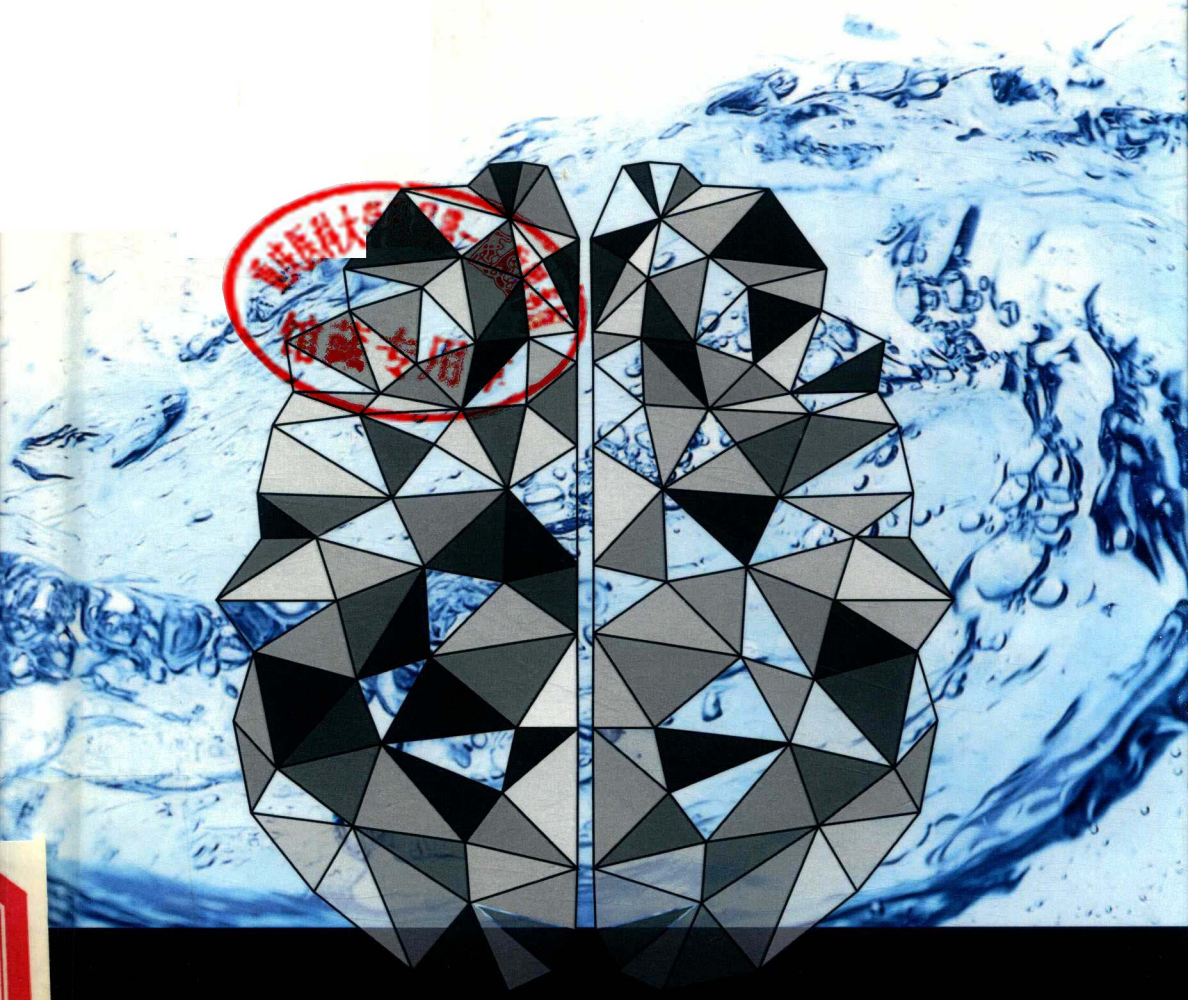
BRAIN EDEMA

FROM MOLECULAR MECHANISMS TO CLINICAL PRACTICE



Edited by
Jérôme Badaut and Nikolaus Plesnila

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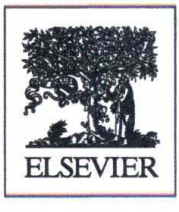
Edited by

JÉRÔME BADAUT
CNRS-University of Bordeaux, Bordeaux, France;
Loma Linda University School of Medicine, Loma Linda, CA, United States

NIKOLAUS PLESNILA
University of Munich Medical Center & Munich Cluster for Systems Neurology (Synergy), Munich, Germany



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BRAIN EDEMA

Dedication

To our wives Isabelle and Carlotta, and to our children Océane, Victor, Linus, and Leonie for their support, love, and patience.

Jérôme Badaut and Nikolaus Plesnila

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Last and not least: many thanks to all those who contributed with their research to the better understanding of the pathogenesis of brain edema. We humbly stand on the shoulders of giants.

Finally, we beg forgiveness to all those whose work we or the authors unintentionally have failed to mention.

Jérôme Badaut and Nikolaus Plesnila
Bordeaux and Munich, January 2017

List of Contributors

Abraham J. Al-Ahmad Texas Tech University Health Sciences Center, Amarillo, TX, United States

Jérôme Badaut CNRS-University of Bordeaux, Bordeaux, France; Loma Linda University School of Medicine, Loma Linda, CA, United States

Andreas Bikfalvi Bordeaux University INSERM U1029, Pessac, France

Devin K. Binder University of California, Riverside, CA, United States

Gregory J. Bix University of Kentucky, Lexington, KY, United States

Roger F. Butterworth University of Montreal, Montreal, QC, Canada

Eduardo Candelario-Jalil University of Florida, Gainesville, FL, United States

Yi-Je Chen University of California, Davis, CA, United States

Vibol Chhor Université Paris, Diderot, Sorbonne, Paris Cité, Paris, France; PremUP, Paris, France

Newton Cho University of Toronto Department of Surgery, Toronto, ON, Canada

Helle Damkier University of Copenhagen, Copenhagen, Denmark; Aarhus University, Aarhus, Denmark

Danielle N. Edwards University of Kentucky, Lexington, KY, United States

Petra Fallier-Becker Institute of Pathology and Neuropathology, University of Tübingen, Tübingen, Germany

Michael G. Fehlings University of Toronto Department of Surgery, Toronto, ON, Canada

Bobbi Fleiss Université Paris, Diderot, Sorbonne, Paris Cité, Paris, France; PremUP, Paris, France; St. Thomas' Hospital, London, United Kingdom

Justin F. Fraser University of Kentucky, Lexington, KY, United States

Jean-François Ghersi-Egea Lyon 1 University, Lyon, France

Pierre Gressens Université Paris, Diderot, Sorbonne, Paris Cité, Paris, France; PremUP, Paris, France; APHP, Robert Debré Hospital, Paris, France; St. Thomas' Hospital, London, United Kingdom

Laureen D. Hachem University of Toronto Department of Surgery, Toronto, ON, Canada

Sebastian Ille Klinikum rechts der Isar Technische Universität München, Munich, Germany

Oliver Kempski University of Mainz, Mainz, Germany

Jan-Pieter Konsman CNRS-University of Bordeaux, Bordeaux, France

Sandro M. Krieg Klinikum rechts der Isar Technische Universität München, Munich, Germany

Sighild Lemarchant CNRS-University of Bordeaux, Bordeaux, France

Ute Lindauer RWTH Aachen University, Aachen, Germany

Andreas F. Mack Institute of Clinical Anatomy and Cell Analysis, University of Tübingen, Tübingen, Germany

Raffaella Moretti Université Paris, Diderot, Sorbonne, Paris Cité, Paris, France; PremUP, Paris, France; Università degli studi di Udine, Udine, Italy; APHP, Robert Debré Hospital, Paris, France

Andre Obenaus Loma Linda University School of Medicine, Loma Linda, CA, United States; University of California, Irvine, CA, United States

Martha E. O'Donnell University of California, Davis, CA, United States

Stéphane Olindo CNRS-University of Bordeaux, Bordeaux, France

Klaus G. Petry Bordeaux University INSERM U1029, Pessac, France

Michelle E. Pizzo University of Wisconsin-Madison, Madison, WI, United States

Nikolaus Plesnila University of Munich Medical Center, Munich, Germany; Munich Cluster for Systems Neurology (Synergy), Munich, Germany

Katrin Rauen University Hospital Zurich, Zurich, Switzerland; University of Munich Medical Center, Munich, Germany

Beatriz Rodriguez-Grande CNRS-University of Bordeaux, Bordeaux, France

Kathleen E. Salmeron University of Kentucky, Lexington, KY, United States

Oliver Schnell Klinikum der Ludwig-Maximilians-Universität München, Campus Großhadern, Munich, Germany; University of Freiburg, Freiburg, Germany

Kevin N. Sheth Yale University School of Medicine, New Haven, CT, United States

Igor Sibon CNRS-University of Bordeaux, Bordeaux, France

J. Marc Simard University of Maryland School of Medicine, Baltimore, MD, United States

Robert G. Thorne University of Wisconsin-Madison, Madison, WI, United States

Luigi Titomanlio Université Paris, Diderot, Sorbonne, Paris Cité, Paris, France; PremUP, Paris, France; APHP, Robert Debré Hospital, Paris, France

Jörg-Christian Tonn Klinikum der Ludwig-Maximilians-Universität München, Campus Großhadern, Munich, Germany

Sebastian Urday Yale University School of Medicine, New Haven, CT, United States

Hartwig Wolburg Institute of Pathology and Neuropathology, University of Tübingen, Tübingen, Germany

Heike Wulff University of California, Davis, CA, United States

Changjun Yang University of Florida, Gainesville, FL, United States

Klaus Zweckberger University of Heidelberg, Heidelberg, Germany

Introduction: Brain Edema Formation—Significance for Patient Outcome

Jérôme Badaut[1] *and Nikolaus Plesnila*[2]

[1]CNRS-University of Bordeaux, Bordeaux, France [2]University of Munich Medical Center & Munich Cluster for Systems Neurology (Synergy), Munich, Germany

HISTORY OF BRAIN EDEMA

Edema is defined as a net increase of tissue water content leading to an increase in tissue volume. Usually tissue swelling has no major consequence and tissue function returns to normal as soon as swelling vanishes. The notable exception is when the swollen tissue cannot expand. Then tissue pressure increases, counteracts perfusion pressure, and results in ischemic tissue damage. In the periphery such a situation is known as compartment syndrome in the brain as intracranial hypertension.

The most frequent cause of increased intracranial pressure (ICP) is brain edema. Today we know that brain edema has a complex pathophysiology, as also evidenced by the content of this book, however, it took a long time and many partly vigorous and irreconcilable scientific discussions until the current concepts on the formation of brain edema were established.

Brain edema was first described by Robert Whytt, a Scottish physician and early neuroscientist in 1768 with the words "Altho there may be no obstruction in any part of the brain [hydrocephalus], a dropsy [accumulation of water] may be formed in it."[1] Whytt and later on in 1808 his countryman John Cheyne, better known as the first describer of the Cheyne–Stokes respiration, observed that edematous brain was soft and exuded fluid upon cutting. Both interpreted this observation as accumulation of water in the brain derived from abnormal vasculature.[1,2] This correct interpretation of vasogenic brain edema was rejected by John Abercrombie, another Scottish physician, in his at that time famous and influential textbook of neurology.[3] As a result the interest in brain edema ceased for almost 100 years.[4] Only in 1905 Martin Reichhardt, a German

physician, described that the volume of the brain may also increase without exudation of water when cutting it and used the term "brain swelling" for this phenomenon in order to differentiate it from brain edema.[5] These and additional observations by Hugo Spatz, another German physician, in the 1920s[6] finally resulted in the classical classification of brain edema into vasogenic and cytotoxic, formerly termed "brain edema" and "brain swelling", respectively, by Igor Klatzo et al. 1958.[7] This and other technical and conceptual advances resulted in a plethora of novel findings on the mechanisms and the disease specific development of brain edema until the 1990s, which were also declared to "The decade of the brain." Thereafter, however, major advances in the field became scarce due to lack of technological developments and brain edema research became less popular.

RECENT ADVANCES IN THE FIELD OF BRAIN EDEMA RESEARCH

The interest in brain edema research resurrected with the development of novel technologies which allowed instigating edema development on the molecular, cellular, and tissue level in experimental animals and in patients. A major step forward was the availability of magnetic resonance imaging (MRI), which allowed studying the presence and movement of water dynamically, regionally, and non-invasively in tissues, including the brain. Different imaging modalities were even suggested to be able to differentiate between vasogenic and cytotoxic brain edema: T2 weighted imaging (T2WI) was related to vasogenic edema, while measuring the apparent diffusion coefficient (ADC) diffusion weighted imaging was believed to identify cytotoxic edema.[8] Consequently, neuroimaging became a very useful and nowadays routine clinical tool for the diagnosis and prognostic of patients suffering from brain edema and a valuable research tool for the investigation of the pathogenesis of brain edema in clinically relevant animal models of human disease (Chapter 3: Noninvasive Imaging Techniques for Brain Edema: From Basic Science to the Clinic). Another recently introduced very valuable research tool for the direct investigation of brain edema on the cellular is 2-photon microscopy, a microscopic technique using pulsed laser light to visualize processes occurring deep in the brain. Using this technology it is now possible to directly visualize opening of the blood–brain barrier and the evolving vasogenic brain edema and to measure cell swelling in the living brain (Chapter 4: Experimental Techniques to Investigate the Formation of Brain Edema In Vivo).[9,10]

Based on these advances in the methodology to study brain edema formation on the cellular level and under various pathological conditions,

such as cerebral ischemia, traumatic brain injury (TBI), and cerebral malignancies, it was recognized that the process of brain edema formation is far more complex than previously anticipated and that the classical neuropathological definition of brain edema into cytotoxic and vasogenic may actually not be sufficient to explain the whole complexity of edema formation.[11] Cytotoxic and vasogenic edema may even represent two extremes of the same injury process and may be far more interconnected to the previously believed. Therefore it was time to bring together a group of experts in the field of brain edema research and gather the most contemporary views on the topic in one comprehensive publication. The book evolving from this joint effort is divided in five main sections: a general introduction on cerebral vessels and the blood–brain barrier, a second section on how to investigate edema, a third part on current molecular and cellular concepts of brain edema formation, a fourth part on disease specific edema formation, and a final fifth part on clinical features and management of brain edema. The following paragraphs will give the reader a short overview on which specific issues will be addressed in each of these sections.

THE PHYSIOLOGY OF CEREBRAL BLOOD VESSELS AND HOW TO INVESTIGATE THEM (PART 1 AND 2)

The importance of cerebral blood vessels has been proposed for several brain disorders. The brain has a high-energy demand and therefore needs a highly specialized vascular system which is actively regulated and fine-tuned in order to redirect blood flow to the areas of neuronal activity, a process termed neurovascular coupling (NVC). NVC is made possible by the neurovascular unit, a functional unit located around cerebral blood vessels composed by endothelium, smooth muscle cells, astrocytes, pericytes, and neurons.[12] The NVU, more specifically the endothelial tight junctions, also harbor the blood–brain barrier (BBB), which controls the traffic of solutes and cells between brain parenchyma and blood stream. The BBB protects the brain from deleterious compounds within blood, while providing the nutrients, hormones, and ions necessary for proper brain function.[13] Any morphological or functional disturbances of this well coordinated unit change CNS homeostasis and may result in an increase in brain water content, that is brain edema. In order to have a better understanding of these basic processes involved in the physiology of the BBB and the formation of brain edema, recent knowledge on the cerebral vasculature (cerebral blood flow and blood–brain interfaces) is reviewed in Chapters 1, 2, and 4, Physiology of Cerebral Blood Vessels, Blood–Brain Interfaces Organization in Relation to Inorganic Anion

Transport, CSF Secretion, and Circulation, and Experimental Techniques to Investigate the Formation of Brain Edema In Vivo.

As mentioned above, current brain edema research greatly benefited from the recent development of a variety of techniques. For example MRI has contributed to depict the temporal and spatial changes in edema formation in various disease states and to build the bridge between clinical and experimental observations of the edema process.[11] How changes in ADC and T2WI were attributed to cytotoxic and vasogenic edema, respectively, is described in Chapter 3: Noninvasive Imaging Techniques for Brain Edema: From Basic Science to the Clinic. The next step when using imaging technology to investigate brain edema is how the observed changes are associated with the molecular and cellular processes of edema formation and resolution. Therefore experimental models are now using new modalities of in vivo imaging associated with genetic and molecular tools to refine the understanding on edema process (Chapters 3 and 4, Noninvasive Imaging Techniques for Brain Edema: From Basic Science to the Clinic and Experimental Techniques to Investigate the Formation of Brain Edema In Vivo). Finally, in vitro models of the BBB are described, which are very helpful to understand the molecular mechanisms responsible for ion movements across the BBB (Chapters 5 and 7, In Vitro Models of the Blood–Brain Barrier to Better Understand the Pathophysiology of Brain Edema and Blood–Brain Barrier Mechanisms of Edema Formation: The Role of Ion Transporters and Channels).

MOLECULAR BASIS AND CONCEPTS IN BRAIN EDEMA FORMATION (PART 3)

As indicated previously, the proper function of the central nervous system is extraordinarily complex and therefore critically depends on a tightly controlled cellular and ionic environment. These functions are linked to short- and long-distance movements of fluid as present in the extracellular space and in cortico-spinal fluid (CSF)/perivascular space, respectively. Which and how movement of fluids in the brain is impaired in various neurological diseases and how this results in edema formation in described in Chapter 6: The Extracellular and Perivascular Spaces of the Brain.

The blood–brain interface represents a large surface area of exchange between the blood and CNS and it has been recognized to participate in the formation of the CSF and the brain interstitial fluid. As many barriers in the body, the BBB also carries a broad spectrum of ion transporters and channels. Until recently the contribution of these processes has not been studied in detail in the context of edema formation. How Na^+ transporters and K^+ channels drive transendothelial transport of ions and water from blood into brain thereby possibly contributing to edema formation during the early hours after injury is dealt with in Chapter 7: Blood Brain

Barrier Mechanisms of Edema Formation: The Role of Ion Transporters and Channels. Targeting these BBB ion transporters and channels appears to be a promising therapeutic avenue for reducing edema and brain damage in acute injuries.[14] In fact, several studies have recently highlighted the critical role of the sulfonylurea binding subunit of the inward-rectifier K^+ channels 1 and 2 ($K_{ir}6.1$ and $K_{ir}6.2$ or SUR1-TRPM4) in the pathogenesis of brain edema across various disease conditions.[15] Glibenclamide, a selective blocker of SUR1-TRPM4, results in improvement in edema, lesion volume, mortality, and neurological function in various experimental models and possibly also in patients (Chapter 10: Sur1-Trpm4-Promising Target for Brain Edema Treatment in Brain Edema: From Molecular Mechanisms to Clinical Practice).

The regulation of cell volume is critical in the brain, which is contained in a rigid outer shell. In fact, neuronal activation leads to constant changes of the ionic and metabolic composition of the brain's extracellular space. These changes are buffered by astrocytes on the expense of constant changes in cell volume. Under pathological conditions, the ability of astrocytes to maintain the homeostasis of the brain is overwhelmed and permanent cell swelling, known as cytotoxic edema, occurs. Since these processes are mediated by specific transporters within the cell membrane therapeutic interventions may be possible, but need to be implemented with care in view of the possible interactions with the neuroprotective activity of astrocytes (Chapter 8: Mechanisms of Cell-Volume Regulation in the Central Nervous System). To facilitate water movements across the cell membrane during cell volume regulation astrocytes express aquaporins, specific water channels, such as AQP4.[16] The role of AQP4 in the process of edema formation varies between injury models and may be beneficial and deleterious. Details are described in Chapter 9: Role of Aquaporins for the Formation and Resolution of Brain Edema.

In contrast to cytotoxic edema, vasogenic edema is associated with the dysfunction of the BBB. The increased permeability of the BBB is preceded by an increased proteolytic activity of matrix metalloproteinases (MMPs) with the direct consequence of degradation of tight junction proteins and basement membrane components, as well as interfering with cell–cell interactions in the neurovascular unit.[17] Understanding how the MMPs contribute to the pathogenesis of cerebral edema could help to identify novel targets to reduce its devastating consequences in many neurological diseases (Chapter 11, Role of Matrix Metalloproteinases in Brain Edema).

BRAIN EDEMA PROCESS IN PRE-CLINICAL MODELS (PART 4)

The present subdivision of brain edema in a cytotoxic and a vasogenic component is a simplified view of the edema process and only

partly illustrates its complexity. This is very well demonstrated by the fact that various forms of edema are present in various diseases: edema is observed in ischemic stroke (Chapter 12, Edema and BBB Breakdown in Stroke), TBI (Chapter 13, Brain Edema Formation in Traumatic Brain Injury), spinal cord injury (SCI, Chapter 14, Spinal Cord Edema After Spinal Cord Injury: From Pathogenesis to Management), acute liver failure (ALF, Chapter 15, Brain Edema in Acute Liver Failure), brain tumors (Chapter 16, Blood–Brain Barrier and Edema in Brain Tumors), epilepsy (Chapter 17, Water Homeostasis Dysfunction in Epilepsy), and neuroinflammatory diseases (Chapter 18, Water Homeostasis Dysfunctions and Edema in Neuroinflammatory Disease).

Acute injuries (stroke, TBI, and SCI) are frequently exhibiting a core lesion (primary injury) which cannot be rescued because it has been already lethally damaged during the initial injury. However, there is a cascade of secondary events including inflammation, reactive oxygen species (ROS), lipid peroxidation, excitotoxicity, and edema formation which further exacerbates the primary damage (secondary injury). The cellular and molecular events are reviewed for each injury to provide some targets to new potential therapies for these diseases (Chapters 12, 13, and 14, Edema and BBB Breakdown in Stroke, Brain Edema Formation in Traumatic Brain Injury, and Spinal Cord Edema After Spinal Cord Injury: From Pathogenesis to Management).

Similar to acute brain injuries, malignant brain tumors such as glioblastomas are associated with edema, most of the time due to the modification of existing or the formation of novel blood vessel. In fact, the newly formed blood vessels show a blood-tumor barrier that is different from the blood–brain barrier in the healthy brain. Tight junctions are morphologically changed and do not express claudin-3, typical for brain endothelial cells. In the extracellular matrix agrin is downregulated and tenascin is upregulated (Chapter 16, Blood–Brain Barrier and Edema in Brain Tumors). It is interesting to highlight that in many of the brain disorders with edema formation, AQP4 expression is increased or decreased.[16] The changes of AQP4 are very likely contributing to water disturbance. Moreover, glial cells are involved in modulation of synaptic transmission, and AQP4 has been suggested to participate in modulation of excitability and therefore in epilepsy (Chapter 17, Water Homeostasis Dysfunction in Epilepsy). Epilepsy is frequently associated with brain tumors, stroke, and TBI. Similarly, neuroinflammation occurs in many pathological states of the CNS including chronic neuroinflammatory diseases (i.e., multiple sclerosis), with sequential processes responsible to alteration of CNS water homeostasis (Chapter 18, Water Homeostasis Dysfunctions and Edema in Neuroinflammatory Disease). Inflammation and infection components can be observed in ALF causing BBB dysfunction. In ALF, the brain edema formation remains the main cause of increase ICP and

mortality (Chapter 15, Brain Edema in Acute Liver Failure). Brain edema and intracranial hypertension are significantly correlated with arterial ammonia concentrations and alterations in expression of genes coding for neuroglial proteins involved in cell volume regulation and in intercellular neural transport have been reported in ALF (Chapter 15, Brain Edema in Acute Liver Failure). Edema and consequently ICP increase are major causes of mortality and long-term disability. All this knowledge on the molecular and cellular mechanisms facilitated the development of promising experimental therapies for brain edema formation (Chapter 19, Experimental Therapies for Brain Edema and Intracranial Hypertension).

CLINICAL FEATURES AND MANAGEMENT OF BRAIN EDEMA (PART 5)

The ultimate goal of brain edema research is to translate findings from the laboratory into clinical management thereby improving patient care. Therefore the last but not least part of the current book (Part 5) deals with the contemporary state-of-the-art clinical movement of brain edema written by academic clinicians with hands-on experience on the topic. Due to the lack of specificity of all currently available treatment modalities against brain edema, clinical brain edema management is mostly independent from the original pathology and focuses on diagnosis and management of ICP, maintenance of cerebral perfusion pressure, and optimal cerebral oxygenation levels. Accordingly, in most cases the first clinical goal is to reduce the space-occupying effects of brain edema by draining CSF using osmotic therapies, remove necrotic tissue, or decompress the brain by craniotomy. The clinical application of all these diagnostic and therapeutic strategies for monitoring of brain edema and the treatment of brain edema in children and in adults suffering from cerebral ischemia, TBI, or brain tumors is described in Chapters 21, 22, 23, 24, and 25: Brain Edema in Developing Brain Diseases, Cerebral Edema in Cerebrovascular Diseases, Traumatic Brain Injury and Edema Treatment, Treatment of Edema Formation in Oncology, and Perspectives on Future Translational Research on Brain Edema.

PERSPECTIVES IN FUTURE TRANSLATIONAL RESEARCH ON BRAIN EDEMA

Finally, the book will end with a personal, but nevertheless as objective as possible, view of the editors and one of the authors on what needs to be done in the future in order to promote translational brain edema research, to develop compounds for the treatment of brain edema, and to

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II

TECHNIQUES TO INVESTIGATE CEREBRAL BLOOD