Borna disease virus and its role in neurobehavioral disease / edited by Kathryn M. Carbone.

Incorporates bibliographical references and index.

ISBN 1-55581-235-X (hardcover)


All Rights Reserved
Printed in the United States of America

To Rudolf Rott, on behalf of all BDV scientists, in appreciation of his foresight, devotion, and many contributions to modern BDV research, and
to my greatest mentor and supporter, my father, Paul P. Carbone (1931–2002), Lasker Award recipient, clinical researcher, and talented clinical oncologist, who provided the foundation for scientific careers for myself and many young researchers; from him I learned always to take the most interesting path, not the path of least resistance.
## Contents

Contributors ................................................................. ix
Foreword ................................................................. xi
Preface ................................................................. xiii

1. Borna Disease Virus: Spanning a Century of Science.  
   *Keizo Tomonaga and Kathryn M. Carbone* ........................ 1

2. Borna Disease Virus Molecular Virology.  
   *Masahiko Kishi, Keizo Tomonaga, Patrick Lai,*  
   *and Juan Carlos de la Torre* ........................................ 23

3. Laboratory Diagnosis.  
   *Christian Sauder, Tetsuya Mizutani,*  
   *and Kazunari Yamaguchi* ........................................... 45

4. Epidemiology and Infection of Natural Animal Hosts.  
   *Kazuyoshi Ikuta, Katsuro Hagiwara, Hiroyuki Taniyama,*  
   *and Norbert Nowotny* ........................................... 87

5. Experimental Infection: Pathogenesis of  
   Neurobehavioral Disease.  
   *Mikhail V. Pletnikov,*  
   *Daniel Gonzalez-Dunia,*  
   *and Lothar Stitz* .................................................. 125

6. Human Borna Disease Virus Infection.  
   *Oliver Planz,*  
   *Karl A. Bechter,*  
   *and Martin Schwemmle* ........................................... 179

Index ................................................................. 227
Contributors

Karl A. Bechter • Department of Psychosomatics/Psychotherapy and Department of Psychiatry II, University of Ulm, Ludwig-Heilmeyer-Strasse 2, 89312 Günzburg, Germany

Kathryn M. Carbone • Office of the Director, Center for Biologics Evaluation and Research, U.S. Food and Drug Administration, HFM 20, 8800 Wisconsin Ave., Bethesda, MD 20892

Juan Carlos de la Torre • Department of Neuropharmacology, Division of Virology, IMM-6, The Scripps Research Institute, 10550 N. Torrey Pines Rd., La Jolla, CA 92037

Daniel Gonzalez-Dunia • Unité des virus lents, CNRS URA 1930, Institut Pasteur, 28 rue du Dr Roux, 75724 Paris Cedex, France

Katsuro Hagiwara • Department of Veterinary Microbiology, Faculty of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido 069-8501, Japan

Kazuyoshi Ikuta • Department of Virology, Research Institute for Microbial Diseases, Osaka University, 3-1 Yamadaoka, Suita, Osaka 565-0871, Japan

Masahiko Kishi • Tsukuba Central Laboratories, Kyoritsu Seiyaku Corporation, Inashiki-gun, Ibaraki, Japan

Patrick Lai • Bioscience, Carlson Hall, Salem International University, Salem, WV 26426-0500

Tetsuya Mizutani • Laboratory of Public Health, Department of Environmental Veterinary Sciences, Graduate School of Veterinary Medicine, Hokkaido University, Kita-ku, Kita-18, Nishi-9, Sapporo 060-0818, Japan

Norbert Nowotny • Clinical Virology Group, Institute of Virology, University of Veterinary Sciences, Vienna, A-1210 Vienna, Austria,
Contributors

and Department of Medical Microbiology, Faculty of Medicine and Health Sciences, United Arab Emirates University, P.O. Box 17666, Al Ain, United Arab Emirates

Oliver Planz  •  Institute for Immunology, Federal Research Center for Virus Diseases of Animals, Paul-Ehrlich-Strasse 28, 72076 Tübingen, Germany

Mikhail V. Pletnikov  •  Department of Psychiatry and Behavioral Sciences, The Johns Hopkins University School of Medicine, Ross 618, 720 Rutland Ave., Baltimore, MD 21205

Christian Sauder  •  Department of Virology, Institute for Medical Microbiology and Hygiene, University of Freiburg, Hermann-Herder-Strasse 11, 79104 Freiburg, Germany

Martin Schwemmle  •  Institute of Medical Virology, University of Zürich, Gloriastrasse 30, 8028 Zürich, Switzerland

Lothar Stitz  •  Institut für Immunologie, Bundesforschungsanstalt für Viruskrankheiten der Tiere, Paul-Ehrlich-Strasse 28, 72076 Tübingen, Germany

Hiroyuki Taniyama  •  Department of Pathology, Faculty of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido 069-8501, Japan

Keizo Tomonaga  •  Department of Virology, Research Institute for Microbial Diseases, Osaka University, 3-1 Yamadaoka, Suita, Osaka 565-0871, Japan

Kazunari Yamaguchi  •  Blood Transfusion Service and Internal Medicine, Kumamoto University School of Medicine, Honjo 1-1-1, Kumamoto 860-8556, Japan
Foreword

This book represents a singular event for all virologists, especially those interested in neuropathogenesis and virus-related neuropsychiatric disorders. The virus du jour is Borna disease virus (BDV), which is the etiological agent of Borna disease (BD). BD is a fatal neurological disease of horses that has been known for over 100 years and is now emerging as a disease in cats, dogs, certain birds, and possibly all warm-blooded animals, including humans. However, due to the difficulty of isolation and detection of BDV, there remains controversy about possible links between BDV and human neuropsychiatric disorders.

Kathryn Carbone and her colleagues have put together a definitive tome that examines real criteria for establishing a BDV infection and the pitfalls of overinterpreting highly sensitive assays. Twenty-five years ago, I was intently researching the assembly of murine and avian retroviruses, focusing on retroviral proteases. At the time, there was suggestive evidence that a human retrovirus might also exist; after several false starts, human T-cell leukemia virus type 1 was isolated and characterized as the etiological agent of adult T-cell leukemia and, later, tropical spastic paraparesis. About 10 years later, these findings and culture methods laid the groundwork for the classical isolation of human immunodeficiency virus type 1 as the etiological agent of AIDS. In some ways, links between BDV in horses and rats are awaiting a similar fate for a direct link to neuropsychiatric diseases in humans. As of now, there is a smoking gun but no definitive association. However, as with the retroviruses, it may only be a matter of time before an association is firmly established.

In closing, I thank Kathryn Carbone, as well as Jeff Holtmeier of ASM Press, for asking me to write a foreword for this important text in a new and emerging area of virology. I hope that the authors, by bringing BDV into the limelight, will spur greater activity in the field of viral neuropathogenesis.

Ronald Luftig
Preface

In the field of Borna disease virus (BDV) research, where each experiment reveals a new mystery more often than an answer, where the subject repeatedly refuses to play by the rules of traditional virology, where revelations of scientific interest in BDV often lead to responses of “What virus?” and where grant funding opportunities are difficult to realize, it is amazing and gratifying to see that worldwide interest in BDV has increased exponentially over the past 20 years. Despite the unique challenges of BDV research, or perhaps because of them, those in the field have always seen tremendous potential benefits from studying this agent. I acknowledge, first and foremost in the BDV field, Rudolf Rott of the Institute for Virology, University of Giessen, Giessen, Germany, who is considered the founder of modern BDV research. Virtually all BDV investigators trace the beginning of their experiences in BDV research to Rudolf Rott or to someone trained by him (see chapter 1).

Despite the increasing international interest in BDV research, the field is still young and controversial. I have tried to bring together BDV scientists whose stars are rising or have already risen to craft an encyclopedia of modern BDV research. Each chapter author was asked to present an overview of the data in the assigned area, to provide a critique of these data with a discussion of the controversies therein (and there are many), and, perhaps most importantly, to suggest the direction in which the future of BDV research should go. In a field where conflicting, unresolved issues tend to polarize, these accomplished BDV researchers have worked hard to provide a balanced view of up-to-date BDV knowledge for other scientists, clinicians, and the public, and I thank them for their selfless efforts and quality performance. It is also important to emphasize that the support and guidance of leaders in the American Society of Microbiology, such as Ronald Luftig, and the ASM Press staff, especially the director, Jeff Holtmeier, were the final common denominators in realizing the efforts of all the BDV scientists who worked diligently on this book.

From 1985 and my baptism in BDV research in Opendra Narayan’s laboratory at Johns Hopkins University, the first laboratory in the United States to take up BDV study, to my role in 2002 as editor of an exciting and up-to-date summary of modern BDV research, I remain enthusiastic about past discoveries and those we have yet to make in the BDV field. Working in an area considered obscure by some and groundbreaking by others, I am constantly reminded of a delightful letter to the editor of The Lancet by
J. Morris (“Originality: who is to judge?” [Lancet 342:930, 1993]): “If the work receives acclaim then it means that it is part of the conventional wisdom, and is not original. If rejected it might be original; if dismissed out of hand, it probably is.” Having worked in the field for almost 2 decades, I have seen all three outcomes in response to BDV discoveries, yet, by these criteria, I hope never to see new BDV research accepted without controversy. I am sure that BDV research will continue to surprise, frustrate, and delight scientists for decades to come.

Kathryn M. Carbone
Index

Note: Page numbers followed by “f” indicate figures; page numbers followed by “t” indicate tables.

Amantadine, for Borna disease, 207–208
Animal(s), Borna disease in, see also specific animals
  clinical manifestations of, 89–91, 89t, 104–112
  diagnosis of, see Diagnosis
  epidemiology of, 10–11, 87–89, 102–104
  future directions in, 115–117
  historical aspects of, 3–9
  host range of, 2, 23–24, 87–88, 125–126
  pathology of, 89t, 91–95, 91f, 104–112,
    Color Plates 1 & 2
  species variation in, 113–115
  subclinical, 95, 96t–98t, 99–102
  transmission of, 112–113
Animal models, for Borna disease, 125–178
  behavioral disease, 141–148, 142f
  central nervous system pathology,
    129–130, 130f, Color Plate 3
  genetic factors in, 164–166
  historical aspects of, 6, 11–12
  immune response, 132–140
    B lymphocytes in, 134
    cellular, 133
    humoral, 132–133
    major histocompatibility complex in,
      134–135
    molecular mechanisms of, 140–141
    natural killer cells in, 138
    neurodevelopmental damage in,
      155–157, Color Plate 5
    T lymphocytes in, 133, 135–140
    molecular mechanisms, 163–164
    neurodevelopmental damage, 148–163
      behavioral deficits in, 159–163
      to brain, 150–155, 152f, 153f, Color Plate 4
      cognitive abnormalities in, 160–162
      emotional disturbances in, 160
      gender differences in, 166–167
      gene expression in, 158
      immune response, 155–157,
        Color Plate 5
      infection inoculation, 148–150, 149f
      monoamine system alterations in,
        158–159
      sensorimotor deficits in, 159–160
      social behavior alterations in, 162–163
      synaptic pathology, 155
      neuropsychiatric aspects of, 167–168
      peripheral nervous system pathology,
        131–132
      time course analysis, 130–131
      virus dissemination and replication,
        127–129
Antibody(ies), Borna disease virus
  in animals, 5
    avidity of, 185–187, Color Plate 6
  in cats, 97t, 98t
  in cattle, 96t, 98t
  in horses, 92–95, 96t, 98t, 99–101, Color Plates 1 & 2
  in humans, 2–3, 180, 181t–183t, 183–187,
    201–206, Color Plate 6
in immune response, 132–133
in ostriches, 98t
in rodents, 97t
in sheep, 95, 96t, 98t, 99, 101–102
Antigen(s), Borna disease virus
detection of, 52–57, 53t, 187–189, 188t
in horses, 92–93
Antigen capture enzyme-linked
imunosorbent assay, 55
Assembly, of Borna disease virus, 31
Astrocytes, Borna disease virus tropism for,
24–25, 127, 138, 149, 154–157, Color Plate 5
Autism, Borna disease and, 150
Autonomic nervous system, Borna disease
of, 131–132
Avidity, of antibodies, in Borna disease,
185–187, Color Plate 6
B lymphocytes, in Borna disease, 134
Behavioral disease, in Borna disease, animal
models for, 141–148, 142f, 159–163
Birds, Borna disease in, 103–104, 111–112
Blood, Borna disease virus nucleic acid in,
191–195, 191t
Borna disease
in animals, see Animal(s), specific animals
diagnosis of, see Diagnosis
host range of, 2, 23–24, 87–88, 125–126
in humans, see Human Borna disease
spread of, from central Europe, 4–9, 5f
Borna disease virus
antibodies to, see Antibody(ies), Borna
disease virus
cell-free preparation of, 24–25
classification of, 2
culture of, 9–10, 188, 188t
species variation in, 113–115
virology of, see Virology, of Borna disease
virus
Brain, Borna disease virus in
clinical manifestations of, in animals,
89–91, 89t, 104–112
detection of, 52–57, 53t, 187–189, 188t
antigen capture ELISA for, 55
immunohistochemistry for, 52–53, 60
Western blot test for, 53–55
in humans, see Human Borna disease
infectivity determination in, 60–62
nucleic acid detection in, 189–191, 189t
persistence of, 139
RNA detection of, 71–77
subclinical, in animals, 95, 96t–98t,
99–102
Capture enzyme-linked immunosorbent
assay, 49–50
Cats, Borna disease in
antibodies in, 97t, 98t
clinical manifestations of, 89t, 107–110
epidemiology of, 103
pathology of, 89t, 107, 109–110
species-specific, 114
transmission of, 113
Cattle, Borna disease in
antibodies in, 96t, 98t
clinical manifestations of, 89t, 104–106
epidemiology of, 102
pathology of, 89t, 105
Cell culture, of Borna disease virus, 9–10,
188, 188t
Cellular immune response, to Borna disease
virus, 133
Central nervous system, see Brain
Cerebellum, in Borna disease, 149, 149f,
152–154, 153f
Cerebrospinal fluid, in Borna disease
filtration of, 208–209
virus detection in, 46, 205–206
Chemokines, in Borna disease, 157
Cholecystokinin deficiency, in Borna
disease, 143
Cholinergic system, in Borna disease, 145
Clinical manifestations, of Borna disease
in animals, 89–91, 89t, 91f, 104–112
in humans, 197–206, 209–216
Cognitive dysfunction, in Borna disease,
160–162
Competitive enzyme-linked
immunosorbent assay, 50
Culture, of Borna disease virus, 9–10, 188,
188t
Cytokines, in Borna disease, 135–141, 157
Dentate gyrus, of hippocampus, Borna
disease virus in, 150–152, 152f, Color Plate 4
Depression, Borna disease virus and
antibody seroprevalence, 181t–183t,
202–203
treatment of, 207–208
Developmental damage, neurologic, in Borna disease, see Animal models, for Borna disease, neurodevelopmental damage

Diagnosis, of Borna disease, 45–84 in animals, 10–11

difficulties in, 62–77
electrochemiluminescence immunoassay, 51–52, 70–71, 183–184, 183t
enzyme-linked immunosorbent assay, 49–52
immunohistochemistry, 52–53
immunoprecipitation test, 51, 69–70, 183
indirect immunofluorescence assay, 46–48, 47f, 65–66
serology, 45–46, 45t, 65–71, 116
in humans, 180, 181t–183t, 183–187, 201–206, Color Plate 6
virus antigen detection, 52–57, 53t, 187–189, 188t
virus infectivity, 60–62
virus RNA detection, 53t, 57–60, 71–77
Western blot assay, 48–49, 53–55, 66–68, 182t, 183–185

Dogs, Borna disease in
clinical manifestations of, 89t, 106–107
epidemiology of, 102–103
pathology of, 89t, 106–107
species-specific, 114

Dopamine, in Borna disease, 143–144, 158–159

Electrochemiluminescence immunoassay,
51–52, 70–71, 183–184, 183t
ELISA, see Enzyme-linked immunosorbent assay
Emotional disturbances, in Borna disease, 160

Encephalitis, Borna disease virus, 206–207
Enzyme immunoassay, reverse
transcription-polymerase chain reaction with, 59–60

Enzyme-linked immunosorbent assay,
49–52, 182t–183t, 183–185
antigen capture, 55
capture, 49–50
classical, 49
competitive, 50
problems with, 68–69
reverse-type sandwich, 50–51, 69, 185

Ependymal cells, Borna disease virus
tropism for, 24–25, 127, 149

Epidemiology, of Borna disease
in animals, 10–11, 87–89, 102–104
spread from central Europe, 4–9, 5f

Experimental infections, see Animal models;
Pathogenesis and pathology

Filtration, of cerebrospinal fluid, for Borna
disease, 208–209

Fluorescence-activated cell sorting analysis,
56–57, 187–188

Free oxygen radicals, in Borna disease,
140–141

Gender differences, in Borna disease,
166–167

General paresis, in syphilis, psychiatric
disorders in, 212–213

Genetic factors, in Borna disease, 164–166

Genome, of Borna disease virus, 25–26, 28,
29f, 30–34
species variation in, 113–115

Glutamic acid decarboxylase deficiency, in
Borna disease, 143

Glycoproteins, of Borna disease virus, 26
immune response to, 133
regulation of, 32–33

Hippocampus, pathology of, in Borna
disease, 143, 151–152, 152f, Color Plate 4

Historical aspects, of Borna disease, 1–21
discovery, 1, 125
in early 20th century, 3–4, 125–126
in late 20th century, 9–14
spread from central Europe, 4–9, 5f
at start of 21st century, 14–16

Horses, Borna disease in
antibodies in, 95, 96t, 98t, 99–101
clinical manifestations of, 89t, 90–91, 91f
epidemiology of, 88–89
historical aspects, 1, 88
as natural host, 23
pathology of, 89t, 91–95, 91f, Color Plates 1 & 2
species-specific, 114–115
transmission of, 112–113

Host range, of Borna disease, 2, 23–24,
87–88, 125–126
Human Borna disease, 179–225
  antigen detection in, 187–189, 188t
  cerebrospinal fluid analysis in, 205–206
  clinical studies of, 195–216
  encephalitis in, 206–207
  epidemiology of, 180, 181t–183t, 183–187
  historical aspects of, 2–3, 5–9, 13–14
  imaging in, 205–206
  nucleic acid detection in, 189–195, 189t, 191t
  perinatal, 196–197
  psychiatric disorders in, 197–206, 209–216
  serologic evidence of, 180, 181t–183t, 183–187, 201–206, Color Plate 6
  transmission of, 113
  treatment of, 207–209
  virus isolation in, 187–189, 188t
Human immunodeficiency virus infection, psychiatric disorders in, 213
Humoral immune response, to Borna disease virus, 132–133
Huntington’s disease, 211
Hydrocephalus, in Borna disease, 129, 130f
Hypothalamus, damage of, in Borna disease, 145
Imaging studies, in Borna disease, 205–206
Immune complexes, in Borna disease, 203
Immune response, to Borna disease virus, 116
  animal models of, 132–140
  B lymphocytes in, 134 cellular, 133
  humoral, 132–133
  major histocompatibility complex in, 134–135
  neurodevelopmental damage in, 155–157, Color Plate 5
  T lymphocytes in, 133, 135–140
Immunoassays, 9
  for Borna disease virus, 9
  electrochemiluminescence, 51–52, 70–71, 183–184, 183t
  enzyme-linked immunosorbent, see Enzyme-linked immunosorbent assay
  indirect immunofluorescence, 46–48, 47f, 65–66, 180, 181t–183t, 184–186, Color Plate 6
  reverse transcription-polymerase chain reaction with, 59–60
Immunocompetency, in Borna disease, 195–197
Immunofluorescence assay, indirect, 46–48, 47f, 65–66, 180, 181t–183t, 184–186, Color Plate 6
Imunohistochemistry, 52–53, 60, 92, 94, Color Plates 1 & 2
Immunoprecipitation test, 51, 69–70, 183
Indirect immunofluorescence assay, 46–48, 47f, 65–66, 180, 181t–183t, 184–186, Color Plate 6
Infectivity, of Borna disease virus, 60–62
Interferons, in Borna disease, 140–141
Interleukin(s), in Borna disease, 140–141, 157
L protein, of Borna disease virus, nucleocytoplasmic transport of, 39–40
Limbic system, damage of, in Borna disease, 161–162
Long reverse transcription-polymerase chain reaction, 60
Magnetic resonance imaging, in Borna disease, 206
Major histocompatibility complex, in Borna disease, 134–135
Matrix proteins, of Borna disease virus, 25–26
Monkeys, Borna disease in, 146
Monoamine brain systems, developmental alterations of, in Borna disease, 158–159
Morphology, of Borna disease virus, 25
Natural killer cells, in Borna disease, 138
Neocortex, Borna disease of, 154–155
Neonatal Borna disease, animal models of, 150–155, 152f, 153f, Color Plate 4
  behavioral deficits in, 159–163
  gene expression in, 158
  immune response in, 155–157, Color Plate 5
  methods for, 148–150, 149f
  monoamine system alterations in, 158–159
neurodevelopmental brain damage, 150–155, 152f, 153f, Color Plate 4
synaptic pathology, 155
Neurodevelopmental damage, in Borna disease, see Animal models, for Borna disease, neurodevelopmental damage
Neuron(s), in Borna disease
degeneration of, in horses, 95
virus tropism for, 24–25, 127–128
Neuronophagia, in Borna disease, in horses, 95
Neurotransmission abnormalities, in Borna disease, 143–145
Neurotrophic factors, in Borna disease, 144–145, 158
Neurotropism, of Borna disease virus, 24–25, 127–128, 148–150, 149f
Neutralizing antibodies, to Borna disease virus, 132–133
Norepinephrine, alterations of, in Borna disease, 158–159
Northern hybridization, 57–58
Nucleocytoplasmic transport, of Borna disease virus, 34–40
Nucleoprotein, of Borna disease virus, 25–26
immune response to, 132
nucleocytoplasmic transport of, 35–37
Obesity syndrome, in Borna disease, 145
Oligodendrocytes, Borna disease virus tropism for, 24–25, 127, 149
Open reading frames, of Borna disease virus genome, 25–26, 32
Organic psychiatric disorders, 209–216
in infections and inflammation, 211–213
with known etiology, and multiple manifestations, 211
pathogenesis of, 214–216
perinatal, 214
types of, 209–210
Ostriches, Borna disease in antibodies in, 98t
clinical manifestations of, 89t, 111–112
epidemiology of, 103–104
pathology of, 89t, 111–112
Paresis, general, psychiatric disorders in, 212–213
Pathogenesis and pathology of Borna disease, 27–34, 29f, 127–148
animal models for, see Animal models in animals, 89t, 91–95, 91f, 104–112,
Color Plates 1 & 2
astrocytes, 24–25, 127, 138, 149,
154–157, Color Plate 5
behavioral disease, 141–148, 142f,
159–163
brain damage, 150–155, 152f, 153f,
Color Plate 4
central nervous system, 129, 130f,
Color Plate 3
cerebellar damage, 152–154, 153f
cytokines, 157
cognitive abnormalities, 160–162
chemokines, 157
dissemination, 127–129
emotional disturbances, 160
gender differences in, 166–167
gene expression, 158
hippocampal damage, 143, 151–152,
152f, Color Plate 4
immune response in, see Immune response, to Borna disease virus microgliosis, 156–157, Color Plate 5
molecular mechanisms, 163–164
monoamine brain systems, 158–159
neocortex damage, 154–155
neurodevelopmental, 148–163
peripheral nervous system, 131–132
in rat model, 129–132, 130f, Color Plate 3
sensorimotor deficits, 159–160
social behavior alterations, 162–163
synaptic, 155
time course analysis, 130–131
virus adsorption, 27–28
virus replication, 127–129
of organic psychiatric disorders, 214–216
Perinatal transmission, of Borna disease, 196–197
Peripheral nervous system, Borna disease of, 131–132
Phosphoprotein transcription activator, of Borna disease virus, 25–26
immune response to, 132
nucleocytoplasmic transport of, 37
phosphorylation of, 128
Polymerase chain reaction, reverse-transcription, 58–60, 71–77, 189–195, 192t
Polypeptides, of Borna disease virus genome, 25–26
Ponies, Borna disease virus antibodies in, 101
Propagation, of Borna disease virus, 31
Proteins, of Borna disease virus, 25–26
Western blot assay for, 48–49
Psychiatric disorders, Borna disease virus and
animal models for, 167–168
antibody seroprevalence, 180, 181t–183t, 183–187, 201–206
antigen detection, 187–189, 188t
cerebrospinal fluid studies in, 205–206
diagnostic system validity, 199–201
encephalitis, 206–207
hypothesis concerning, 197–198
imaging studies, 205–206
models for, 195–197
organic brain syndrome concept, 209–216
treatment of, 207–209
virus-specific nucleic acid detection, 191–195, 191t
Purkinje cells, of cerebellum, Borna disease virus in, 153–154
QYNAD peptide, in inflammatory neurologic disorders, 207
Rabbits, Borna disease in, 146
Receptors, for Borna disease virus, 128
Replication, of Borna disease virus, 28, 29f, 30–31
animal models for, 127–129
Retina, Borna disease virus in, in horses, 93
Reverse-transcription PCR, 58–60, 71–77, 189–195, 192t
Reverse-type sandwich enzyme-linked immunosorbent assay, 50–51, 69, 185
Ribonucleoprotein, Borna disease virus spread as, 128
RNA, of Borna disease virus
detection of, 53t, 57–60, 71–77
splicing of, 33–34
Rodents, Borna disease in,
see also Animal models, for Borna disease
antibodies in, 97t
transmission of, 113
Saliva, Borna disease virus in, 150
Schizophrenia, Borna disease virus and antibody seroprevalence, 181t–183t, 184, 203–204
cerebrospinal fluid analysis in, 205–206
hypothesis concerning, 197–198
imaging in, 205
treatment of, 208
virus-specific nucleic acid detection, 189, 189t, 191
Schwann cells, Borna disease virus tropism for, 24–25, 128, 149
Sensorimotor deficits, in Borna disease, 159–160
Serologic tests, for Borna disease, 45–46, 45t, 65–71, 116
psychiatric disorders and, 180, 181t–183t, 183–187, 201–205
Serotonin, alterations of, in Borna disease, 159
Sheep, Borna disease in
antibodies in, 95, 96t, 98t, 99, 101–102
clinical manifestations of, 89t, 90–91
epidemiology of, 88–89
historical aspects, 1, 88
as natural host, 23
pathology of, 89t, 91–95
transmission of, 112
Shrews, Borna disease in, 146–147
Social behavior, in Borna disease, 162–163
Somatostatin, deficiency of, in Borna disease, 143
Spatial discrimination, in Borna disease, 161
Staggering disease, in cats, 107–110
Synaptic pathology, in Borna disease, 155
Syphilis, psychiatric disorders in, 212–213
T lymphocytes, in Borna disease, 92, 133, 135–140
Tears, Borna disease virus in, 150
Transcription, of Borna disease virus genes, 28, 29f, 30–31
Transforming growth factor β2, in Borna disease, 136
Transmission, of Borna disease, 24, 112–113
Tree shrews, Borna disease in, 146–147
Tropism, of Borna disease virus, 24–25, 127–128, 148–150, 149f
Tumor necrosis factor alpha, in Borna disease, 140–141, 157
Urine, Borna disease virus in, 150
Vaccines, Borna disease virus, 115
Virology, of Borna disease virus, 2, 23–43
adsorption into host cell, 27–28
assembly, 31
cell-to-cell propagation, 31
cycle of infection, 27–34, 29f
genome, 25–26, 28, 29f, 30–34, 113–115
host range, 2, 23–24, 87–88, 125–126
morphology, 25
nucleocyttoplasmic transport, 34–40
physical characteristics, 25
proteins encoded by, 25–26
release, 31
replication, 28, 29f, 30–31, 127–129
RNA splicing regulation, 33–34
transcription, 28, 29f, 30–31
tropism, 24–25, 127–128, 148–150, 149f
Western blot assay, 48–49, 53–55, 66–68, 182t, 183–185
X protein, of Borna disease virus, 26, 37–39
Index

Note: Page numbers followed by “f” indicate figures; page numbers followed by “t” indicate tables.

Amantadine, for Borna disease, 207–208
Animal(s), Borna disease in, see also specific animals
clinical manifestations of, 89–91, 89t, 104–112
diagnosis of, see Diagnosis
epidemiology of, 10–11, 87–89, 102–104
future directions in, 115–117
historical aspects of, 3–9
host range of, 2, 23–24, 87–88, 125–126
pathology of, 89t, 91–95, 91f, 104–112,
    Color Plates 1 & 2
species variation in, 113–115
subclinical, 95, 96t–98t, 99–102
transmission of, 112–113
Animal models, for Borna disease, 125–178
behavioral disease, 141–148, 142f
central nervous system pathology,
    129–130, 130f, Color Plate 3
genetic factors in, 164–166
historical aspects of, 6, 11–12
immune response, 132–140
    B lymphocytes in, 134
    cellular, 133
    humoral, 132–133
    major histocompatibility complex in,
        134–135
    molecular mechanisms of, 140–141
    natural killer cells in, 138
    neurodevelopmental damage in,
        155–157, Color Plate 5
    T lymphocytes in, 133, 135–140
molecular mechanisms, 163–164
neurodevelopmental damage, 148–163
    behavioral deficits in, 159–163
    to brain, 150–155, 152f, 153f, Color Plate 4
cognitive abnormalities in, 160–162
emotional disturbances in, 160
gender differences in, 166–167
gene expression in, 158
immunoe response, 155–157,
    Color Plate 5
infection inoculation, 148–150, 149f
monoamine system alterations in,
    158–159
sensorimotor deficits in, 159–160
social behavior alterations in, 162–163
neuropsychiatric aspects of, 167–168
peripheral nervous system pathology,
    131–132
time course analysis, 130–131
virus dissemination and replication,
    127–129
Antibody(ies), Borna disease virus
    in animals, 5
    avidity of, 185–187, Color Plate 6
    in cats, 97t, 98t
    in cattle, 96t, 98t
    in horses, 92–95, 96t, 98t, 99–101, Color Plates 1 & 2
    in humans, 2–3, 180, 181t–183t, 183–187,
        201–206, Color Plate 6

227
index

in immune response, 132–133
in ostriches, 98t
in rodents, 97t
in sheep, 95, 96t, 98t, 99, 101–102
Antigen(s), Borna disease virus
detection of, 52–57, 53t, 187–189, 188t
in horses, 92–93
Antigen capture enzyme-linked
immunosorbent assay, 55
Assembly, of Borna disease virus, 31
Astrocytes, Borna disease virus tropism for,
24–25, 127, 138, 149, 154–157, Color
Plate 5
Autism, Borna disease and, 150
Autonomic nervous system, Borna disease
of, 131–132
Avidity, of antibodies, in Borna disease,
185–187, Color Plate 6
B lymphocytes, in Borna disease, 134
Behavioral disease, in Borna disease, animal
models for, 141–148, 142f, 159–163
Birds, Borna disease in, 103–104, 111–112
Blood, Borna disease virus nucleic acid in,
191–195, 191t
Borna disease
in animals, see Animal(s), specific animals
diagnosis of, see Diagnosis
host range of, 2, 23–24, 87–88, 125–126
in humans, see Human Borna disease
spread of, from central Europe, 4–9, 5f
Borna disease virus
antibodies to, see Antibody(ies), Borna
disease virus
cell-free preparation of, 24–25
classification of, 2
culture of, 9–10, 188, 188t
species variation in, 113–115
virology of, see Virology, of Borna disease
virus
Brain, Borna disease virus in
clinical manifestations of, in animals,
89–91, 89t, 104–112
detection of, 52–57, 53t, 187–189, 188t
antigen capture ELISA for, 55
immunohistochemistry for, 52–53, 60
Western blot test for, 53–55
in humans, see Human Borna disease
infectivity determination in, 60–62
nucleic acid detection in, 189–191, 189t
persistence of, 139
RNA detection of, 71–77
subclinical, in animals, 95, 96t–98t, 99–102
Capture enzyme-linked immunosorbent
assay, 49–50
Cats, Borna disease in
antibodies in, 97t, 98t
clinical manifestations of, 89t, 107–110
epidemiology of, 103
pathology of, 89t, 107, 109–110
species-specific, 114
transmission of, 113
Cattle, Borna disease in
antibodies in, 96t, 98t
clinical manifestations of, 89t, 104–106
epidemiology of, 102
pathology of, 89t, 105
Cell culture, of Borna disease virus, 9–10,
188, 188t
Cellular immune response, to Borna disease
virus, 133
Central nervous system, see Brain
Cerebellum, in Borna disease, 149, 149f,
152–154, 153f
Cerebrospinal fluid, in Borna disease
filtration of, 208–209
virus detection in, 46, 205–206
Chemokines, in Borna disease, 157
Cholecystokinin deficiency, in Borna
disease, 143
Cholinergic system, in Borna disease, 145
Clinical manifestations, of Borna disease
in animals, 89–91, 89t, 91f, 104–112
in humans, 197–206, 209–216
Cognitive dysfunction, in Borna disease,
160–162
Competitive enzyme-linked
immunosorbent assay, 50
Culture, of Borna disease virus, 9–10, 188,
188t
Cytokines, in Borna disease, 135–141, 157
Dentate gyrus, of hippocampus, Borna
disease virus in, 150–152, 152f, Color
Plate 4
Depression, Borna disease virus and
antibody seroprevalence, 181t–183t,
202–203
treatment of, 207–208
Developmental damage, neurologic, in Borna disease, see Animal models, for Borna disease, neurodevelopmental damage

Diagnosis, of Borna disease, 45–84 in animals, 10–11 difficulties in, 62–77

electrochemiluminescence immunoassay, 51–52, 70–71, 183–184, 183t)
enzyme-linked immunosorbent assay, 49–52
immunohistochemistry, 52–53
immunoprecipitation test, 51, 69–70, 183
indirect immunofluorescence assay, 46–48, 47f, 65–66

serology, 45–46, 45t, 65–71, 116
in humans, 180, 181t–183t, 183–187, 201–206, Color Plate 6

virus antigen detection, 52–57, 53t, 187–189, 188t
virus infectivity, 60–62
virus RNA detection, 53t, 57–60, 71–77
Western blot assay, 48–49, 53–55, 66–68, 182t, 183–185

Dogs, Borna disease in clinical manifestations of, 89t, 106–107 epidemiology of, 102–103 pathology of, 89t, 106–107 species-specific, 114

Dopamine, in Borna disease, 143–144, 158–159

Electrochemiluminescence immunoassay, 51–52, 70–71, 183–184, 183t

ELISA, see Enzyme-linked immunosorbent assay

Emotional disturbances, in Borna disease, 160

Encephalitis, Borna disease virus, 206–207

Enzyme immunoassay, reverse transcription-polymerase chain reaction with, 59–60

Enzyme-linked immunosorbent assay, 49–52, 182t–183t, 183–185 antigen capture, 55
capture, 49–50
classical, 49
competitive, 50
problems with, 68–69
reverse-type sandwich, 50–51, 69, 185

Ependymal cells, Borna disease virus tropism for, 24–25, 127, 149

Epidemiology, of Borna disease in animals, 10–11, 87–89, 102–104 spread from central Europe, 4–9, 5f

Experimental infections, see Animal models; Pathogenesis and pathology

Filtration, of cerebrospinal fluid, for Borna disease, 208–209

Fluorescence-activated cell sorting analysis, 56–57, 187–188

Free oxygen radicals, in Borna disease, 140–141

Gender differences, in Borna disease, 166–167

General paresis, in syphilis, psychiatric disorders in, 212–213

Genetic factors, in Borna disease, 164–166

Genome, of Borna disease virus, 25–26, 28, 29f, 30–34
species variation in, 113–115

Glutamic acid decarboxylase deficiency, in Borna disease, 143

Glycoproteins, of Borna disease virus, 26 immune response to, 133
regulation of, 32–33

Hippocampus, pathology of, in Borna disease, 143, 151–152, 152f, Color Plate 4

Historical aspects, of Borna disease, 1–21
discovery, 1, 125
in early 20th century, 3–4, 125–126
in late 20th century, 9–14
spread from central Europe, 4–9, 5f
at start of 21st century, 14–16

Horses, Borna disease in antibodies in, 95, 96t, 98t, 99–101
clinical manifestations of, 89t, 90–91, 91f
epidemiology of, 88–89
historical aspects, 1, 88
as natural host, 23
pathology of, 89t, 91–95, 91f, Color Plates 1 & 2
species-specific, 114–115
transmission of, 112–113

Host range, of Borna disease, 2, 23–24, 87–88, 125–126
Human Borna disease, 179–225
  antigen detection in, 187–189, 188t
  cerebrospinal fluid analysis in, 205–206
  clinical studies of, 195–216
  encephalitis in, 206–207
  epidemiology of, 180, 181t–183t, 183–187
  historical aspects of, 2–3, 5–9, 13–14
  imaging in, 205–206
  nucleic acid detection in, 189–195, 189t, 191t
  perinatal, 196–197
  psychiatric disorders in, 197–206, 209–216
  serologic evidence of, 180, 181t–183t, 183–187, 201–206, Color Plate 6
  transmission of, 113
  treatment of, 207–209
  virus isolation in, 187–189, 188t
Human immunodeficiency virus infection, psychiatric disorders in, 213
Humoral immune response, to Borna disease virus, 132–133
Huntington’s disease, 211
Hydrocephalus, in Borna disease, 129, 130f
Hypothalamus, damage of, in Borna disease, 145
Imaging studies, in Borna disease, 205–206
Immune complexes, in Borna disease, 203
Immune response, to Borna disease virus, 116
  animal models of, 132–140
  B lymphocytes in, 134
  cellular, 133
  humoral, 132–133
  major histocompatibility complex in, 134–135
  molecular mechanisms of, 140–141
  natural killer cells in, 138
  neurodevelopmental damage in, 155–157, Color Plate 5
  T lymphocytes in, 133, 135–140
Immunofluorescence assay, indirect, 46–48, 47f, 65–66, 180, 181t–183t, 184–186, Color Plate 6
Indirect immunofluorescence assay, 46–48, 47f, 65–66, 180, 181t–183t, 184–186, Color Plate 6
Interferons, in Borna disease, 140–141
Interleukin(s), in Borna disease, 140–141, 157
Interferon(s), in Borna disease virus, 60–62
L protein, of Borna disease virus, nucleocytoplasmic transport of, 39–40
Limbic system, damage of, in Borna disease, 161–162
Long reverse transcription-polymerase chain reaction, 60
Magnetic resonance imaging, in Borna disease, 206
Major histocompatibility complex, in Borna disease, 134–135
Matrix proteins, of Borna disease virus, 25–26
Monkeys, Borna disease in, 146
Monoamine brain systems, developmental alterations of, in Borna disease, 158–159
Morphology, of Borna disease virus, 25
Natural killer cells, in Borna disease, 138
Neocortex, Borna disease of, 154–155
Neonatal Borna disease, animal models of, 150–155, 152f, 153f, Color Plate 4
  behavioral deficits in, 159–163
  gene expression in, 158
  immune response in, 155–157, Color Plate 5
  methods for, 148–150, 149f
  monoamine system alterations in, 158–159
neurodevelopmental brain damage, 150–155, 152f, 153f, Color Plate 4
synaptic pathology, 155
Neurodevelopmental damage, in Borna disease, see Animal models, for Borna disease, neurodevelopmental damage
Neuron(s), in Borna disease
degeneration of, in horses, 95
virus tropism for, 24–25, 127–128
Neuronophagia, in Borna disease, in horses, 95
Neurotransmission abnormalities, in Borna disease, 143–145
Neurotrophic factors, in Borna disease, 144–145, 158
Neuropathosis, of Borna disease virus, 24–25, 127–128, 148–150, 149f
Neutralizing antibodies, to Borna disease virus, 132–133
Norepinephrine, alterations of, in Borna disease, 158–159
Northern hybridization, 57–58
Nucleocytoplasmic transport, of Borna disease virus, 34–40
Nucleoprotein, of Borna disease virus, 25–26
immune response to, 132
nucleocytoplasmic transport of, 35–37
Obesity syndrome, in Borna disease, 145
Oligodendrocytes, Borna disease virus tropism for, 24–25, 127, 149
Open reading frames, of Borna disease virus genome, 25–26, 32
Organic psychiatric disorders, 209–216
in infections and inflammation, 211–213
with known etiology, and multiple manifestations, 211
pathogenesis of, 214–216
perinatal, 214
types of, 209–210
Ostriches, Borna disease in antibodies in, 98t
clinical manifestations of, 89t, 111–112
epidemiology of, 103–104
pathology of, 89t, 111–112
Paresis, general, psychiatric disorders in, 212–213
Pathogenesis and pathology of Borna disease, 27–34, 29f, 127–148
animal models for, see Animal models in animals, 89t, 91–95, 91f, 104–112,
Color Plates 1 & 2
astrocytes, 24–25, 127, 138, 149,
154–157, Color Plate 5
behavioral disease, 141–148, 142f,
159–163
brain damage, 150–155, 152f, 153f,
Color Plate 4
central nervous system, 129, 130f,
Color Plate 3
cerebellar damage, 152–154, 153f
cytokines, 157
cognitive abnormalities, 160–162
dissemination, 127–129
emotional disturbances, 160
gender differences in, 166–167
gene expression, 158
immunologic response in, see Immune response, to Borna disease virus
microgliosis, 156–157, Color Plate 5
molecular mechanisms, 163–164
monoamine brain systems, 158–159
neocortex damage, 154–155
neurodevelopmental, 148–163
peripheral nervous system, 131–132
in rat model, 129–132, 130f, Color Plate 3
sensorimotor deficits, 159–160
social behavior alterations, 162–163
synaptic, 155
time course analysis, 130–131
tissue damage, 27–28
virus replication, 127–129
of organic psychiatric disorders, 214–216
Perinatal transmission, of Borna disease, 196–197
Peripheral nervous system, Borna disease of, 131–132
Phosphoprotein transcription activator, of Borna disease virus, 25–26
immune response to, 132
nucleocytoplasmic transport of, 37
phosphorylation of, 128
Polymerase chain reaction, reverse-transcription, 58–60, 71–77, 189–195, 192t
Polypeptides, of Borna disease virus genome, 25–26
Ponies, Borna disease virus antibodies in, 101
Propagation, of Borna disease virus, 31
Proteins, of Borna disease virus, 25–26
Western blot assay for, 48–49
Psychiatric disorders, Borna disease virus and
animal models for, 167–168
antibody seroprevalence, 180, 181t–183t, 183–187, 201–206
antigen detection, 187–189, 188t
cerebrospinal fluid studies in, 205–206
diagnostic system validity, 199–201
encephalitis, 206–207
hypothesis concerning, 197–198
imaging studies, 205–206
models for, 195–197
organic brain syndrome concept, 209–216
treatment of, 207–209
virus-specific nucleic acid detection, 191–195, 191t
Purkinje cells, of cerebellum, Borna disease virus in, 153–154
QYNAD peptide, in inflammatory neurologic disorders, 207
Rabbits, Borna disease in, 146
Receptors, for Borna disease virus, 128
Replication, of Borna disease virus, 28, 29f, 30–31
animal models for, 127–129
Retina, Borna disease virus in, in horses, 93
Reverse-transcription PCR, 58–60, 71–77, 189–195, 192t
Reverse-type sandwich enzyme-linked immunosorbent assay, 50–51, 69, 185
Ribonucleoprotein, Borna disease virus spread as, 128
RNA, of Borna disease virus
detection of, 53t, 57–60, 71–77
splicing of, 33–34
Rodents, Borna disease in, see also Animal models, for Borna disease
antibodies in, 97t
transmission of, 113
Saliva, Borna disease virus in, 150
Schizophrenia, Borna disease virus and
antibody seroprevalence, 181t–183t, 184, 203–204
cerebrospinal fluid analysis in, 205–206
hypothesis concerning, 197–198
imaging in, 205
treatment of, 208
virus-specific nucleic acid detection, 189, 189t, 191
Schwann cells, Borna disease virus tropism for, 24–25, 128, 149
Sensorimotor deficits, in Borna disease, 159–160
Serologic tests, for Borna disease, 45–46, 45t, 65–71, 116
psychiatric disorders and, 180, 181t–183t, 183–187, 201–205
Serotonin, alterations of, in Borna disease, 159
Sheep, Borna disease in
antibodies in, 95, 96t, 98t, 99, 101–102
clinical manifestations of, 89t, 90–91
epidemiology of, 88–89
historical aspects, 1, 88
as natural host, 23
pathology of, 89t, 91–95
transmission of, 112
Shrews, Borna disease in, 146–147
Social behavior, in Borna disease, 162–163
Somatostatin, deficiency of, in Borna disease, 143
Spatial discrimination, in Borna disease, 161
Staggering disease, in cats, 107–110
Synaptic pathology, in Borna disease, 155
Syphilis, psychiatric disorders in, 212–213
T lymphocytes, in Borna disease, 92, 133, 135–140
Tears, Borna disease virus in, 150
Transcription, of Borna disease virus genes, 28, 29f, 30–31
Transforming growth factor β2, in Borna disease, 136
Transmission, of Borna disease, 24, 112–113
Tree shrews, Borna disease in, 146–147
Tropism, of Borna disease virus, 24–25, 127–128, 148–150, 149f
Tumor necrosis factor alpha, in Borna disease, 140–141, 157
Urine, Borna disease virus in, 150
Vaccines, Borna disease virus, 115
Virology, of Borna disease virus, 2, 23–43
  adsorption into host cell, 27–28
  assembly, 31
  cell-to-cell propagation, 31
  cycle of infection, 27–34, 29f
  gene expression regulation, 32–34
  genome, 25–26, 28, 29f, 30–34, 113–115
  host range, 2, 23–24, 87–88, 125–126
  morphology, 25
  nucleocyttoplasmic transport, 34–40
  physical characteristics, 25
  proteins encoded by, 25–26
  release, 31
  replication, 28, 29f, 30–31, 127–129
  RNA splicing regulation, 33–34
  transcription, 28, 29f, 30–31
  transmission, 24
  tropism, 24–25, 127–128, 148–150, 149f
  Western blot assay, 48–49, 53–55, 66–68, 182t, 183–185
  X protein, of Borna disease virus, 26, 37–39