Advances and Technical Standards in Neurosurgery

Vol. 30

Edited by
J. D. Pickard (Editor-in-Chief)
N. Akalan, C. Di Rocco,
V. V. Dolenc, R. Fahlbusch,
J. Lobo Antunes, M. Sindou,
N. de Tribolet, C. A. F. Tulleken

SpringerWienNewYork

SpringerWienNewYork

Sponsored by the
European Association of Neurosurgical Societies

Advances
and Technical Standards
in Neurosurgery

Vol. 30

SpringerWienNewYork

With 40 partly coloured Figures

Printed in Austria

SpringerWienNewYork is a part of Springer Science Business Media
springeronline.com

Library of Congress Catalogue Card Number 74-10499

Typesetting: Asco Typesetters, Hong Kong
Printing: Druckerei Theiss GmbH, 9431 St. Stefan, Austria

Printed on acid-free and chlorine-free bleached paper

SPIN: 10997697

ISSN 0095-4829
ISBN 3-211-21403-8 SpringerWienNewYork

Preface

As an addition to the European postgraduate training system for young neurosurgeons, we began to publish in 1974 this series of *Advances and Technical Standards in Neurosurgery* which was later sponsored by the European Association of Neurosurgical Societies.

This series was first discussed in 1972 at a combined meeting of the Italian and German Neurosurgical Societies in Taormina, the founding fathers of the series being Jean Brihaye, Bernard Pertuiset, Fritz Loew and Hugo Krayenbuhl. Thus were established the principles of European co-operation which have been born from the European spirit, flourished in the European Association, and have been associated throughout with this series.

The fact that the English language is now the international medium for communication at European scientific conferences is a great asset in terms of mutual understanding. Therefore we have decided to publish all contributions in English, regardless of the native language of the authors.

All contributions are submitted to the entire editorial board before publication of any volume for scrutiny and suggestions for revision.

Our series is not intended to compete with the publications of original scientific papers in other neurosurgical journals. Our intention is, rather, to present fields of neurosurgery and related areas in which important recent advances have been made. The contributions are written by specialists in the given fields and constitute the first part of each volume.

In the second part of each volume, we publish detailed descriptions of standard operative procedures and in depth reviews of established knowledge in all aspects of neurosurgery, furnished by experienced clinicians. This part is intended primarily to assist young neurosurgeons in their postgraduate training. However, we are convinced that it will also be useful to experienced, fully trained neurosurgeons.

We hope therefore that surgeons not only in Europe, but also throughout the world, will profit by this series of *Advances and Technical Standards in Neurosurgery*.

The Editors

Contents

List of Contributors XV

Advances

Depolarisation Phenomena in Traumatic and Ischaemic Brain Injury. A. J. Strong and R. Dardis, Section of Neurosurgery, Department of Clinical Neurosciences, King's College, London, UK

Abbreviation List 4
History, Definitions and Introduction 5
Cortical Spreading Depression 7
The "Onset" Phase of CSD 7
Initiation of CSD 7
The DC Potential Transient 8
Mass Neuronal Activity: Grafstein – 1956 8
Changes in Extracellular Ion Concentrations $[K^+]_e$, $[Na^+]_e$, $[Cl^-]_e$, $[Ca^{2+}]_e$ 9
Changes in Membrane Potential and Conductance During CSD 10
Redistribution of Water: Tissue Impedance 10
Mode of Propagation of CSD 10
Propagation of CSD via Glial and/or Neuronal Gap Junctions 11
The Recovery Phase of CSD, and the Responses of Cerebral Metabolism and Blood Flow to CSD 12
Glucose Utilisation During Recovery from CSD 13
Haemodynamic Response 15
Histology of the Cortex Following CSD 15
Molecular Responses to CSD 15
CSD as an Initiator of Inflammation 16
Pre-Ischaemic Conditioning with CSD as Protection in Experimental Stroke 16
Factors Determining Ease of Induction of CSD 17
Species Differences and Cytoarchitecture 17
Drugs and Anaesthetic Agents 18
Factors Precipitating Migraine with Aura 18
Genotype 18
Haemodynamic and Metabolic Conditions in the Cortex 18

Peri-Infarct Depolarisations (PIDS) 19
Historical 19
Detection with Electrodes, and Characteristics of PIDs in Experimental in Vivo Models 19
The Response of CBF to a Peri-Infarct Depolarisation 20
Detection and Tracking of PIDs with Imaging 20
Initiation of PIDs 23
Terminal Depolarisation 23
Evolution of PID Patterns with Time, Pathogenic Potential, and Recruitment of Penumbra into Core Territory 24
Species Variations in PID Frequency 25
Effects of Drugs and Anaesthetic Agents on PID Frequency 25
Relationship of Cortical Glucose Availability with PID Frequency 25
The Metabolic "Signature" of PIDs 26
The Role of Depolarisations in Pathophysiology of CNS Disorders in Humans 27
Migraine 29
Transient Global Amnesia 29
Trauma 30
Depolarisation and Concussion 30
Recurrent Depolarisations Following Experimental Traumatic Brain Injury (TBI) 30
Direct Detection and Characterisation of Depolarisations in Humans, and Their Role in Human Traumatic Brain Injury 31
Cerebrovascular Disease 33
Occlusive Stroke 33
Intracerebral Haemorrhage 34
Subarachnoid Haemorrhage (SAH) 34
Non-Invasive Detection of Depolarisations in Ischaemic and Traumatic Brain Injury 35
Characterisation of Depolarisation Events in the Injured Human Brain 35
The Biological Significance of CSD 37
Summary 38
Acknowledgements 39
Key Original Papers and Reviews 39
References 40

What is Magnetoencephalography and why it is Relevant to Neurosurgery? F. H. Lopes da Silva, Section Neurobiology, Swammerdam Institute for Life Sciences, University of Amsterdam, Amsterdam, The Netherlands

Abstract 51
Introduction 52
Some Basic Notions: From Applied Physics to Biophysics 53
Clinical Applications of MEG in a Neurosurgical Setting 54
Magnetic Functional Source Imaging of the Sensorimotor Strip 55

Functional Localization of Somatosensory Cortex 55
Functional Localization of Motor Cortex 57
Comparison Between MEG and fMRI Regarding the Functional Localization of Somatomotor Cortex 57
MEG in Epilepsy: Identification of Epileptiform Inter-Ictal Foci 59
Functional Localization of Speech Relevant Brain Areas 61
Discussion and Future Developments 63
References 64

Basic and Clinical Aspects of Olfaction. B. N. Landis[1,2], T. Hummel[2], and J.-S. Lacroix[1], [1] Unité de Rhinologie-Olfactologie, Service d' Oto-Rhinologie-Laryngologie, Hopitaux Universitaires de Genève, Genève, Switzerland, [2] Smell and Taste Clinic, Department of Otolaryngology, University of Dresden Medical School, Dresden, Germany

Abstract 70
Anatomy 70
Main Olfactory System 70
Trigeminal System 71
Gustatory System 72
Vomeronasal System 73
Olfactory Coding 73
Measurement of Olfactory Function 75
Psychophysical Methods of Olfactory Testing 75
Electrophysiological/Imaging Techniques Used to Test Olfactory Testing 77
Causes and Symptoms of Smell Disorders 79
Most Common Causes 80
Olfactory Loss Following Infections of the Upper Respiratory Tract (URTI) 80
Posttraumatic Olfactory Loss 81
Sinunasal Causes 82
Neurodegenerative Causes 82
Idiopathic 83
Less Frequent Causes 83
Endocrine Diseases 83
Epilepsy 83
General Pathologies 84
Post-Surgery/Anesthesia 84
Drug-Induced/Toxic 84
Congenital 85
Symptoms 85
Quantitative Olfactory Disorders 85
Qualitative Olfactory Disorders 85
Surgical Risks to the Olfactory System 86
Endoscopic Sinus/Transnasal Surgery 86

Craniotomy 87
Recovery of Smell Disorders 88
Treatment of Olfactory Disorders 89
Surgical 89
Conservative/Medication 89
Acknowledgements 91
References 91

Cranial Venous Outflow Obstruction and Pseudotumor Cerebri Syndrome. B. K. Owler[1,2], G. Parker[3], G. M. Halmagyi[1], I. H. Johnston[1], M. Besser[1,2], J. D. Pickard[4], and J. N. Higgins[5], [1] T. Y. Nelson Departments of Neurosurgery and Neurology, Institute of Clinical Neurosciences, Royal Prince Alfred Hospital, Sydney, Australia, [2] Department of Surgery, University of Sydney, Sydney, Australia, [3] Department of Radiology, Royal Prince Alfred Hospital, Sydney, Australia, [4] Department of Neurosurgery, Academic Neurosurgical Unit, University of Cambridge, Addenbrookes Hospital, Cambridge, UK, [5] Department of Neuroradiology, Addenbrookes Hospital, Cambridge, UK,

Abstract 108
Introduction 109
Historical Perspective 109
Prevalence of Cranial Venous Outflow Obstruction in PTS 112
Interaction Between Venous Sinus Hypertension and CSF Pressure 114
Effects of Raised Venous Pressure in Adults and Children 115
Effects of Raised Venous Pressures in Infants 120
Effects of Raised CSF Pressure 124
Venous Sinus Obstruction in PTS: Cause or Effect? 128
Non-Obstructive Venous Hypertension 138
Cerebrospinal Fluid Dynamics in Pseudotumor Cerebri Syndrome 140
Investigation of Venous Aetiology in Pseudotumor Cerebri Syndrome 142
Treatment of Venous Sinus Obstruction 146
Direct Surgical Treatment 147
Endovascular Treatment 147
Venous Sinus Angioplasty 148
Venous Sinus Stenting 149
Technical Consideration 156
Related Disorders 157
Dural AV Fistulas 157
Other Headache Disorders 158
Conclusions 160
References 160

Technical Standards

Sacral Neuromodulation in Lower Urinary Tract Dysfunction. J. R. Vignes[1], M. De Seze[2], E. Dobremez[3], P. A. Joseph[2], and J. Guérin[1], [1] Department of Neuro-

surgery, Medical School Hospital, Hôpital Pellegrin, Bordeaux, France, [2] Neurorehabilitation Unit, Medical School Hospital, Hôpital Pellegrin, Bordeaux, France, [3] Department of Pediatric Urology, Medical School Hospital, Hôpital Pellegrin, Bordeaux, France

Abstract 179
Introduction 179
Anatomy and Physiology of the Lower Urinary Tract 180
  Spinal Levels 180
    Efferent Pathway 180
    Afferent Pathway 182
    Spinal Centers 182
  Pontine Centers 183
  Suprapontine Controls 183
  Reflex Mechanisms Controlling Micturition 184
    Storage Reflexes 184
    Voiding Reflexes 184
Historical Evolution of Functional Therapy for Lower Urinary Tract Dysfunction 185
  Spinal Cord Stimulation 185
  Intravesical Stimulation 185
  Pelvic Nerve Stimulation 186
  Stimulation of Pelvic Floor Muscles 186
  Stimulation of Sacral Never Roots 186
  Sacral Nerve Deafferentation 187
  Sacral Neuromodulation 187
Methods and Techniques for Sacral Nerve Stimulation 188
  Sacrum Anatomy 188
    Posterior Sacrum 188
    Sacral Foramen 189
    Anterior Sacrum 189
  Localization of Sacral Foramen 189
    Anatomical Landmarks 189
    Radiological Landmarks 191
  Surgical Approach 191
    Peripheral Nerve Evaluation 192
    Implantation of Neurostimulator 194
Clinical Application of Sacral Neuromodulation 195
  Indications 195
  Evaluation 196
  Pediatric Setting 197
The Overactive Bladder 198
  Definition 198
  Diagnosis of Overactive Bladder 199
    Clinical Parameters 199
    Urodynamic Parameters [60] 199

Classification of Overactive Bladder 199
Etiology 200
Results of Sacral Neuromodulation 201
Urge Incontinence 201
Chronic Urinary Retention 202
Pain 203
Long-Term Effectiveness 203
Impact on Quality of Life 204
Results for Neurogenic Bladder 204
Predictive Factors for Sacral Neuromodulation 204
Complications of Sacral Neuromodulation 205
Complications of Peripheral Nerve Evaluation 205
Complications of Sacral Nerve Neuromodulation 205
Pain 205
Infection 206
Problem of Nerve Injury 206
Technical Problems and Device-Related Complications 207
Surgical Revision 207
Conclusion 207
Therapeutic Alternatives and Developing Treatments in Overactive Bladder 208
Medical Therapeutics 208
Surgical Alternatives 209
Perspectives in Electric Stimulation 210
Cost of Sacral Neuromodulation 211
General Issues in Urge Incontinence Costs 211
Expected Cost per Patient of Sacral Nerve Stimulator Implant Treatment 211
Conclusion 213
Acknowledgements 213
References 213

Prevention and Treatment of Postoperative Pain with Particular Reference to Children. A. Chiaretti and A. Langer, Paediatric Intensive Care Unit, Catholic University Medical School, Rome, Italy

Abstract 226
Introduction 226
Acute Pain Assessment in Paediatric Age 229
Specific Aspects of Post-Operative Pain 234
Post-Operative Pain Management 237
By the Patient 239
By the Ladder 241
Step 1 242
Step 2 242
Step 3 242

Non-Opioid Analgesics 243
a. NSAIDs With Low Potency and Short Elimination Halflife 244
b. NSAIDs With High Potency and Short Elimination Halflife 245
c. NSAIDs With Intermediate Potency and Elimination Halflife 245
d. NSAIDs With High Potency and Long Elimination Halflife 245
Opioid Analgesics 246
Opioid Classification 248
'Weak' Versus 'Strong' Opioids 249
Factors in Opioid Selection 251
Pain Intensity 251
Co-Existing Disease 252
Selecting the Appropriate Route of Systemic Opioid Administration 253
Non-Invasive Routes 253
Invasive Routes 254
Scheduling of Opioid Administration 255
'Around the Clock' Dosing 255
'As Needed' Dosing 256
Patient-Controlled Analgesia 256
Management of Opioid Adverse Effects 259
Respiratory Depression 259
Nausea and Vomiting 260
Urinary Retention 261
Physical Dependence 261
Adjuvant Analgesics 262
Corticosteroids 262
Topical and Local Anaesthetics 263
Neuroleptics 265
Benzodiazepines 265
Conclusions 265
References 266

List of Contributors

Besser, M., T. Y. Nelson Departments of Neurosurgery and Neurology, Institute of Clinical Neurosciences, Royal Prince Alfred Hospital, Sydney, Australia

Chiaretti, A., Paediatric Intensive Care Unit, Catholic University Medical School, Rome, Italy

Dardis, R., Section of Neurosurgery, Department of Clinical Neurosciences, King's College, London, UK

De Seze, M., Neurorehabilitation Unit, Medical School Hospital, Hôpital Pellegrin, Bordeaux Cedex, France

Dobremez, E., Department of Pediatric Urology, Medical School Hospital, Hôpital Pellegrin, Bordeaux Cedex, France

Guérin, J., Department of Neurosurgery, Medical School Hospital, Hôpital Pellegrin, Bordeaux Cedex, France

Halmagyi, G. M., T. Y. Nelson Departments of Neurosurgery and Neurology, Institute of Clinical Neurosciences, Royal Prince Alfred Hospital, Sydney, Australia

Higgins, J. N., Department of Neuroradiology, Addenbrookes Hospital, Cambridge, UK

Hummel, T., Smell and Taste Clinic, Department of Otolaryngology, University of Dresden Medical School, Dresden, Germany

Johnston, I. H., T. Y. Nelson Departments of Neurosurgery and Neurology, Institute of Clinical Neurosciences, Royal Prince Alfred Hospital, Sydney, Australia

Joseph, P. A., Neurorehabilitation Unit, Medical School Hospital, Hôpital Pellegrin, Bordeaux Cedex, France

Lacroix, J.-S., Unité de Rhinologie-Olfactologie, Service d' Oto-Rhinologie-Laryngologie, Hopitaux Universitaires de Genève, Genève, Switzerland

Landis, B. N., Smell and Taste Clinic, Department of Otolaryngology, University of Dresden Medical School, Dresden, Germany

Langer, A., Paediatric Intensive Care Unit, Catholic University Medical School, Rome, Italy

Lopes da Silva, F. H., Section Neurobiology, Swammerdam Institute for Life Sciences, University of Amsterdam, Amsterdam, The Netherlands

Owler, B. K., Department of Surgery, University of Sydney, Sydney, Australia

Parker, G., Department of Radiology, Royal Prince Alfred Hospital, Sydney, Australia
Pickard, J. D., Department of Neurosurgery, Academic Neurosurgical Unit, University of Cambridge, Addenbrookes Hospital, Cambridge, UK
Strong, A. J., Section of Neurosurgery, Department of Clinical Neurosciences, King's College, London, UK
Vignes, J. R., Department of Neurosurgery, Medical School Hospital, Hôpital Pellegrin, Bordeaux Cedex, France

Advances

Offprint from
Advances and Technical Standards in Neurosurgery, Vol. 30
Edited by J.D. Pickard

Depolarisation Phenomena in Traumatic and Ischaemic Brain Injury

A. J. Strong and R. Dardis

Section of Neurosurgery, Department of Clinical Neurosciences, King's College, London, UK

With 11 Figures

Contents

Abbreviation List 4
History, Definitions and Introduction 5
Cortical Spreading Depression 7
The "Onset" Phase of CSD 7
Initiation of CSD 7
The DC Potential Transient 8
Mass Neuronal Activity: Grafstein – 1956 8
Changes in Extracellular Ion Concentrations $[K^+]_e$, $[Na^+]_e$, $[Cl^-]_e$, $[Ca^{2+}]_e$ 9
Changes in Membrane Potential and Conductance During CSD 10
Redistribution of Water: Tissue Impedance 10
Mode of Propagation of CSD 10
Propagation of CSD via Glial and/or Neuronal Gap Junctions 11
The Recovery Phase of CSD, and the Responses of Cerebral Metabolism and Blood Flow to CSD 12
Glucose Utilisation During Recovery from CSD 13
Haemodynamic Response 15
Histology of the Cortex Following CSD 15
Molecular Responses to CSD 15
CSD as an Initiator of Inflammation 16
Pre-Ischaemic Conditioning with CSD as Protection in Experimental Stroke 16
Factors Determining Ease of Induction of CSD 17
Species Differences and Cytoarchitecture 17
Drugs and Anaesthetic Agents 18
Factors Precipitating Migraine with Aura 18
Genotype 18
Haemodynamic and Metabolic Conditions in the Cortex 18
Peri-Infarct Depolarisations (PIDS) 19

Historical 19
Detection with Electrodes, and Characteristics of PIDs in Experimental in Vivo Models 19
The Response of CBF to a Peri-Infarct Depolarisation 20
Detection and Tracking of PIDs with Imaging 20
Initiation of PIDs 23
Terminal Depolarisation 23
Evolution of PID Patterns with Time, Pathogenic Potential, and Recruitment of Penumbra into Core Territory 24
Species Variations in PID Frequency 25
Effects of Drugs and Anaesthetic Agents on PID Frequency 25
Relationship of Cortical Glucose Availability with PID Frequency 25
The Metabolic "Signature" of PIDs 26
The Role of Depolarisations in Pathophysiology of CNS Disorders in Humans 27
Migraine 29
Transient Global Amnesia 29
Trauma 30
Depolarisation and Concussion 30
Recurrent Depolarisations Following Experimental Traumatic Brain Injury (TBI) 30
Direct Detection and Characterisation of Depolarisations in Humans, and Their Role in Human Traumatic Brain Injury 31
Cerebrovascular Disease 33
Occlusive Stroke 33
Intracerebral Haemorrhage 34
Subarachnoid Haemorrhage (SAH) 34
Non-Invasive Detection of Depolarisations in Ischaemic and Traumatic Brain Injury 35
Characterisation of Depolarisation Events in the Injured Human Brain 35
The Biological Significance of CSD 37
Summary 38
Acknowledgements 39
Key Original Papers and Reviews 39
References 40

Abbreviation List

ADC	Apparent diffusion coefficient
ATP	Adenosine triphosphate
Ca^{2+}	Calcium ion
CA1	The CA1 region of the hippocampus
Cl^-	Chloride ion
Cl^-_e	Extracellular chloride ion
CSD	Cortical spreading depression

CBF	Cerebral blood flow
DC	Direct current
ECoG	Electrocorticography
ECS	Extracellular space
Hb(O)	Haemoglobin (oxidised form)
HSP	Heat shock protein
HSD	Hypoxic spreading depression – like depolarisation
IEG	Immediate early gene
IL	Interleukin
IP3	Inositol trisphosphate
K^+	Potassium ion
K_e	Extracellular potassium ion
MCAO	Middle cerebral artery occlusion
mM	Millimoles per litre
mRNA	Messenger ribonucleic acid
mV	Millivolts
Na^+	Sodium ion
PID	Peri-infarct depolarisation
pO_2	The partial pressure of oxygen
NO	Nitric oxide
Na-K ATPase	Sodium-potassium ATPase
NIRS	Near infrared spectroscopy
nm	Nanometres
NAD(H)	Nicotinamide adenine dinucleotide (reduced form = NADH)
Vm	Neuronal membrane potential
BDNF	Brain derived neurotrophic factor
NF-κB	Nuclear factor kappa-B
NMDA	N-methyl-D-aspartate
TPA	Tissue plasminogen activator
TBI	Traumatic brain injury

History, Definitions and Introduction

In 1944 a young Brazilian physiologist, Aristides Leão, was studying for his doctorate in Harvard University. According to Somjen [1], he was attempting to study propagation of epileptic activity in the cerebral cortex, and he approached the problem by applying electrical stimulation to the frontal convexity cortex of anaesthetised rabbits, and recording from an array of corticography electrodes posterior to this (Fig. 1). Instead of seeing propagating epileptic activity, he observed a period of electrical silence, which was first seen adjacent to the stimulating electrodes, and did indeed propagate from the site of stimulation backwards along the cere-

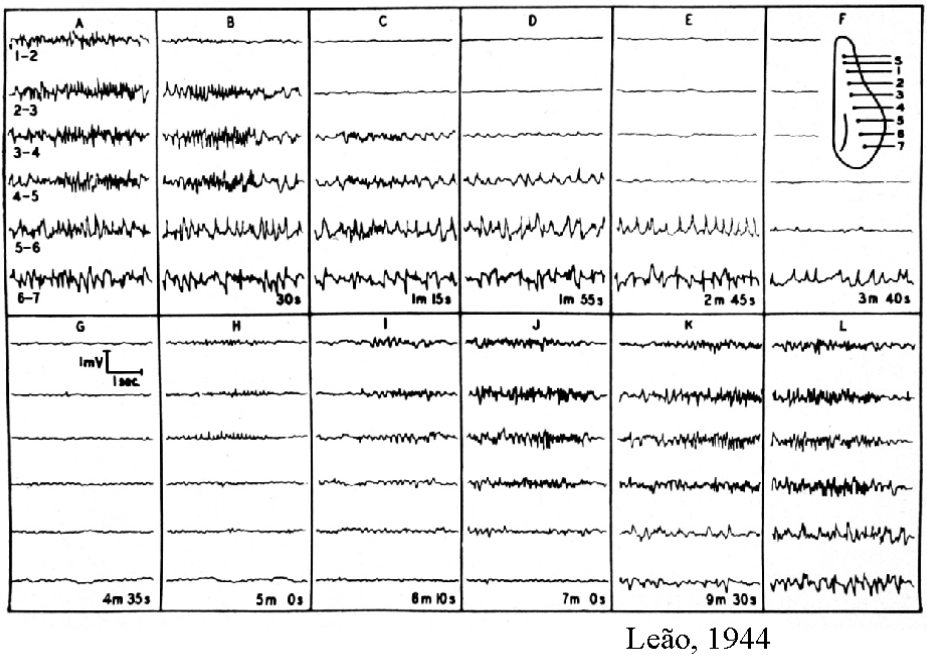

Fig. 1. Leão's original demonstration of cortical spreading depression, demonstrating a time sequence of twelve separate recordings spanning some 10–11 minutes, from a linear array of seven electro-corticographic (*ECoG*) electrodes extending antero-posteriorly over the right hemisphere of a rabbit anaesthetised with barbiturate. A pair of bipolar electrical stimulating electrodes are placed at the front of the hemisphere, and following stimulation, a wave of electrical silence is seen to propagate backwards from the site of stimulation, followed after approximately 7–9 minutes by spontaneous recovery at each site. (Reproduced with permission from Leão [2])

bral hemisphere – at a rate of some 3 millimetres per minute. The phenomenon resolved after 5–15 minutes, with – apparently – full resumption of cortical electrical activity. He reported his findings in a landmark paper entitled "Spreading depression of activity in the cerebral cortex" [2]. The event which he described became known as "spreading depression" or "cortical spreading depression" [of Leão] (CSD), and has remained a subject of intense interest to neurophysiologists. Although the electrophysiological and haemodynamic features have become very well characterised, with mass focal depolarisation of neurones and glia as the defining event, its most enigmatic challenges have remained its uncertain physiological role in grey matter, and its relevance – if any – to human disease states.

Since 1977–1978, stroke research laboratories have become aware of a feature of cerebral cortex in the ischaemic penumbra which shares certain

characteristics with CSD, but also differs from it in critical aspects. ''Peri-infarct depolarisations'' (PIDs) arise spontaneously in cortex at the edge of the core ischaemic territory and propagate in the penumbra, but unlike CSD, they are harmful in that they cause progressive recruitment of the penumbra into the core territory, thus enlarging the infarct [3]. Somjen refers to such events as *hypoxic spreading depression-like depolarisations (HSD)* [1]. The evolution of this concept, and increasing awareness among some clinicians of its existence, has prompted increasing speculation as to whether CSD or PIDs occur in the injured human brain. Demonstrations of CSD-like events in models of traumatic brain injury, the imaging in the laboratory of propagation of PIDs across the cerebral cortex in models of focal cerebral ischaemia, the knowledge that not only cerebral cortex but also deep nuclei and the hippocampus may be subject to CSD, and particularly the recent confirmation that such events do indeed occur in patients with serious head injury [4], seem likely to open a fresh chapter in clinical brain injury research. This is an area of research to which neurosurgeons are uniquely placed to contribute.

The features of cortical spreading depression as it is observed in the experimental laboratory have been the subject of a number of authoritative reviews extending over many years, and the reader seeking the most detailed information is directed to them [1, 5–7]. We have relied extensively on these reviews as well as on the original sources. In this review, we shall draw together the principal physiological, chemical and haemodynamic features of CSD and PIDs, and consider their possible functions and effects in the context of acute ischaemic and traumatic injuries to the human brain. We shall also explore methods for detection of depolarisations in the injured human brain, and the actual and potential impact of this information on our understanding of the pathophysiology of the injured human brain and on our clinical management of traumatic and ischaemic brain injury. The broader term ''depolarisation'' will be used where neither CSD nor PID is specifically under discussion.

Cortical Spreading Depression

The ''Onset'' Phase of CSD

Initiation of CSD

Leão's observations were made in rabbits under barbiturate anaesthesia, and the stimulus to the cortex was bipolar electrical current delivered from an induction coil, but several other stimuli are also effective. Dialysis through an implanted microcatheter or superfusion of the exposed cortex with potassium chloride (KCl) at 130 mM or more is effective in the rat brain [8], as is local application of KCl with a wick. Neurosurgeons should

also be aware that needling of the cortex is effective, and it seems inescapable that more complex surgical manipulations of similar, *susceptible* tissue are likely to be effective if, as seems clear from the recent findings in patients [4], CSD does indeed occur in the human brain. There is also experimental evidence that spreading depression occurs in the spinal cord [9]. What determines susceptibility, by which is meant the frequency of occurrence of CSD (rather than vulnerability to damage from depolarisations), is an important theme of this review. The factors which are currently believed to affect this are species differences, location in the brain, haemodynamic and metabolic conditions in the cortex, anaesthesia, and systemic metabolic variables (essentially – in the present state of knowledge – plasma glucose). All of these factors are best considered after we have first reviewed the basic electrophysiological, haemodynamic and metabolic properties of CSD.

The DC Potential Transient

For the purposes of a discussion focussed on brain injury, the CSD complex is best considered in its two phases, onset and recovery, since, as we shall see, it is probably deficiencies in the recovery process that underlie the differences between CSD and PIDs. When Leão measured the DC potential difference between a point on the cortex in the path of the propagating wave of depression and a remote reference point, he noted a transient negativity of some 10 to 15 mV. The observation has been repeated many times, and when sought, the DC potential transient is an invariable feature of both the CSD and PID patterns of depolarisation. The nature of the DC potential transient – presumably indicating a brief accumulation of negative charge in the cortex – is still unknown, although an increase in one or more anions, – lactate, amino-acids, or bicarbonate – has been suggested as a cause [10].

Mass Neuronal Activity: Grafstein – 1956

Studying areas of cerebral cortex isolated electrically by subpial transection but with perfusion intact, Grafstein recorded unit activity with an extracellular microelectrode, and found a short phase of intense firing at the onset of the DC potential change, followed by prolonged silence [11] (Fig. 2). There is no suggestion that this transient neuronal activity conveys any physiological information, and as we shall see it is initiated by local changes in the extracellular environment. The observation suggests that excitatory or depolarising influences on neurones – not necessarily synaptic – contribute to the initiation of the CSD event as it reaches a new locus. It is of interest for current researchers studying models of stroke that

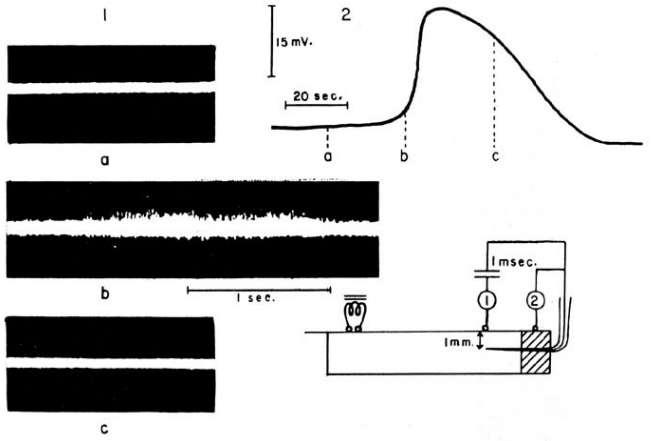

Fig. 2. Comparison of extracellular microelectrode recording (*Panel 1, a,b,c*) and simultaneous recording of DC potential (*Panel 2*) in a slab of cerebral cortex isolated electrically by subpial transections (Grafstein, 1956). The cortex was stimulated remote from the recording electrodes, initiating a wave of spreading depression. In 1a, no spontaneous neuronal firing is present prior to arrival of the wave, but as depolarisation commences there is a *brief* phase of intense neuronal firing (*b*) followed by silence (*c*) when depolarisation has begun to recover. (Reproduced with permission from Grafstein [11])

Grafstein was able to suspend and then restore resolution of the DC potential transient by first occluding and then releasing the middle cerebral artery (MCAO) in rabbits, showing that resolution of the DC potential is energy-dependent. Her proposal that potassium ion liberated by neuronal depolarisation caused subsequent depolarisation of adjacent neurons still forms the basis of current thinking on mechanisms of CSD propagation (see below).

Thus Grafstein's 1956 paper demonstrated or inferred three of the key features of CSD – mass neuronal depolarisation, mediation by potassium ion, at least in part, and the dependence of recovery on availability of perfusion and energy. The findings and inferences have remained substantially unchallenged, and form the foundation of our understanding of depolarisation events in the cerebral cortex; the paper is perhaps one of the key contributions to neuroscience in the past 50 years.

Changes in Extracellular Ion Concentrations $[K^+]_e$, $[Na^+]_e$, $[Cl^-]_e$, $[Ca^{2+}]_e$

A transient, marked increase in K_e from the normal 3 mM to 60 mM or more is a striking and regular feature of CSD, and lasts for approximately 30–40 seconds in total, often resolving with an undershoot below

the baseline [12]. There are accompanying decreases in $[Na_e]$ [13], in $[Cl^-]_e$ and in $[Ca^{2+}]_e$ [14].

Changes in Membrane Potential and Conductance During CSD

The first intracellular recordings from a neuron during passage of a wave of CSD were made by Collewijn and Van Harreveld, who concluded, after allowing for the simultaneous change in extracellular potential, that neuronal membrane potential (V_m) reached zero briefly [15]. This pattern of depolarisation to zero volts is different from that of the action potential, where V_m may reach +20 mV, and could imply simultaneous opening of several or all membrane conductances in CSD; this might represent mechanical opening of membrane pores with no ion-specific conductance properties, but according to Somjen it is not necessary to postulate such special channels in order to explain the membrane potential changes in CSD [1].

Redistribution of Water: Tissue Impedance

An increase in electrical impedance of tissue is largely a measure of cell swelling, and Leão and Martins-Ferreira demonstrated an increase in impedance during CSD in 1953 [16]. Measurements of extracellular space volume using indicators such as tetramethylammonium, together with morphological evidence, support this, and the basis most probably lies in the excess of the decrease in $[Na^+]_e$ over the increase in $[K^+]_e$ [13]. This would imply a net movement of ions into cells, accompanied by osmotically obliged water, in turn raising impedance to current flow in the ECS. However, Somjen points out [1] that there is evidence that when impedance is measured some current flow is through rather than around cell membranes, perhaps more especially glia, and that there is also evidence of a marked drop in neuronal membrane resistance during SD [17, 18]. Whatever their precise nature, these changes in CSD appear closely related to the transient reduction in apparent diffusion coefficient (ADC) that can be detected in the rat [19] and cat [20] brains during CSD using magnetic resonance diffusion-weighted imaging (see also page 33: Section on Occlusive Stroke).

Mode of Propagation of CSD

Early experimental studies of propagation of spreading depression were aided by the use, principally by Martins-Ferreira and Oliveira Castro [21], of the isolated chick retina, in which the presence and propagation of spreading depression is evident to the naked eye from a transient change in optical properties. They were able to establish a ''ring'' of retina in which

the phenomenon could be constrained to propagate in circular fashion, at a rate measured at 3.7 mm/minute – similar to that originally described by Leão, and they found that alkaline conditions, or increased K_e or Cl_e, all accelerated propagation, whereas acidification or an increase in Mg_e slowed it.

In one of her 1956 papers [11], and noting the likelihood of neuronal depolarisation (as the basis for the brief phase of spontaneous spike discharges), Grafstein suggested that the resulting liberation of *potassium* ion into the ECS could occur in sufficient concentration to cause adjacent neurones to depolarise, thus causing – or at least supporting – propagation. The simultaneous reduction in ECS volume (see above) would increase the effective $[K]_e$, thus facilitating depolarisation of neurones in the path of the wave.

The *separate* idea that potassium ion might diffuse slightly further in the ECS and cause depolarisation in *non*-contiguous neurones was explored in detail by Gardner-Medwin, who determined a rate for cortical extracellular diffusion of K^+, and showed that this was slower than that of CSD propagation [22]. A further argument against extracellular diffusion of K_e as the basis of propagation is that in CSD, no increase in K_e can be recorded in the cortex prior to the DC depolarisation (unlike PIDs, where a gradual, prior increase in K_e *does* occur [23, 24].

A second candidate agent explaining propagation is glutamate released into the extracellular space (ECS) by mass neuronal depolarisation, and in turn depolarising adjacent neurons. Van Harreveld induced CSD by application of compounds in brain extracts, one of which was glutamate [25], and he and Fifkova later demonstrated release of glutamate during CSD in the retina [26]. However, glutamate dialysed into the cortical ECS does not elicit CSD, nor does inhibition of glutamate reuptake [8, 27].

Propagation of CSD via Glial and/or Neuronal Gap Junctions

The possible roles of intercellular coupling either of neurones or of astrocytes in initiation and propagation of CSD have received much attention in the last few years. In the case of astrocytes, it is now abundantly clear that in cultures of astrocytes studied with intracellular calcium-sensitive dyes, waves of transient increase in intracellular calcium ion (Ca_i) can be initiated – by glutamate [28], nitric oxide (NO) [29] or mechanical stimulation [30] – and will then propagate across the culture at a rate very similar to that of CSD in the intact cortex [6]. Nedergaard has shown that in mixed glia-neuronal cultures, such glial waves are associated with elevations in neuronal calcium concentrations [31]. Transmission of calcium waves through glial cultures is believed to occur through glial gap junctions – specialised and specific membrane openings whose molecular

structure is now well-characterised and which are usually readily permeable to ions and compounds of smaller molecular weight; examples are inositol trisphosphate (IP_3) and potassium. IP_3 is thought to mediate propagation of Ca_i waves through its role as a ligand for IP_3-receptor-Ca-conductance complexes on the endoplasmic reticulum, and glial gap junctions are also thus a probable substrate for the mechanism of "spatial buffering" of increases in K_e, as envisaged by Somjen [32]. Propagation is also mediated by an extracellular agent, ATP [33].

At least in the cell culture preparations in which glial communication has been studied, the capacity to propagate Ca_i waves seems exceptionally well supported, by a range of agents that include ATP [33], nitric oxide [29], and inositol trisphosphate (IP_3), the latter via glial gap junctions [34]. The demonstration that an intracellular calcium wave *precedes* the arrival of spreading depression [35] also lends support to the idea that CSD propagation is mediated primarily by glia. A further argument for the concept is based on the fact that halothane, which blocks glial gap junctions [36], also reduces the frequency of CSD in the gyrencephalic brain [37], and reduces MCAO infarct volume and PID frequency by an effect either on perfusion or on intrinsic PID susceptibility [38].

Other findings argue against this hypothesis. First, CSD is more readily elicited in areas of grey matter with relatively *lower* glia : neuron ratio, such as the CA1 layer of the hippocampus (in experimental studies) [39], and the occipital cortex in humans [40, 41] (if it is accepted that migraine with visual aura is a manifestation of CSD, as discussed below). Secondly, the use of specific agents toxic to glia such as fluorocitrate or fluoroacetate fails to prevent CSD [42, 43]. Third, CSD can occur in the absence of Ca_i waves [44].

The Recovery Phase of CSD, and the Responses of Cerebral Metabolism and Blood Flow to CSD

Resolution of the cation transients might in theory be due either to restitution of normal, resting distributions by active transport, or in the case of the increased $[K]_e$, to diffusion through the extracellular space (which would necessarily be slower than the observed resolution rate [22]), to spatial buffering by the astrocytes through gap junctions [32], or to passive elution through cerebral perfusion (probable only under conditions of energy failure [45]). Grafstein's experiment with MCAO described above is perhaps the earliest evidence for a role for energy-dependent active transport in the recovery phase, and evidence for the concept has steadily accumulated. Demonstration of the cation transients that are an integral feature of CSD makes it almost inevitable that restoration of resting cation distributions should necessitate a considerable increase in ATP utilisation.

Indeed CSD, and epileptic seizures, are perhaps the most extreme forms of activation challenge to reactivity of cerebral metabolism and blood flow (CBF).

Detailed studies by Rosenthal & Somjen and their colleagues of CSD in the normally perfused brain indicated transient oxidation of the mitochondrial respiratory chain [46]. In the light of subsequent work demonstrating transient *increases* in perfusion [47] and in tissue pO_2 during CSD [48], one simple interpretation of Rosenthal's work is that the redox potentials of the respiratory chain coenzymes are in equilibrium, and are determined by the balance between the rate of ATP hydrolysis and availability to mitochondria of molecular oxygen from cerebral perfusion.

Glucose Utilisation During Recovery from CSD

Studies of normal, functional activation in the human brain using positron emission transverse tomography [49] indicated for the first time that the rate of glucose utilisation increased in greater proportion to oxygen utilisation, suggesting upregulation of glycolysis rather than of oxidative glucose utilisation. The finding of transient increases in brain lactate of some 30% in experimental studies of somatosensory activation [50] supported this interpretation, and suggested a degree of dependence on glycolytic generation of ATP during activation. The very large cation shifts that occur in CSD make it highly likely that similar and greater – but still transient – changes in glycolysis would occur during repolarisation after CSD. However, an extracellular lactate transient need not necessarily mean a shift to anaerobic metabolism, and Back and colleagues showed that in the normally perfused brain CSD is accompanied by an *in*crease in partial tissue pressure of oxygen [48]; this may be attributed to the hyperaemic response to CSD which is described below.

The model of the cerebral metabolic response to activation developed by Magistretti and colleagues [51] envisages that glycolytic activity is predominantly in the astrocytic compartment (where almost all glycogen in the brain is held [52, 53]), stimulated by an increase in extracellular glutamate during functional activation. It is further proposed that astrocytes deliver lactate to neurons, which, relying on lactate dehydrogenase activity in reverse, convert lactate to pyruvate. This pyruvate is then metabolised via the tricarboxylic acid cycle. Glucose transport across the blood brain barrier is highly efficient, to the extent that total unidirectional flux into the brain under non-activated conditions is approximately twice the rate of utilisation by glycolysis [54]. This, allied with the hyperaemic response to CSD discussed below, endows the cortex with its capacity to meet the challenges of activation. It is not appropriate to pursue further this important topic in this context, and the reader is referred to work by Magis-

tretti and colleagues [55], to a review questioning some aspects of this ''compartmented glial glycolysis'' model [56], and to the review by Chen and Swanson of astrocytic function and changes in brain injury [57]. Changes in glucose metabolism in focal ischaemia and during PIDs are described later in this review.

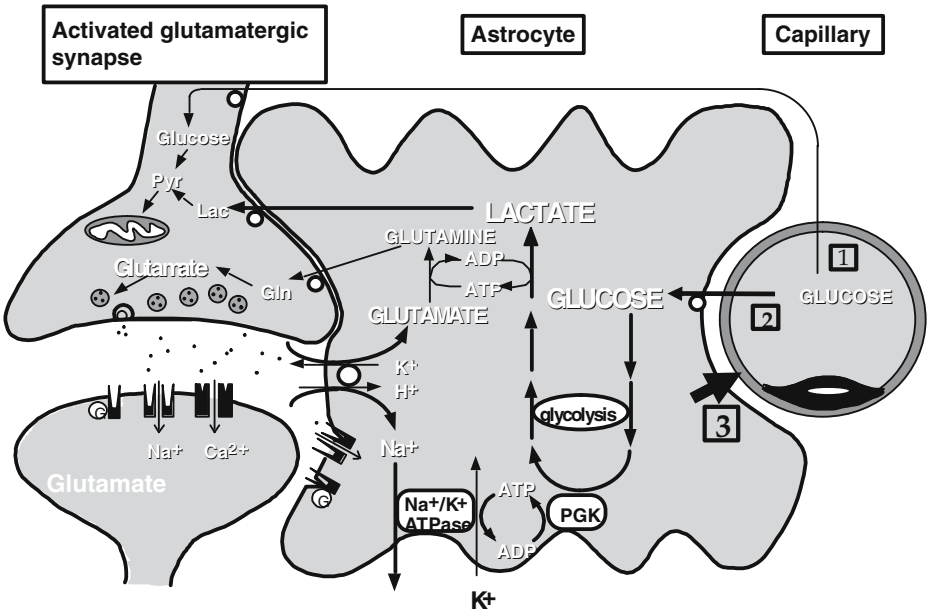

Fig. 3. Schematic diagram illustrating current concepts of the role of astrocytes in cerebral perfusion and metabolism (adapted with permission from Tsacopoulos and Magistretti [55]: Copyright 1996 by the Society for Neuroscience). Cerebral capillaries are extensively invested by astrocyte end feet, and extraction of glucose from blood to brain (probably the astrocyte compartment) is highly efficient (*arrow 2*). During activation, and especially in cortical spreading depression, the glycolytic pathway in astrocytes is upregulated, and the different kinetics of glial and neuronal lactate dehydrogenases favour net movement of lactate from astrocytes to neurons; the (limited) brain glycogen pool is located in astrocytes. Under resting conditions, glycolysis in neurons may be sufficient to meet energy demands (*arrow 1*). Neurotransmitter glutamate released into the synaptic cleft is re-accumulated into astrocytes by high-affinity cotransport with Na^+ ion, making use of the normal electrochemical gradient generated by Na^+/K^+ ATPase.

Several mechanisms regulate cerebral perfusion, with a prominent role proposed for astrocytes (*arrow 3*) [140]. First, their high membrane conductance for K^+ allows astrocytes to buffer the increased extracellular levels resulting from activation, with a direct vasodilator effect of K^+ on the microcirculation via the astrocyte cytosol and end feet. Adenosine- and nitric oxide-based mechanisms also contribute. Recent work by Zonta *et al.* now supports an additional mechanism of astrocyte-mediated vasodilation during activation [141]

Haemodynamic Response

Leão himself was the first to demonstrate hyperaemia in association with CSD; he observed a doubling in width of pial surface arterioles during CSD [58]. If CSD induced in the prefrontal region of the rat is assumed to propagate anteroposteriorly in the cerebral hemisphere at a constant rate, serial coronal sectioning of the hemisphere after it has been frozen at a single time point will provide in the section sequence a time series of the response of the brain to the propagation wave. Using autoradiography for CBF, and reasoning in this way, Lauritzen *et al.* showed that CSD is closely followed by an intense ($>200\%$) but brief (2 minutes) transient hyperaemia [47]. An extended phase of mild hypoperfusion (80–90% control) follows, lasting for some 60 minutes. This feature of CSD was later used by the same group to allow mapping with isotope scanning of a phase of hypoperfusion associated with migraine with aura that propagated forwards in the cerebral hemisphere at a rate in accordance with that of CSD – a finding that argues quite strongly for CSD as the basis of migraine with aura [59].

Histology of the Cortex Following CSD

A careful histological study by Nedergaard & Hansen [60] found no evidence of classical ischaemic pathological changes in the cortex following CSD *in the normally perfused cortex* of rats. As will be described later, the situation is very different in focal ischaemia.

Molecular Responses to CSD

Expression after induction of CSD of some of the immediate early genes (IEG) that respond to stress has been studied extensively, principally in rats, mice and transgenic mice. The IEG responses to MCAO have also been studied. In many such MCAO studies, increases in gene expression extend to the whole hemisphere rather than remaining within the core and penumbral regions. It is generally believed that such widespread upregulation represents a response to a depolarisation event that started as a PID in the ischaemic territory but then propagated throughout the rest of the hemisphere as CSD. According to Sharp *et al.* [61] this applies to c-fos and jun-B. Cyclooxygenase-2 is also induced by CSD [62]. In some cases, the association is relatively specific: for example, the degree of induction of the mRNAs encoding brain-derived neurotrophic factor and heat-shock protein-72 in response to CSD induced in the rat is dependent on the number of CSDs [63]. It needs to be stated that in MCAO other gene expression patterns may relate more to cell damage than to CSD. Thus HSP70, a heat shock protein, behaves as a protein chaperone, increasing in

the presence of denatured proteins [64], although expression in the infarct core may be limited by ATP depletion [65].

CSD as an Initiator of Inflammation

That cerebral ischaemia causes an increase in levels of interleukin-1β (IL-1β: an inflammatory cytokine) in the brain is well established [66–68]. CSD has a similar effect: Jander and colleagues recently showed that mRNA levels for IL-1β and tumour necrosis factor-α (TNF-α, also an inflammatory cytokine) are increased 24- and 60-fold respectively 4 hours after CSD induction with KCl [69]. Expression of the IL-1β protein was largely confined to microglia in the superficial cortical layers. These authors suggest that ''cytokine expression following CSD forms part of a physiological stress response that contributes to the development of ischaemic tolerance in this and other preconditioning paradigms'' (see below). That IL-1β can promote CNS repair has also been shown [70]. Another view of the effects of IL-1β comes from the work of Blamire *et al.*, who examined the effects of microinjection of recombinant IL-1β into the striatum of 3-week-old rats, and found significant reduction in apparent diffusion coefficient (ADC) and increases in cerebral blood volume and blood brain barrier permeability [71]. ADC reductions are usually attributed to a shift of water from extra- to intracellular compartments, but a reduction in water mobility in the intracellular compartment may occur [72]; both explanations are in keeping with an adverse effect of IL-1β.

Pre-Ischaemic Conditioning with CSD as Protection in Experimental Stroke

In experimental studies of stroke in rats, it is possible to confer a degree of protection from the effects of a period of ischaemia by prior induction of CSDs [73]. Levels of mRNAs for FOS, BDNF, and tPA, are increased by preischaemic conditioning with CSD [74]. TNF-α and IL1-β are believed to contribute to increased tolerance of ischaemia [75, 76], and an antagonist to nuclear factor κ-B (NF κ-B) blocked NF κ-B activity and reduced the pre-conditioning effect [77].

It seems very likely that one or more of the currently identified expression cascades – or other(s) still to be detected, underlie the protective effect of preischaemic conditioning with CSD, and increasing understanding of the molecular response to CSD may in time allow us to identify which of the several genes upregulated by CSD is/are responsible for the protective effects of preconditioning, and so perhaps lead to novel therapy for cerebral ischaemia, or at least better protection of the brain when some degree of prospective risk exists.

Factors Determining Ease of Induction of CSD

Species Differences and Cytoarchitecture

It has long been clear that CSD is more readily induced – and its repetition maintained – in rats than in larger experimental animals [5], with primates seen as the most "resistant" group of species. However, it is certainly possible to induce CSD in the primate brain [78]. A specific attempt to compare PID frequency in cats and squirrel monkeys after MCAO showed that PIDs do indeed occur spontaneously in a primate species, but failed to confirm a species difference in frequency of PIDs because of wide variability within both species [79]. However, the results revealed a clear dependence of PID frequency on plasma glucose level: this is discussed below in the context of PIDs.

One of the most widely canvassed explanations for species differences starts with the observation that lissencephaly is characteristic of the CSD-prone species, whereas the more resistant brains are gyrencephalic. There are however also regional differences in susceptibility within the brain of a given species, with the hippocampus particularly liable to CSD, together with – in migraineurs-with-aura – the occipital cortex. A clue to the puzzle comes from consideration of the cytoarchitecture and glial : neuronal ratios of different brain regions and in the brains of different species. Thus neurons are particularly tightly packed, glia relatively sparse, and CSD frequent, in the CA1 layer of the hippocampus. Migraine with aura typically commences with a visual aura on or near the fixation point (although auras apparently arising from the somatosensory cortex also occur), and the glia : neuron ratio in the occipital cortex is lower than elsewhere in neocortex [40, 41].

Tower and Young compared the glia : neuron ratio with brain size in a group of mammals ranging from mice to whales and elephants, and, using a log : log plot, demonstrated a convincing hierarchy in which the glia : neuron ratio increases in proportion with brain size [80]. Primates are distributed appropriately for their brain size within this hierarchy, rather than all of them possessing a high glia : neuron ratio independent of brain size, as might be predicted on "evolutionary" grounds. The issue is of interest in relation to the discussion above on mechanisms of CSD propagation, and the relationship of CSD propensity with Tower and Young's hierarchy is more in keeping with a *homœostatic* role for glia in the context of CSD than with one in which they *propagate* CSD.

Spreading depression has also been observed in experiments on the spinal cord [9, 81], and the possibility therefore arises that perilesion depolarisations might contribute to the evolution of spinal cord damage – at least in grey matter – not only in trauma but also in vascular lesions.