Preface

The workings of the brain have long been a fascination for scientists. Yet, faced with the obvious anatomical and biochemical complexity of the brain, understanding its functions more than superficially seemed an impossible goal. Equipped with no more sophisticated analytical techniques than, for instance, 'grind and find', early biochemists could do little more than identify neurotransmitters, work out the basic processes of neurotransmission and provide simplistic explanations for the neuropharmacological actions of simple drugs. Clearly this state of affairs was woefully inadequate to provide biochemical explanations for pain, pleasure or addiction, or to tackle the major neurological disorders, let alone scratch the surface of phenomena such as mood, anxiety or memory.

The advent of the Molecular Biology Era has revolutionized our research technology, and with it our thinking. Our ability to isolate and manipulate specific genes, identify their protein products and determine their functions has given us unprecedented power to analyse complex biological systems, and nowhere are the fruits of this more obvious than in brain research. The brain is now no longer *Terra Incognita* but *The New Frontier*.

The authors of the essays in this volume, acknowledged experts in their specialties, have illustrated the power of molecular biology to dissect the molecular functioning of the brain. The early part of the volume has related essays on neurotransmitters and their receptors by Mark Wheatley, Giampietro Schiavo and Gudrun Stenbeck, and Jane Haley. Aspects of neuronal development and neurodegeneration are discussed by Guy Tear, Pico Caroni, and Samantha Budd and David Nicholls. The molecular biology of opiate action (Dominique Massotte and Brigitte Kieffer) is crucial to understanding these drugs and their addictive properties, but also to explaining natural analgesia. The concept of neuronal networks is nicely illustrated for the olfactory system by Doron Lancet's group. Neurodegenerative and affective disorders are major healthcare problems that can be expected to yield to analysis by molecular genetical approaches. In these areas we have essays by Philip Strange (schizophrenia), John Hardy's group (Alzheimer's disease), Adriano Aguzzi et al. (spongiform encephalopathies; prion diseases) and Jean-Louis Mandel and colleagues (trinucleotide expansion disorders). Emily Huang and Chuck Stevens then provide an exciting account of how molecular biology is beginning to explain a phenomenon as complex as memory. The volume ends with a thought-provoking essay on Future Developments by Susan Greenfield.

The brief given to authors was to convey the excitement of their field, point to future developments, and encourage their audience — undergraduates in their senior years and starting postgraduates — to want to become part of the research effort that will open up the *New Frontier*. I think that they will succeed — so after reading these essays all that will remain to be done is to *Go West Young (Wo)Man!*

Steve Higgins
University of Leeds, 1998

Authors

Guy Tear is an MRC Senior Research Fellow in the Department of Biochemistry at Imperial College, London. His current research is an investigation of the molecules required for axon guidance during the development of the Drosophila central nervous system. Before moving to Imperial College, he received his PhD from Cambridge University and undertook a period of postdoctoral research at the University of California, Berkeley.

Mark Wheatley graduated from the University of London with a BSc in Biochemistry in 1980. His studies on the D_2 dopamine receptor in the laboratory of Philip Strange resulted in the degree of PhD in Biochemistry being awarded by the University of Nottingham in 1983. Between 1983 and 1987 he was a Research Fellow at the National Institute for Medical Research in London, working with Drs Ed Hulme and Nigel Birdsall on the structure and function of the muscarinic acetylcholine receptor. In 1988 he was appointed to a lectureship in Biochemistry at the University of Birmingham. He is currently Senior Lecturer in Biochemistry and his research interests address the structure and function of the G-protein-coupled receptors for peptide hormones, particularly vasopressin and oxytocin.

Giampietro Schiavo graduated in 1992 from the laboratory of C. Montecucco, University of Padua, Italy, with a thesis on the effect of tetanus and botulinum neurotoxins on neurotransmitter release. He is now pursuing his interest in the mechanism of neurosecretion as group leader at the Imperial Cancer Research Fund in London. **Gudrun Stenbeck** graduated in 1993 from the University of Heidelberg, Germany (F. Wieland's laboratory), with a thesis on the characterization of the coatomer subunits of COPI-coated vesicles involved in Golgi transport. She is now a lecturer at University College London. Her interest is in the molecular mechanism of bone remodelling. Both authors had postdoctoral training, on the molecular basis of neurotransmitter release, in the laboratory of J.E. Rothman, at the Memorial Sloan-Kettering Cancer Center in New York.

Samantha Budd is currently undertaking postdoctoral research at the CNS Research Institute, Brigham & Women's Hospital, Harvard Medical School, Boston. She completed her PhD with David Nicholls in Dundee in 1997. **David Nicholls** is Professor of Neurochemistry in the Neurosciences Institute of the University of Dundee. He has a long-standing interest in mitochondrial function, including brown fat uncoupling, Ca^{2+} transport and their *in situ* function in isolated nerve terminals and cultured neurons. He is the author of *Proteins, Transmitters and Synapses* (published by Blackwell Science)

and co-author of *Bioenergetics 2* (published by Academic Press). His current interest is in mitochondrial (dys)function during excitotoxicity.

Pico Caroni is a staff member of the Friedrich Miescher Institute (FMI, Basel, Switzerland), an institute supported by Novartis that is dedicated to basic research in biology. He obtained a PhD in biochemistry at the ETH in Zürich under Ernesto Carafoli, and was a postdoctoral fellow in Regis Kelly's group at UCSF. In 1985 he joined Martin Schwab's group at the Brain Research Institute of the University of Zürich, where he established the existence of oligodendrocyte components that inhibit axonal growth. In 1989 he moved to the FMI, where his research interests focus on structural plasticity in the adult nervous system.

Dominique Massotte performed her doctoral work on structure–function studies of membrane proteins in Liège, Belgium, and at the European Molecular Biology Laboratory in Heidelberg, Germany, and graduated from Liège. She received a postdoctoral fellowship at the Max-Planck Institute in Cologne (Germany) where she trained in molecular biology and developed the baculovirus expression system. She now holds a CNRS research position at the Ecole Supérieure de Biotechnologie de Strasbourg (France) where she initiated a structure–function study of human opioid receptors. **Brigitte Kieffer** graduated in Chemistry and Biochemistry from the University of Strasbourg, France, and was recipient of a postdoctoral fellowship at the Friedrich Miescher Institute in Basel, Switzerland, where she trained in molecular biology. She started her own research as an associate professor at the Ecole Supérieure de Biotechnologie de Strasbourg where she initiated the molecular biology of opioid receptors. She now is a professor at the Faculty of Pharmacy (France) where she runs a genetic engineering teaching programme, and leads a research group studying opioid receptor function at the Ecole Supérieure de Biotechnologie de Strasbourg.

Jane Haley studied for a BSc in Pharmacology at University College London (UCL) and worked for Wellcome upon graduation. She returned to UCL in 1987 to undertake a PhD, during which she became interested in a possible role for nitric oxide in longer-duration pain states and spinal hyperalgesia. She continued this work at the University of Minnesota, U.S.A., and extended her research to include the involvement of nitric oxide in the induction of long-term potentiation (LTP). She moved to Stanford University in 1993 where she also investigated carbon monoxide involvement in LTP. She is currently a postdoctoral researcher at UCL examining G-protein modulation of ion channels.

Yitzhak Pilpel obtained his degree in Biology from the Tel Aviv University, Israel, in 1993, and is now studying towards a PhD in the Department of Molecular Genetics at the Weizmann Institute of Science, Rehovot, Israel. He is currently researching bioinformatics and molecular

modelling of the olfactory receptor proteins. **Alona Sosinsky** graduated in Biophysics from the St Petersburg Technical University, Russia, in 1993, and is now studying towards a PhD in the Department of Molecular Genetics at the Weizmann Institute of Science. His current research interests are centred on gene structure and expression of olfactory genes. **Doron Lancet** obtained a BSc in Chemistry and Physics at the Hebrew University, Jerusalem, Israel, in 1970. He studied towards his PhD at the Weizmann Institute of Science and undertook postdoctoral research at Harvard University with Jack Strominger. There followed a period as a postdoctoral research associate at Yale University School of Medicine, with Gordon Shepherd. He is currently a professor in the Department of Molecular Genetics at the Weizmann Institute of Science with interests in molecular biology, genetics, human genomics of the sense of smell, molecular recognition and the origin of life. He is also Head of the Genome Center at the Weizmann Institute.

Philip Strange graduated from Cambridge University with a BA in Chemistry in 1970 and a PhD in Organic Chemistry in 1973. Following postdoctoral research in Berkeley, California (D.E. Koshland's laboratory), and Mill Hill, London (A.S.V. Burgen's laboratory), he has held positions at the universities of Nottingham (Lecturer in Biochemistry) and Kent (Reader in Biochemistry and then Professor of Neuroscience) before taking up his current position as Professor of Neuroscience at the University of Reading in 1998.

John Hardy was born in Nelson, Lancashire (1954) and spent his childhood in Lancashire and Cheshire in northern England. He completed his degree in Biochemistry at Leeds University in 1976 and his PhD in Neurochemistry at Imperial College in 1979. After postdoctoral positions in Newcastle upon Tyne (1979–1983) and Umea, Sweden (1983–1985), he returned to Imperial College as a Lecturer (1985), then a Senior Lecturer (1989), before taking a Chair at the University of South Florida in 1992. Since 1995 he has been at the Mayo Clinic, Jacksonville, Florida. **Michael Hutton** completed his undergraduate training at the University of Manchester (1985–1988) before moving on to do a PhD in Molecular Neuroscience at the University of Cambridge (1989–1992) working in the laboratory of Eric Barnard on ligand-gated ion channels. After completing postdoctoral training in Cambridge (1992–1994), he joined John Hardy's group at the University of South Florida, and moved with him to the Mayo Clinic in 1996. Hutton now runs his own laboratory, having been appointed as a Senior Associate Consultant and Assistant Professor in 1997. His current research focuses on the role of the Tau protein in neurodegeneration. **Jordi Perez-Tur** obtained his degree in Biology in 1987 from the Universitat de Valencia-Estudi General, Spain, and his PhD (Molecular Biology) from Universidad Autonoma de Madrid, Spain, in the Centro de Biologia Molecular in 1993. He moved to his

first postdoctoral stage in 1993, when he joined the group of Marie-Christine Chartier at INSERM, Lille, France. His second postdoctoral position (1995–1996) was under the direction of John Hardy at the University of South Florida, and in 1996 he moved with Hardy to the Mayo Clinic. In 1998 he was appointed Assistant Professor and has been recently appointed Associate Consultant.

Adriano Aguzzi is Professor for Neuropathology at the Institute of Neuropathology, University Hospital Zurich, Switzerland. He is leading a research group of around 20 co-workers, who are involved in work on the pathogenesis of prion diseases and neurocarcinogenesis. Among the people in the 'prion group' are **Michael A. Klein**, **Ivan Hegyi** and **Rico Frigg**, all of whom have a Masters degree. Their projects focus on the peripheral pathogenesis and lymphotropism of prion diseases. **Thomas Blättler** finished his thesis on the transfer of scrapie infectivity from spleen to brain in 1996. **Alex Raeber** started his scientific career in the laboratory of Stanley Prusiner, before he joined Charles Weissmann in 1993. He is now senior postdoc in the laboratory and is supervising a group of several PhD students. **Sebastian Brandner** joined Adriano Aguzzi in 1993. He established the neurografting technique and used it for the study of prion neurotoxicity. **Christine Musahl**, a postdoctoral fellow since 1997 in the laboratory, established a transgenic mouse model to study the role of PrP-specific antibodies in the pathogenesis of prion diseases.

Astrid Lunkes obtained her PhD in 1995 at the University of Düsseldorf, Germany, working on the positional cloning of spinocerebellar ataxia 2. In 1996 she joined the laboratory of Jean-Louis Mandel to investigate functional aspects involved in the pathogenesis of Huntington's disease using a cellular model approach. **Yvon Trottier** graduated from Laval University (Québec), investigating the role of cytochromes *P*-450IA in chemical carcinogenesis in human cells. Since 1992, she has been studying the mechanism whereby polyglutamine expansion causes neurodegenerative disorders, like Huntington's disease and spinocerebellar ataxia. **Jean-Louis Mandel** is Professor of Genetics at the Faculty of Medicine of Strasbourg and Head of Human Molecular Genetics at the Institut de Génétique et Biologie Moléculaire et Cellulaire, Strasbourg. In 1982, he initiated a project on mapping and identification of disease genes, leading notably to the discovery, in 1991, of unstable mutations in the fragile X mental retardation syndrome, the isolation of the gene responsible for adrenoleukodystrophy, and, most recently, to the cloning of the myotubular myopathy gene. Since 1991, he has been involved in the analysis of diseases caused by trinucleotide repeat expansions (including Huntington's disease, spinocerebellar ataxia and Friedreich ataxia).

Emily P. Huang is a research associate with the Howard Hughes Medical Institute and Molecular Neurobiology Laboratory at the Salk Institute in La Jolla, California, U.S.A. **Charles F. Stevens** is a Howard Hughes Medical

Institute Investigator and Professor of Molecular Neurobiology at the Salk Institute in La Jolla, California, U.S.A.

Susan Greenfield read for a first degree at St Hilda's College, Oxford, and worked for a DPhil in the University Department of Pharmacology. She held postdoctoral fellowships in Oxford, Paris and New York, until being appointed, in 1985, as University Lecturer in Synaptic Pharmacology and Fellow and Tutor in Medicine, Lincoln College. Since then she has also held a Visiting Research Fellowship at the Institute of Neuroscience, La Jolla, and was the 1996 Visiting Distinguished Scholar, Queens University, Belfast. The title of Professor of Pharmacology was conferred in 1996. In 1997 she was awarded an Honorary DSc by Oxford Brookes University, and is to receive Honorary DSc degrees, in 1998, from the University of St Andrew's and Exeter University. She became Director of The Royal Institution of Great Britain in 1998. Apart from her primary research, where she heads a multidisciplinary group studying how diverse neurons prone to degeneration share a common yet non-classical feature. Greenfield has developed an interest in the physical basis of the mind and has edited or authored a number of publications on the subject.

Greenfield also makes contributions to the public understanding of science. In 1994 she was the first woman to be invited to give the Royal Institution Christmas lectures and has subsequently made a wide range of broadcasts on TV and radio. She is currently preparing a major six-part series on the brain and mind, to be broadcast in the year 2000. In 1995 she was elected to the Gresham Chair of Physics. She was general editor in 1996 for *The Human Mind Explained* (Cassell) and has recently authored *The Human Brain: A Guided Tour* (Weidenfeld & Nicholson) which reached the bestseller list. In addition, she writes a fortnightly column for *The Independent on Sunday* on aspects of science, as well as contributions to *The Times*, *The Times Higher Education Supplement*, *The Sunday Times*, *The Independent* and *The Daily Telegraph*. She was ranked by Harpers and Queen as number 14 in the '50 Most Inspirational Women in the World'.

Abbreviations

$\Delta\psi$	membrane potential
ACh	acetylcholine
AChR	acetylcholine receptor
AD	Alzheimer's disease
AIF	apoptosis-inducing factor
AMPA	α-amino-3-hydroxy-5-methylisoxazolepropionate
AP5	amino-5-phosphonopentanoate
ApoE	apolipoprotein E
APP	amyloid precursor protein
BBB	blood–brain barrier
BSE	bovine spongiform encephalopathy
CAM	cell adhesion molecule
CaMKII	Ca^{2+}/calmodulin-dependent kinase
CAP-23	cortical cytoskeleton-associated protein of 23 kDa
CJD	Creutzfeldt–Jakob disease
CNS	central nervous system
comm	commissureless
CREB	cAMP response element binding protein
DCC	deleted in colorectal cancer
DRG	dorsal root ganglion
DRPLA	dentatorubral–pallidoluysian atrophy
D_{2S}, D_{2L}	short and long forms respectively of the D_2-dopamine receptor
ECM	extracellular matrix
EDRF	endothelium-derived relaxing factor
eNOS	endothelial NOS
GABA	γ-aminobutyric acid
GAP	growth-associated protein
GC	guanylate cyclase
GFAP	glial fibrillary acidic protein
GluR	glutamate receptor
GPCR	G-protein-coupled receptor
GPI	glycosylphosphatidylinositol
HD	Huntington's disease
HO	haem oxygenase
5-HT	5-hydroxytryptamine
i3	third intracellular loop
IgCAM	immunoglobulin CAM
iNOS	inducible NOS
KO mice	knock-out mice
LANP	leucine-rich acidic nuclear protein

LGIC	ligand-gated ion channel
LTP	long-term potentiation
mAChR	muscarinic AChR
MJD	Machado–Joseph disease
MPP^+	1-methyl-4-phenylpyridinium
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MRI	magnetic resonance imaging
mtDNA	mitochondrial DNA
NK_2R	tachykinin NK_2 receptor
N-CAM	neural CAM
NMDA	*N*-methyl-D-aspartate
NOS	nitric oxide synthase
nNOS	neuronal NOS
NSF	*N*-ethylmaleimide-sensitive factor
nvCJD	new variant CJD
OR	olfactory receptor
Δp	proton motive force
PD	Parkinson's disease
PET	positron emission tomography
PKA	cAMP-dependent protein kinase
PNS	peripheral nervous system
POMC	prepro-opiomelanocortin
PRA	prenylated Rab acceptor
PrP^C	normal prion protein
PrP^{Sc}	pathologically changed isoform of PrP^C
PS-1(-2)	presenilin-1(-2)
PSD	postsynaptic density protein
R, R*	inactive and active receptor forms respectively
RAGS	repulsive axon guidance signal
robo	roundabout
SBMA	spinal and bulbar muscular atrophy
SCA	spinocerebellar ataxia
SH2	Src homology 2
SNAP	soluble NSF accessory protein
SNAP-25	synaptosomal-associated protein of 25 kDa
SNARE	SNAP receptor
SSV	small synaptic vesicle
t-SNARE	target membrane SNARE
TM	transmembrane
VAMP	vesicle-associated membrane protein
v-SNARE	vesicular SNARE