Preface

Over the last century, multiple sclerosis (MS) has gone from a poorly understood, untreatable neurologic disease to a disease whose mechanisms are for the most part understood, and a disease with many treatment options. This volume captures the current status of our understanding of the biology of the disease. Enormous progress has been made in the understanding and treatment of MS, especially in the relapsing and inflammatory stages. If one looks historically from the time MS was first recognized as a distinct clinical and pathologic entity, the major question was whether it was related to an infectious cause. Insights into the role of immune mechanisms in the disease came from the development of the animal model of MS, experimental allergic encephalomyelitis (EAE), which demonstrated that an autoimmune process could cause a paralytic disease in animals that resembled MS. The animal model was first developed in the guinea pig and rat and then in the mouse. With advances in immunology, the mouse model has become a mainstay for investigating MS and, although not a perfect model of the human disease, some Food and Drug Administration (FDA)-approved drugs to treat MS have directly come from the EAE model, including glatiramer acetate and natalizumab.

The other major advance related to potential disease mechanisms was the discovery of increased γ globulin in cerebrospinal fluid (CSF), the cause of which could have been related to infection or a localized immune response in the brain. No transmissible agent has been identified as the cause of MS, even though it is believed that viruses such as Epstein–Barr virus (EBV) may trigger the disease. The increased γ globulin is now thought to be a localized CNS immune response. Ironically, the first FDA-approved drug to treat MS, β interferon, was tested based on the hypothesis that MS was a viral disease. Nonetheless, the success of immunotherapy in MS points to the immune system as the primary culprit, triggered by a complex interaction between genes and environment. MRI provided the breakthrough technology to diagnose and monitor treatment in MS and to use as a biomarker to test new MS therapies in phase 2 trials.

Although MS has been a success story for immunotherapy, there have been surprises along the way, such as the lack of an effect of anti-tumor necrosis factor (TNF) drugs and the dramatic effect of anti-B-cell therapy, which has changed our thinking about the immune underpinnings of the disease. Not all anti-B-cell therapy has been effective, however, and atacicept has made MS worse. With the success of immunotherapy in relapsing MS, it has become harder to conduct clinical trials in relapsing forms of the disease. This has placed a focus on precision medicine and ways in which to define treatments that a patient should receive based on clinical, magnetic resonance imaging (MRI), and immunologic parameters.

The major unmet therapeutic need in MS is the development of treatments for progressive forms of the disease. In progressive MS, there is a compartmentalized disease process in the CNS that is both immune dependent and independent. The immune-dependent process involves activation of the innate immune system (microglia and astrocytes) and the immune-independent process involves axonal neurodegeneration. It is likely that if we treat the inflammatory stages aggressively and early that progressive MS will become less common. Nonetheless, when some people are diagnosed with MS they have had the illness for a number of years as evidenced by MRI, and the processes driving progressive disease have already been set in motion. As with relapsing disease, a biomarker (especially an MRI marker) that is linked to disease progression would be a major advance in developing new therapies.

As one looks to the future, a hitherto unexplored area in MS is the microbiome, an area that has had a major impact across all of medicine. Although abnormalities in the microbiome have been identified in MS, the role the microbiome plays in the disease will require a great deal of study. Finally, if one looks very far into the future, the question arises as to whether MS could one day be prevented. With a better understanding of the environment and genetics, it may theoretically be possible to prevent MS with immune modulation or "vaccination" given to people at risk during childhood. This would especially be the case if an infectious agent truly linked to the disease was identified. This biologic mechanisms of MS described in this volume will hopefully one day lead to an ability to prevent the disease.

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