflammatory cytokines, endocrine influences, axonal loss, and altered patterns of cerebral