Allergy and the Nervous System
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Preface

Until a few decades ago, many allergic manifestations were largely regarded as being psychosomatic in origin. This was particularly thought to apply to asthma even though it had been demonstrated that skin allergic reactions could be adoptively transferred from one patient to another with serum in the famous Prausnitz-Kustner reaction [1]. The identification of the role of mast cells in allergy and their content of histamine helped to emphasize the biological nature of allergic reactions [2], and this was finally resolved with the identification of IgE as the key antibody responsible in mice by Ishizaka and Ishizaka [3]. The final confirmation that this not only applied to rodents but also humans in the clinical setting, came with the discovery of a human IgE equivalent by Johansson and Bennich [4].

The subsequent identification that asthma was an inflammatory disease [5], as with many discoveries in medicine, really engendered a paradigm shift away from a consideration of the role of the brain and nervous system in allergy and especially in asthma. In recent times it has become increasingly clear that the immune and nervous systems are integrated and that constant bidirectional communication is occurring between them, and the term psychoneuroimmunology has been used to describe this [6]. Most immune cells possess receptors for neurotransmitters and neurotrophic factors, and indeed also have the capacity to synthesize many of them. That the brain is often involved in modulating inflammation and immune activity has now been well described in the literature, and we showed some time ago that it was possible to condition mast cells to degranulate using a Pavlovian conditioning model [7]. More recently, the potential role of chronic stress in allergic disease has been identified and raises the important question of the role of psychosocial circumstances as determinants of various allergic conditions.

The mechanisms and pathways whereby the nervous system may be involved in beneficial or detrimental outcomes in allergy are still somewhat obscure, but new light is being shed on this complex biology through technological and conceptual advances. These include magnetic resonance imaging of the brain and epigenetics. The chapters in this book cover many but not all aspects of the potential and actual role of the nervous system in the modulation of allergy, and our hope is that they
may help restore some balance in our thinking about allergic disease and offer a more holistic approach to its understanding and treatment.

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References