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Foreword

Current approach to hyperammonemia

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Hyperammonemia, defined as increased concentrations of ammonia in blood, is an unspecific marker for a disturbance in the detoxification, or less likely in the production, of neurotoxic nitrogenous compounds. There is a large number of possible underlying disorders, either inherited or acquired, which all may present shortly after birth or remain undetected well into adulthood.

The brain is the organ that is most susceptible to increased concentrations of ammonia, in particular during infantile and early childhood development. Ammonia-induced damage to the brain may fast become irreversible depending on the duration and extent of hyperammonemia. In the case of the most vulnerable patients, neonates and infants, hyperammonemia must be regarded as life threatening if levels in blood exceed 500 $\mu\text{mol/l}$, corresponding to a tenfold increase above the upper limit of normal.

The mechanisms by which brain function is severely hampered or irreversibly destroyed are still not fully elucidated but they certainly depend, among others, on the age of a patient. Well-established single concepts of ammonia toxicity to the brain include alterations in neuronal differentiation, cell homeostasis, neurotransmitter systems, amino acid pathways, cerebral energy metabolism and oxidative stress, but the concerted interplay of some or all of the aforementioned changes remains yet to be understood.

This book tries to shed some light onto the various biochemical, analytical and clinical aspects of hyperammonemia. It brings together experts from

many fields, basic scientists and researchers as well as clinicians caring for pediatric or adult patients. At the beginning, the reader will find a description of ammonia metabolism in humans (Chapter 1) and of the main mechanisms by which ammonia affects the brain (Chapter 2). Physiological and pathophysiological concepts are then explained in more detail, again with a focus on ammonia neurotoxicity and including several more recent findings from basic science (Chapters 3 & 4). Since this book also aims to guide clinicians during their practical work, Chapter 5 will deal with the many precautions that are required for reliable ammonia determination. To address several specific aspects concerning their management, the most relevant inherited conditions that may lead to hyperammonemia are discussed separately for pediatric (Chapter 6) and for adult (Chapter 7) patients. Both of these chapters describe not only the primary causes of hyperammonemia, which are defined as conditions directly involving urea cycle function, but in addition also secondary causes, in which urea cycle function is affected in an indirect way by an inherited or acquired defect. Since ammonia is regarded as a key toxin in the pathogenesis in hepatic encephalopathy, Chapter 8 is dedicated to describe the underlying pathology in this acquired condition. Furthermore, the recent achievements in illustrating the effects of brain ammonia toxicity by neuroimaging are introduced and technically explained in Chapter 9. Finally, this book deals in three chapters with: the main aspects of the medical management of acute hyperammonemia in various disorders, as well as their long-term treatment (Chapter 10); extracorporeal detoxification as currently the most effective way to treat severe acute hyperammonemia (Chapter 11); and organ- and cell-based replacement therapies as emerging ways to improve patient outcomes (Chapter 12). In the closing chapter, promising novel therapeutic approaches are addressed.

The implications of hyperammonemia have many facets. It certainly is a challenge for neurobiological basic research as well as for pharmacologists and clinicians. For affected patients and their families, hyperammonemia may end in disaster. This book will address the current approach to the main aspects of hyperammonemia, describe the state of the art of management and provide a future perspective.

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