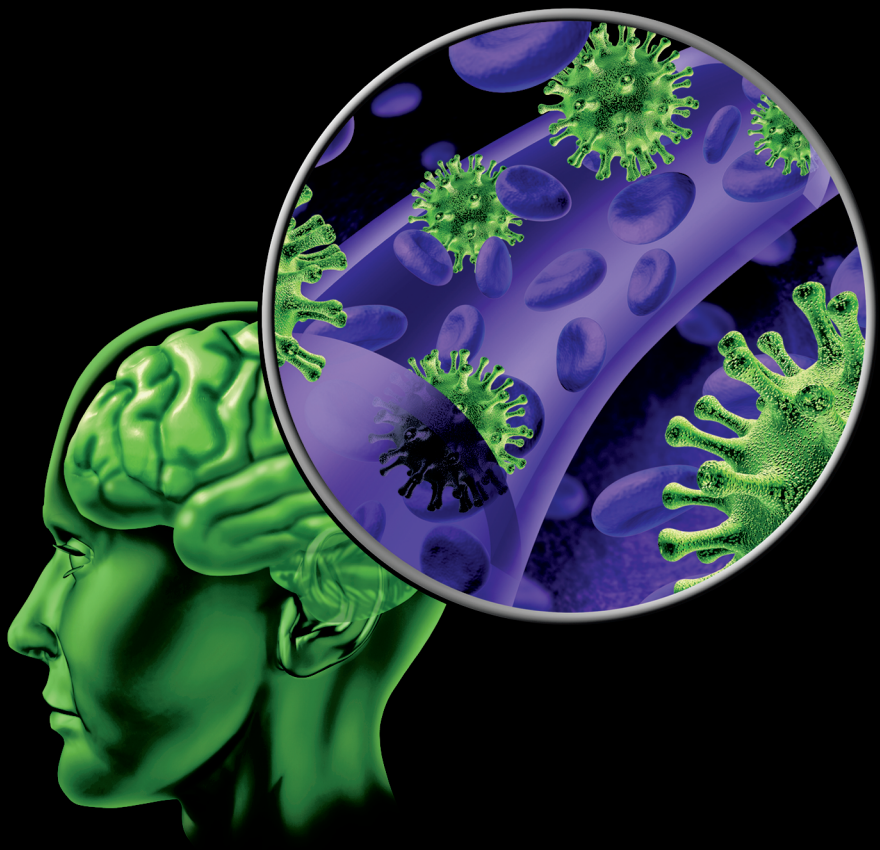

Neuroviral Infections

General Principles and DNA Viruses

Edited by
Sunit K. Singh and Daniel Růžek

CRC Press
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CRC Press
Taylor & Francis Group
Boca Raton London New York

CRC Press is an imprint of the
Taylor & Francis Group, an **informa** business

CRC Press
Taylor & Francis Group
6000 Broken Sound Parkway NW, Suite 300
Boca Raton, FL 33487-2742

Version Date: 20130126

International Standard Book Number-13: 978-1-4665-6722-1 (eBook - PDF)

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Preface

Neurovirology is an interdisciplinary field that represents a melding of virology, clinical neuroscience, molecular biology, and immunology. Apart from clinical neuroscience, neurovirology includes molecular virology, biochemical virology, diagnostic virology, and molecular pathogenesis, and is inextricably bound to the field of immunology. Neurovirology became an established field within the past 30 years. Since then, there has been tremendous explosion of information related to viral infections of the central nervous system, and several new viruses have been discovered as well. The aim of this book is to present an up-to-date overview on major neuroviral infections caused by DNA viruses and general principles of infections to virologists, specialists in infectious diseases, teachers of virology, and postgraduate students of medicine, virology, neurosciences, or immunology. We hope that it will serve as a useful resource for all others interested in the field of viral infections of the central nervous system.

An inclusive and comprehensive book such as this is clearly beyond the capacity of an individual's effort. Therefore, we are fortunate and honored to have a large panel of internationally renowned virologists as chapter contributors, whose detailed knowledge on viral neuroinfections have greatly enriched this book.

We conceptualized this book in two sections, beginning with general introductory chapters and concluding with the specific information pertinent to individual major DNA viruses and their diseases. Section I, "Principles of Viral Infections of the Nervous System," provides basic information on the history of neurovirology, pathogenesis of neuroviral diseases, neuroinflammation, and animal models in neurovirology, and summarizes recent methods of diagnosis of the neuroviral infections and new therapeutic approaches. Section II, "Neurotropic DNA Viruses and Their Diseases," contains chapters on the main neurotropic DNA viruses and virus families. Each chapter consists of a review on the classification, epidemiology, clinical features, and diagnostic and therapeutic approaches of one or a group of related viruses.

The professionalism and dedication of executive editor Barbara Norwitz and senior project coordinator Jill Jurgensen at CRC Press contributed greatly to the final presentation of the book. Our appreciations extend to our families for their understanding and support during the compilation of this book.

Sunit K. Singh
Daniel Růžek

Acknowledgement

This book is dedicated to a magnanimous group of virologists, whose willingness to share their in-depth knowledge and expertise has made this extensive overview on viral neuroinfections possible.

Editors

Dr. Sunit Kumar Singh completed his bachelor's degree program from GB Pant University of Agriculture and Technology, Pantnagar, India, and master's degree program from the CIFE, Mumbai, India. After receiving his master's degree, Dr. Singh joined the Department of Paediatric Rheumatology, Immunology, and Infectious Diseases, Children's Hospital, University of Wuerzburg, Wuerzburg, Germany, as a biologist. Dr. Singh completed his PhD degree from the University of Wuerzburg in the area of molecular infection biology. Dr. Singh has completed his postdoctoral trainings at the Department of Internal Medicine, Yale University, School of Medicine, New Haven, Connecticut, USA, and the Department of Neurology, University of California Davis Medical Center, Sacramento, California, USA, in the areas of vector-borne infectious diseases and neuroinflammation, respectively.

He has also worked as visiting scientist at the Department of Pathology, Albert Einstein College of Medicine, New York, USA, Department of Microbiology, College of Veterinary Medicine, Chonbuk National University, Republic of Korea; and the Department of Arbovirology, Institute of Parasitology, Ceske Budejovice, Czech Republic. Presently, he is serving as a scientist and leading a research group in the area of neurovirology and inflammation biology at the prestigious Centre for Cellular and Molecular Biology, Hyderabad, India. His main areas of research interest are Neurovirology and Immunology.

There are several awards to his credit, including the Skinner Memorial Award, Travel Grant Award, NIH-Fogarty Fellowship, and Young Scientist Award. Dr. Singh is associated with several international journals of repute as associate editor and editorial board member.

Dr. Daniel Růžek is a research scientist at the Institute of Parasitology, Academy of Sciences of the Czech Republic, and an assistant professor at the Department of Medical Biology, Faculty of Science, University of South Bohemia. He received his PhD in the field of molecular and cellular biology and genetics from the Academy of Sciences of the Czech Republic and the University of South Bohemia. He had postdoctoral training at the Department of Virology and Immunology, Texas Biomedical Research Institute (formerly Southwest Foundation for Biomedical Research), San Antonio, Texas, USA. His primary field is virology with research emphasis on vector-borne viruses, especially tick-borne encephalitis virus, Omsk hemorrhagic fever virus, dengue virus, West Nile virus, and so forth. In 2009, he was awarded with a prestigious international Sinnecker–Kunz Award for young researchers.

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Section I

Principles of Viral Infections of the Nervous System

1 Neuroviral Infections
A Historical Perspective

Georg Gosztonyi and Manfred Sell

Diseases of the nervous system that we regard now as those of viral origin have been known and described already in antiquity and in the middle ages. A Babylonian description from 2000 BC mentioned the simultaneous occurrence of headache and fever. This might be the earliest known report of meningitis or encephalitis (Johnson 1982b). There are also scattered references on the occurrence of poliomyelitis, yellow fever, and shingles in the forthcoming centuries, but the most precise accounts on a nervous system disease were those concerning rabies. In Egypt, rabid animals were regarded with superstitious fear. Thus, the Egyptian god of the dead, Anubis, was represented by the figure of a man with the head of the jackal. Although the contagious nature of rabies was indicated by Aristotle in the fourth century BC, describing that the bite of a rabid dog would transmit the disease to animals of all other species, there was little progress in exploring the nature of the disease until the beginning of the nineteenth century. Studies on experimental transmission of rabies by inoculating mad dog's saliva to healthy dogs, cats, and rabbits started at that time. Subsequently, the rabbit became the preferred experimental animal model for pathogenesis-related studies (Wilkinson 1988). Louis Pasteur adopted the rabbit for studies of his group, and as a result of their efforts, they proved conclusively the long suspected neurotropic character of the causative agent of rabies. Furthermore, by a series of passages of the street virus, they achieved its attenuation and established the "fixed virus," with well-defined incubation time. With this virus, Pasteur started in 1884 the postexposure vaccination, the first effective antirabies treatment of human patients (Pasteur et al. 1884). These results gave impetus to understand the mechanism of pathogenesis of rabies. Although Pasteur was the supporter of the hematogenic spread of the agent in the organism (Pasteur et al. 1884), this view was replaced very soon by the concept of neural spread. Cantani, a professor of internal medicine in Naples, was the first who proved the neural spread of rabies in 1888. He established that the transection of the limb nerves after peripheral inoculation prevented the evolution of the disease (Cantani 1888). One year later, two of his pupils, Di Vestea and Zagari (1889), published a more elaborate study on this subject in the *Annales de l'Institut Pasteur*; the recognition of the neural spread of rabies is attributed in the literature to these authors. On the basis of histological studies, Schaffer (1890) in Budapest provided evidence for the neural spread of rabies in humans: the most severe changes developed in spinal cord segments corresponding to the site of the animal bite. These studies clearly ascertained that the agent of rabies has such an elementary affinity to neural structures that it spreads exclusively along

these pathways to the central nervous system (CNS). Shortly after the publication of these results, the concept of the virus, as an infectious agent, was born. Iwanowski reported in 1892 that a plant pathogen, tobacco mosaic virus, is a filterable microorganism. The filterable nature of the rabies agent was verified by Remlinger (1903).

The relation of rabies and of other infectious diseases to the nervous system was further documented by early histopathological studies around the turn of the nineteenth/twentieth centuries. Adventitial and perivascular lymphomonocytic infiltrates, diffuse tissue infiltrations by microglial cells, glial stars, and neuronophagic nodules were the hallmarks of the inflammatory character of these diseases. It became clear that for viral infections, nonpyogenic (i.e., lymphomonocytic) inflammation was distinctive. In a few of the encephalitides, the appearance of cytoplasmic and nuclear inclusion bodies was interpreted as indicators of the viral nature of the infectious process. Typical instances are the cytoplasmic Negri inclusions in rabies (Negri 1903) and the nuclear inclusions in the Borna disease of horses (Figure 1.1) (Joest and Degen 1909). A further feature of viral encephalitides is the virus-induced cytopathic effect of neurons in the form of swelling, tigrolysis/chromatolysis, or pyknosis. The nature of the histopathologic signs, however, apart from the inclusion bodies in a few types of encephalitides, was not characteristic for individual infectious processes. The actually peculiar feature for the individual disease types was the *topical distribution* of the described histopathological changes.

The study of the distribution pattern of the lesions led Constantin Levaditi (1874–1953) to the first formulation of the specific affinity of viruses to well-defined neural structures. Levaditi was a prominent microbiologist of Romanian origin, a pupil of Elie Metchnikoff, who spent most of his career at the Pasteur Institute in Paris and became its "Chef de service" in 1926. He denoted the diseases with this specific affinity *ectodermoses neurotropes* on the basis of the observation that their agents have a variably expressed, dual affinity to ectodermal structures, that is, to the epidermis

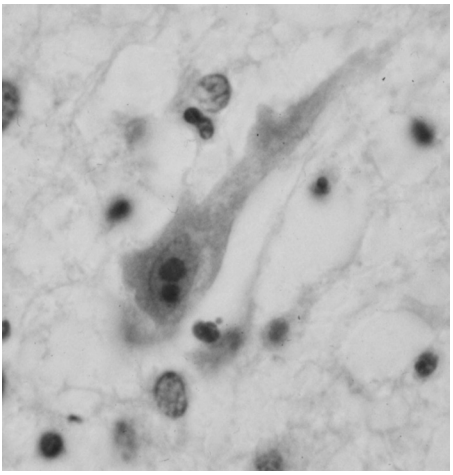

FIGURE 1.1 Joest–Degen nuclear inclusion body in a neuron. Borna encephalitis of the horse. Immunohistochemical labeling with an α-Borna polyclonal antibody.

and cornea, on the one hand, and to the invaginated part of the ectoderm, the brain, and the spinal cord, on the other (Levaditi 1921, 1922). Levaditi set up a scale of neurotropic agents as follows: vaccinia, herpes virus, agent of the epidemic encephalitis (von Economo), furthermore, of rabies and poliomyelitis (Heine-Medin). While the epidermal and corneal affinities prevailed over that of the brain with the first two agents, in epidemic encephalitis, there seemed to be an equal affinity to both epidermal germinal layers. Finally, in rabies and poliomyelitis, the epidermal and corneal affinities were suppressed compared to the affinity to the brain and spinal cord. A few years later, Levaditi complemented his scale with diseases exhibiting ectodermal affinities, discovered or better studied in the meantime: vesicular stomatitis; Japanese, American, and equine encephalomyelitides; and Borna disease (Levaditi and Voet 1935; Levaditi 1938).

The quality and the distribution of the histopathological changes in the viral encephalitides have been the basis for the study of neurotropism for decades. At the same time, nevertheless, these features have also been the basis for the classification of all the inflammatory processes of the nervous system. At the end of the 1920s, Heinrich Pette (1887–1964) devoted much attention to these phenomena. Pette was a neurologist and a neuropathologist, as well as an outstanding researcher of inflammatory diseases of the nervous system. From 1934 on, he was professor and director of the University Clinic for Neurology in Hamburg-Eppendorf. In 1948, he founded an Institute for the Study of Poliomyelitis and Multiple Sclerosis at the University of Hamburg. After his death, his research institute adopted his name (Bauer 1998).

In 1929, Pette established his concept of classification of the inflammatory diseases of the nervous system (Pette 1929). He recognized that these diseases can be divided into two groups: (1) acute inflammatory diseases predominantly of the gray matter and (2) acute inflammatory diseases predominantly of the white matter. The first group incorporated three neurotropic diseases, which Levaditi also included into his *ectodermoses neurotropes*: poliomyelitis, rabies, and epidemic encephalitis. Qualitatively, the histological picture of these diseases was very similar, consisting of adventitial/perivascular lymphomonocytic infiltrates, glial nodules, neuronal degeneration, and neuronophagias. There are, however, essential differences in the distribution of the lesions. Poliomyelitis predominates in the anterior horns of spinal cord segments, rabies predominates in the brain stem and spinal cord, and epidemic encephalitis predominates in the periaqueductal gray matter, substantia nigra, and the wall of the third ventricle. The histology of the second group was qualitatively quite different: perivenular or more extensive demyelinating foci with moderate inflammation and intense, mainly focal microglial proliferation. The diseases belonging to this second group were recognized in the 1920s; they were acute inflammatory CNS diseases presenting some time after vaccination (most frequently after vaccinia against smallpox) and after exanthematous diseases (measles, chickenpox, rubella). The same histological picture was described also in an acute, sometimes relapsing CNS disease: acute disseminated encephalomyelitis. Pette clearly characterized the distinctive features of both groups: in the first one, the neurons were damaged primarily, the myelin remained intact, and the brunt of the changes was in the gray matter; in the second, myelin was destroyed and the pathological changes were restricted mainly to the white matter. He also gave indications as to the

etiology: poliomyelitis, rabies, and epidemic encephalitis were clearly primary viral diseases; behind the demyelinating group, he suspected constitutional and immunological factors as uniform etiological agents, despite the fact that these diseases were precipitated by contact with different types of viruses. A few years later, Rivers et al. (1933) and Rivers and Schwentker (1935) reported that by injection of brain extracts to monkeys, a demyelinating disease can be induced, *experimental allergic encephalitis*. In his comprehensive monograph on encephalitides, Pette (1942) also applied the adjective *allergic* to characterize the human demyelinating diseases. In this way, these diseases, owing to their specific features and unique etiology, have been unequivocally separated from the primary viral encephalitides.

In 1930, Hugo Spatz, in his comprehensive chapter on the morphology of encephalitides in the *Handbuch der Geisteskrankheiten* (Handbook of Mental Diseases), adopted the classification proposed by Pette, separating the acute inflammatory diseases affecting predominantly the gray matter, viz., the white matter of the CNS. Spatz, however, applied the much shorter term *polioencephalitis* to the first group (Spatz 1930, 1931). This term was already widely used to characterize a group of nonpurulent encephalitides at the end of the nineteenth century (Vogt 1912); it was, however, applied mainly to denote "pseudoencephalitides," as, for example, the polioencephalitis hemorrhagica superior Wernicke. For the second group, that of inflammatory diseases affecting predominantly the white matter, the term *leukoencephalitis* has been adopted. The restriction of the inflammatory process to the gray matter in the polioencephalitis group was explained by the presumption that viruses are present mainly in the cell bodies of neurons, as they have an affinity for the nerve cells themselves: *gangliocytotropism* or *neurocytotropism* (Környey 1933, 1943). Spatz (1930, 1931) particularly emphasized the similarities between members of the polioencephalitis group, that is, poliomyelitis, rabies, and epidemic encephalitis; their affinities for various levels of the spinal cord and brain stem; and the discontinuous, patchy distribution of the inflammatory lesions. Epidemic encephalitis (lethargic encephalitis, von Economo encephalitis) deserves special attention. This infectious disease emerged in 1916 in Vienna and spread to the remainder of Europe and to North America in the form of smaller or greater epidemics, with mortality rates up to 50%. This epidemic partially coincided with the great "Spanish" influenza pandemic of 1918–1919 but was distinct from that and lasted longer, up to 1930, when it gradually declined. Histopathologically, this polioencephalitis was characterized by perivascular lymphomonocytic infiltrates, with most severe expression in the mesencephalon and in the wall of the third ventricle. The substantia nigra was particularly severely damaged (Economo 1931). The leading clinical symptoms were fever, somnolence, lethargy, oculomotor palsies, and myoclonic jerks. In part of the cases, months or years after complete clinical recovery, progressive Parkinsonian symptoms developed. In these patients, complete loss of pigmentation of the substantia nigra could be established on pathological examination. Although this encephalitis bears the typical clinical and pathological features of a viral infection, the isolation of a viral agent remained unsuccessful, even in the very rare, sporadic cases or small groups of cases occurring after the great epidemic (Dale et al. 2004; Lopez-Alberola et al. 2009). Thus, the etiology of this disease remains enigmatic.

Spatz (1930, 1931) also included the Borna disease of horses in the group of polioencephalitides and, with Seifried, performed a comprehensive comparative study of the polioencephalomyelitides (Seifried and Spatz 1930). In this study, special emphasis was placed on analogous features of epidemic encephalitis and Borna disease of horses. The extensive involvement of the mesencephalon, in particular, was most impressive. The authors suggested that the agents of these two diseases might be closely related. This assumption, however, could not be proven. The agent of the Borna disease has been characterized as an enveloped, nonsegmented, single-stranded, negative RNA virus (Briese et al. 1994; Cubitt et al. 1994), and it was recognized that persistent infections by this virus occur also in humans, most frequently in mental patients (Bode et al. 1995). Since, however, the agent of epidemic encephalitis has not been identified, the close relationship of these two encephalitides could not be ascertained.

No clear relations could be assessed between other members of the polioencephalitis group either; their agents belong to quite different taxonomic groups. Apparently, there are other factors that determine the specific affinity of viruses to definite neuronal formations. In the 1930s, it was generally accepted that this affinity can be quite strict. Pette (1938, 1942) characterized this feature with the term *special neurotropism* (spezielle Neurotropie) in contrast to *general neurotropism* (allgemeine Neurotropie), an overall affinity of viruses to neural tissue.

In the meantime, *experimental studies* on viral encephalitides made great progress. The distribution patterns of inflammatory lesions in various neurotropic virus infections and in various phases of these infections were monitored by histopathological techniques. It was realized that the distribution patterns in the early phases of infection depended greatly on the *portal of entry* of the virus into the nervous system (Sabin and Olitsky 1938). Környey (1939) drew attention to the importance of the *time factor* in the formation of the distribution pattern in the course of the evolution of the encephalitic process: the localization of the histological changes in the fully developed phase of the disease becomes independent of the portal of entry, and progressively, the neurotropic features of the agent become decisive. In certain types of encephalitides, however, the portal of entry remains the decisive factor throughout the entire course. Herpes simplex virus may cause two characteristic types of encephalitides in humans. The more frequent manifestation is an acute, necrotizing inflammatory process in the frontobasal and temporal regions bilaterally, but with a unilateral preponderance. It was assumed that this unilateral distribution pattern is the consequence of penetration of the virus through the olfactory nerves and its intracerebral spread along neuronal chains of the limbic system (Johnson and Mims 1968). The less frequent form manifests itself as a brain stem encephalitis, which might be the consequence of a centripetal spread of activated herpesvirus from the latently infected trigeminal ganglion. According to another view, however, fronto- and temporobasal infection results from the spread of herpesvirus from the Gasserian ganglia along the trigeminal nerve fibers innervating the meninges of the anterior and middle cranial fossae (Davis and Johnson 1979).

Around the middle of the last century, novel histological techniques emerged that complemented conventional methods and opened new horizons in the study of the phenomenon of neurotropism. Electron microscopy and immunohistochemistry

offered new data on viral infections of the nervous system, fundamentally altering and extending our views about neurotropism. *Electron microscopy* allowed the visualization of virus particles, the various phases of their assembly, their localization in various compartments of the host cell, and, most importantly, the determination of the cell type that harbors the virus (Figure 1.2). The assessment of this cytotropism within the CNS has led to a better understanding of both the distribution patterns and the pathogenesis of various virus infections (Gosztonyi and Cervós-Navarro 1988). Classic examples are subacute sclerosing panencephalitis (SSPE) and progressive multifocal leukoencephalopathy (PML). In SSPE, electron microscopy disclosed the lack of production of complete measles virus particles within the CNS and the presence of paramyxovirus nucleocapsids in the nuclei and cytoplasm of neurons and in the nuclei of oligodendroglial cells (Bouteille et al. 1965). This double cellular tropism of the agent, also shown by immunocytochemistry (Figure 1.3), explains why SSPE is a panencephalitis and why widespread demyelination is present in the white matter. In PML, ZuRhein and Chou (1965) discovered crystalline arrays of papovavirus particles in characteristically altered nuclei of oligodendrocytes. This finding documented that myelin breakdown can also ensue as a direct consequence of the cytopathic effect of a primary virus infection, not only as a sequel of an autoimmune process, as in the postvaccinial/parainfectious encephalomyelitides and in acute disseminated encephalomyelitis. Furthermore, papovavirus particles have occasionally been found also in astrocytes (Mazlo and Herndon 1977; Mazlo and Tariska 1982).

In conventional electron microscopic technique the volumes of tissue samples are small. Therefore, in experimental neuroanatomy and neuropathology the introduction of perfusion fixation of the CNS with osmium tetroxide (Palay et al. 1962), later, with glutaraldehyde and paraformaldehyde, meant a great step forward. A further

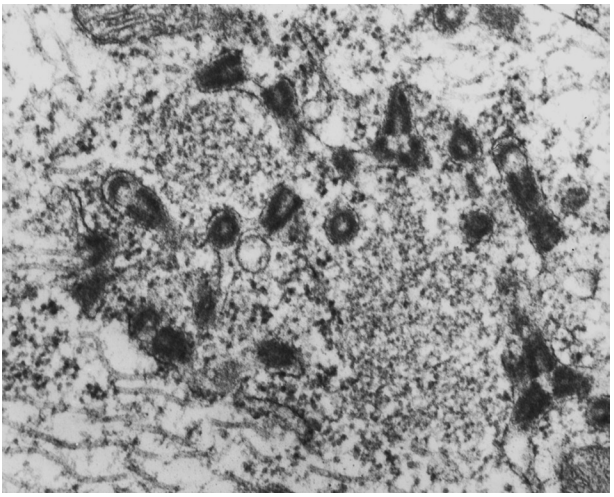

FIGURE 1.2 Electron microscopic picture of rabies virus replication in the mouse brain. Experimental rabies encephalitis.

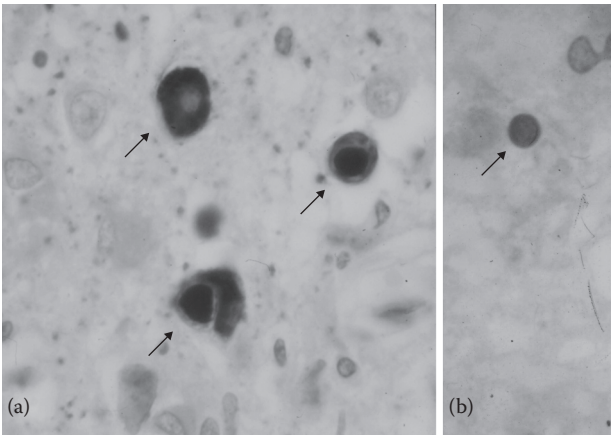

FIGURE 1.3 **(See color insert.)** Subacute sclerosing panencephalitis. Immunohistochemical labeling with an α-measles polyclonal antibody. (a) Labeled nuclear and cytoplasmic inclusion bodies in neurons (arrows). (b) Labeled oligodendroglial nucleus (arrow).

development of this technique was the embedding of entire brain or head slices of mice and rats in synthetic resin, cutting the whole surface area into thin sections by "hot knife microtomy," selection of appropriate regions by light microcopy and excision of the selected small regions from a subsequent 200–300 μm thick tissue slice, and processing them to ultramicrotomy (McGee-Russell et al. 1990).

The introduction of *immunohistochemistry* exerted an even stronger impact on the study of neuroviral infections, since it allowed the survey of large brain areas for the assessment of the extension and distribution of virus infections (Figure 1.3). These studies not only have revealed the presence and distribution of virus-specific antigens but also could precisely define the cell types that harbored the viruses by the use of cell-type-specific markers and double immunocytochemical labeling techniques (Gosztonyi and Cervós-Navarro 1988). When the distribution patterns of virus antigens were compared with cytopathic changes and inflammatory infiltrations indicating virus-induced effects, as shown on conventionally stained preparations, it could be ascertained that the viral antigens were more widely distributed than the morphological alterations. Neurons with cytopathic changes almost always harbored viral antigens, but many neurons that were light microscopically normal in appearance were also positive for viral antigens, at least in the actual phase of virus spread within the CNS. This means that viruses may exert tropism toward a great number of neurons, and in some of them, the presence of virus does not grossly interfere with the functions of the cell, but in others, the virus is *cytopathogenic* and its replication results in the disintegration of the host neuron. Consequently, immunocytochemistry has enabled us to differentiate between *neurotropism*, the affinity of a virus to a definite cell type, and *selective vulnerability*, the virus-induced selective destruction of the host cell. A good example of this virus–host cell interrelationship can be found in the hippocampal formation of rats persistently infected with Borna disease virus (BDV). Both dentate gyrus and the CA3 subfield of the hippocampal

pyramidal cell layer are infected with BDV and both express the p24 viral protein, but the granule neurons of the dentate gyrus undergo a severe selective degeneration, while the CA3 pyramidal neurons remain morphologically intact (Gosztonyi and Ludwig 1995).

The adjective *selective* is the standard expression in the Anglo-American literature to characterize this phenomenon (Johnson 1980, 1982a, 1982b). In the French and German literature, the adjective *elective* is being used ("vulnerabilité élective," viz., "elektive Vulnerabilität").

The architecture of the CNS is characterized by a great diversity of its constituents. That diverse neuronal systems react in a quite differentiated way to various noxae was first formulated as *pathoclisis* (Pathoklise) by C. and O. Vogt (Vogt and Vogt 1922), who defined it as a structural or constitutional propensity of certain neuronal populations to react with disease to specific pathogenetic factors. While pathoclisis predominantly referred to the "endogenous" systemic atrophies, it was also used for lesions evoked by hypoxic, vascular, viral, and other exogenic factors (Pette 1938). Later on, the term *selective vulnerability* progressively replaced the concept of pathoclisis. The neurobiological basis of selective vulnerability has been poorly elucidated. It may be that host factors regulating viral synthetic processes are expressed in different ways in various neuronal populations. On the other hand, viral products may interfere with cell functions that are specific for definite cell types.

As to cell tropism, immunohistochemistry has enriched our knowledge even more than electron microscopy. Thus, it could be documented that in rabies, viral antigens are almost exclusively harbored by neurons (Gosztonyi et al. 1993). By contrast, in Borna disease, viral antigens were found not only in neurons but also in astrocytes, oligodendrocytes, ependymal, and plexus epithelial cells, in both naturally and experimentally infected animals (Gosztonyi et al. 1993; Ludwig et al. 1985, 1988). Accordingly, in Borna disease, both gray and white matters are involved; thus, Borna disease is rather a panencephalitis, in contradiction to Spatz (1930), Seifried and Spatz (1930), and others. Rabies, however, remains a classical polioencephalitis.

The phenomenon of viral tropism to certain types of cells and tissues is determined by specific *cell surface receptors.* These receptors are normal constituents of the cytomembrane, which play key roles in normal cell physiology, but they may also be used by viruses for their attachment to and entry into the cell, thus having decisive roles for tissue tropism and virus host range. For the binding of a virus to a cell receptor, certain structures on the virus surface—the envelope glycoproteins in enveloped viruses, the nucleocapsid proteins in nonenveloped viruses, and the *viral attachment* proteins—have an equally important role. Definite cell surface receptors may allow attachment for several types of viruses, and, on the other hand, definite types of viruses may be attached to several types of receptors.

As to neuroviral infections, the importance of surface receptors was first emphasized by Holland and McLaren for polioviruses (Holland 1961; Holland and McLaren 1961). For the concept of neurotropism, it was an important step forward when Lentz et al. (1982) published their observation that nicotinic acetylcholine receptors at the neuromuscular junction may serve as portals of entry for rabies virus, a strict neurotropic agent. Binding the rabies virus to the chick neuromuscular junction could be prevented by α-bungarotoxin and D-tubocurarine. Soon thereafter, on the basis

of tissue culture studies, doubt was cast on the acetylcholine receptor hypothesis (Reagan and Wunner 1985). Despite these doubts, this hypothesis has been widely accepted, since it offers a plausible explanation for the affinity of rabies virus to motor nerve endings and striated muscle and for the very wide host range of the agent.

In the early 1980s, the acetylcholine hypothesis gave rise to the idea that if an infectious agent has a very strict affinity for the nervous system, its cellular receptor must be sought among surface structures that are highly specific for and occur almost exclusively in neural tissue. On the basis of the assessments of Lentz et al. (1982) and of findings that another RNA agent, BDV, apparently has an affinity for receptors of the excitatory amino acids, while GABAergic systems seem to be exempt from this infection, it has been postulated that viral neurotropism may be explained by the affinity of the infectious agents for *neurotransmitter receptors* (Gosztonyi and Ludwig 1984).

Subsequent years have brought a significant increase in our knowledge concerning virus receptors in the nervous system, as reviewed by Schweighardt and Atwood (2001). The acetylcholine hypothesis offered sufficient explanation for the uptake of rabies virus in the periphery, that is, in neuromuscular junctions and in muscle tissue, but it did not elucidate its spread along neuronal chains and its widespread distribution in the CNS. Therefore, further cell membrane specializations have been proposed as putative rabies virus receptors: neural cell adhesion molecule (NCAM, CD56) (Thoulouze et al. 1998), the low-affinity neurotrophin receptor p75(NTR) (Jackson and Park 1999), NMDAR1 (NR1), and possibly GABA receptors (Gosztonyi and Ludwig 2001). However, explaining how all these putative rabies virus receptors are also expressed in glial cells, while rabies virus presence is restricted to nerve cells (i.e., it is strictly *neuronotropic*), is still an open question. The affinity of BDV for excitatory amino acid receptors, in particular, for the kainate 1 (KA-1) receptor has been reinforced (Gosztonyi et al. 1993; Gosztonyi and Ludwig 1995, 2001). Reovirus type 3 was found to exhibit affinity to the β-adrenergic receptor (Lin et al. 1988), and the agent of PML uses serotonin receptors to infect glial cells (Elphick et al. 2004). The affinity of viruses to neurotransmitter receptors, however, seems to characterize only those agents that establish, shortly after penetration into the body, contact with neural structures. Other viruses, which replicate after penetration first in extraneural sites, utilize receptors that occur both in extraneural and neural tissues.

The most prominent example of viral system electivity is the genuine affinity of poliomyelitis virus to the voluntary motor system. Poliovirus induces lytic inflammatory destruction of spinal ventral horn motoneurons (Figure 1.4), brain stem motoneurons, and, to a lesser degree, the motoneurons of the motor cortex. For the explanation of this selective involvement of the motoneurons, no neurotransmitter system that would have an exclusive expression in these types of neurons is known. A further peculiarity of poliomyelitis is that it occurs only in the order of higher primates, that is, in humans and apes. The poliovirus receptor was defined in 1989; it proved to be a membrane protein, a new member of the immunoglobulin receptor superfamily (Mendelsohn et al. 1989). This receptor, however, occurs not only in the voluntary motor system but also in many other areas of the nervous system, and even in extraneural organs and tissues (Mendelsohn et al. 1989). The elucidation of

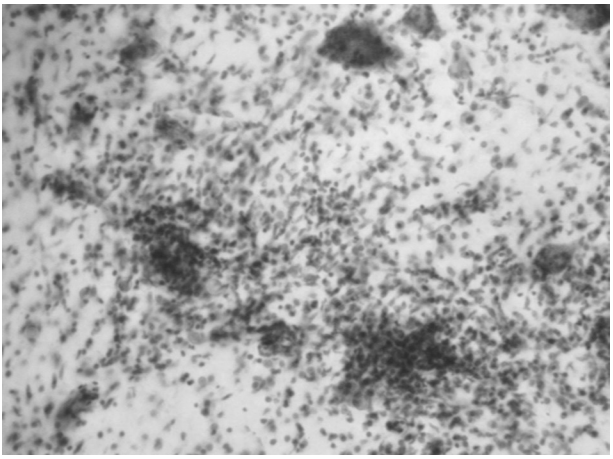

FIGURE 1.4 Poliomyelitis. Ventral horn of the spinal cord. Destruction of two motoneurons in neuronophagic nodules. Nissl stain.

this question was promoted by the generation of transgenic mice carrying the human poliovirus receptor (Ren et al. 1990). While normal mice are resistant to poliovirus infection, a virulent infection can be produced with typical histological signs of poliomyelitis in transgenic mice. Subsequently, the strict species selectivity and neuronal system selectivity could be elucidated. The poliovirus contains an internal ribosomal entry site (IRES), which initiates translation and is indispensable for protein synthesis (Wimmer and Nomoto 1993). However, IRES is only efficient in case of an adequate interaction with host cell-specific factors. This "IRES-dependent virus tropism" is the basis for explaining the strict affinity of poliovirus to the voluntary motor system (Ohka and Nomoto 2001).

This example shows that although receptors play an important role in virus tropism, they are, with some exceptions, not the sole determinants. In the early 1980s, it was already suspected that the possession of the appropriate receptor is no guarantee that a cell can be infected (Dimmock 1982; Marsh and Helenius 1989). Additional factors or receptor modifications are needed to permit virus attachment. In the 1990s, an intensive search was carried out to identify these additional factors. For some viruses, secondary receptors or coreceptors are needed for adhesion and entry (Callebaut et al. 1993; Weiss and Tailor 1995). It has become clear that virus attachment and penetration represent a very complex, multistep process and not a simple ligand/receptor relationship.

The phenomenon of virus attachment was perhaps most thoroughly studied in infections by the human retrovirus HIV-1 (Schweighardt and Atwood 2001). The direct involvement of the CNS by HIV-1 manifests itself as a peculiar type of encephalitis, in which the primary targets of this virus are not neural elements but macrophages/microglial cells of mesodermal origin. The major cell type that is infected by HIV is the $CD4^+$ T helper cell. Their virus-induced lytic decay leads to severe immunosuppression, the principal feature of AIDS. Besides T4 helper cells, monocytes/

macrophages also harbor and replicate HIV, but they do not undergo lysis, thus fulfilling the role of a virus reservoir. The specific receptor for HIV is the CD4 antigen on the surface of lymphocytes and monocytes/macrophages. For the entry of HIV into the host cell, however, not infrequently two chemokines, CCR5 and CXCR4, as coreceptors, are necessary (Berger et al. 1999). The HIV infection of the CNS ensues by the transgression of the blood–brain barrier by HIV-carrying monocytes/macrophages ("Trojan horse" mechanism), which, subsequently, proliferate and spread the infection. A couple of macrophages fuse and form multinucleated giant cells. The perivascular accumulation of HIV-positive macrophages and multinucleated giant cells are the typical hallmarks of HIV encephalitis (Figure 1.5). These infiltrates occur predominantly in the white matter of the brain. HIV encephalitis developed only in 30%–40% of AIDS patients. Characteristically, its occurrence is more frequent in the risk group of intravenous drug users, in contrast to male homosexuals (Bell et al. 1998). This differential distribution is most probably due to the enhancing effect of opiates on HIV replication. Although neurons are not productively infected by HIV, there is a significant reduction in the density of cortical neurons, which is the substrate of the development of cognitive impairment in neuro-AIDS (Ketzler et al. 1990; Wiley et al. 1991). This defect is most probably the result of a neurotoxic injury by secreted retroviral proteins, gp120, gp41, and Tat (Gosztonyi and Ludwig 2001; Nath and Geiger 1998).

Until the 1950s, almost all viral encephalitides were regarded as acute events, terminating either fatally or with more or less complete recovery. In 1954, however, Bjorn Sigurdsson, a veterinarian at the Institute of Experimental Pathology in Iceland, described several sheep diseases with protracted incubation periods and progressive clinical courses terminating in death. These diseases, with the most characteristic representant, scrapie, proved to be transmissible later. Sigurdsson (1954) conceived the term *slow infection* to characterize these diseases. In a few years, Gajdusek and Zigas (1957) described a human disease, endemic in Papua New Guinea, called kuru, with similar course as the sheep disease scrapie. Both diseases

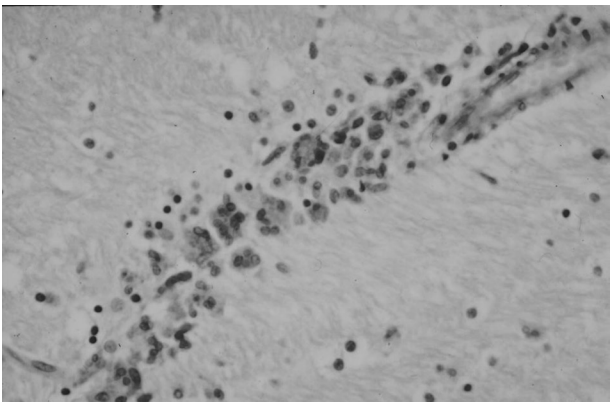

FIGURE 1.5 **(See color insert.)** HIV encephalitis. Perivascular accumulation of macrophages and multinucleated giant cells in the cerebral white matter. H&E stain.

were characterized histologically by noninflammatory loss of neurons and a spongiform change in gray matter areas.

Following these recognitions, increasing interest was directed to this protracted type of viral pathogen–host relationship, for which the name *persistent infection* was proposed. Traditionally, this relationship encompasses three overlapping subtypes: *latent, chronic*, and *slow infections* (Boldogh et al. 1996; Liebert 2001).

Latent infection is characterized by the continued presence of virus in a host in which no infectious virus can be detected, but which is capable of reactivation to produce infectious virus (Wildy et al. 1982). Herpes simplex viruses, HSV-1 and HSV-2, are very widespread human pathogens, the agents of orofacial and genital herpes, giving the most frequent examples of latent infection with frequent recurrences. The sites of latency are the trigeminal and sacral sensory ganglia (Borchers and Field 2001). Most infrequently, HSV-1 causes severe necrotizing encephalitis in the cerebral hemispheres and sometimes in the brain stem. Varicella–zoster virus also establishes classical latency in sensory ganglia. After childhood varicella, the viruses remain latent in the ganglia, and in adulthood, recurrences occur, causing vesicular, herpetiform skin eruptions in dermatomal distribution. Epstein–Barr virus and cytomegalovirus are further examples of human herpesvirus latency. Besides the human herpesviruses, there are many veterinary pathogens in the herpesvirinae subfamily: B virus in primates, equine and bovine herpesviruses, pseudorabies virus in the pig, and several feline and canine herpesviruses.

All these agents also establish classical latency in neural tissue (reviewed by Borchers and Field 2001).

Chronic infections, the second subgroup of persistent infections, are characterized by the continued presence of the virus in the host after the primary infection and may present in the form of chronic or recurrent disease. PML is a demyelinating disease presenting in immunosuppressed conditions, after organ transplantation and also in AIDS. ZuRhein and Chou (1965) discovered that in this disease, in the demyelinating foci, the nuclei of enlarged oligodendrocytes contain masses of papovavirus-like particles. This was the first observation that a virus infection of oligodendrocytes may result in a progressive demyelinating disease. SSPE is another example of a chronic progressive CNS disorder, which develops months or years after acute measles. The tropism of measles virus to CNS cells is determined by the ubiquitously occurring complement receptor CD46. The neurotropic SSPE agent is a mutated measles virus with a defective virus gene expression. Because of this, only nucleocapsids are assembled in neurons and glial cells, but the formation of envelope proteins is defective; thus, virus budding, the formation of full viruses, is missing (ter Meulen et al. 1983; Liebert 1997). AIDS is also characterized by a long latency period, followed by a chronic progressive course. Involvement of the CNS by HIV ensues in ca. 30%–40% of the cases, as discussed above.

After the discovery of scrapie and kuru in the 1950s, it has been recognized that several further human and animal diseases share their features.

In humans, besides kuru, Creutzfeldt–Jakob disease, Gerstmann–Sträussler–Scheinker disease, and fatal familial insomnia were the most important representants; in animals, these were scrapie, bovine spongiform encephalopathy, and mink encephalopathy. Long latency period and a protracted, slowly progressive course

were the common clinical features. Histopathologically, lack of inflammatory infiltrations, vacuolization, spongiform change (Figure 1.6), strong reactive astrocytosis, and proliferation of macrophages were the hallmarks. In view of the common clinical and pathological features, these diseases were ranged as *slow infections*, as the third subtype, to the persistent infections. With regard to the pathological peculiarities, these diseases also became known as the nosological group of spongiform encephalopathies. Because of the absence of inflammatory infiltrations, some of these diseases were regarded initially as neurodegenerative disorders. Subsequently, however, it was discovered that the diseases of all the members of this group were transmissible by brain tissue to other species, as well as to healthy members of the same species. Therefore, the name *transmissible spongiform encephalopathy* was coined for this group. A further surprising feature of the human diseases was that a certain percentage of these were dominantly inherited. Thus, the enigma of how a disease could be both infectious and genetic at the same time was presented. The search for the nature of the agent transmitting the disease revealed that it contained neither DNA nor RNA. Furthermore, its behavior to chemical agents was not conforming either to the nature of a virus. It was the merit of Stanley Prusiner to postulate that the scrapie agent is of a proteinaceous nature (Prusiner 1982). He proposed the new term *prion* to denote the small infectious particle, which is resistant to inactivation by most procedures that modify nucleic acids. Subsequent studies have clarified that the pathogens of the other diseases in the group of spongiform encephalopathies have a nature identical with that of scrapie. Consequently, for the designation of this nosological entity, the name *prion diseases* was conceived.

The prion protein (PrP) is a physiological component of the cell membrane, expressed constitutively and in particularly high levels in neurons. It is encoded by the PRNP gene on the short arm of chromosome 20 in humans and has a normal cellular turnover. Mutations of this gene result in the production of pathological isoforms of the PrP that are not metabolized normally. A change in the conformation of this protein results in pathological alterations in the neuronal metabolism. A

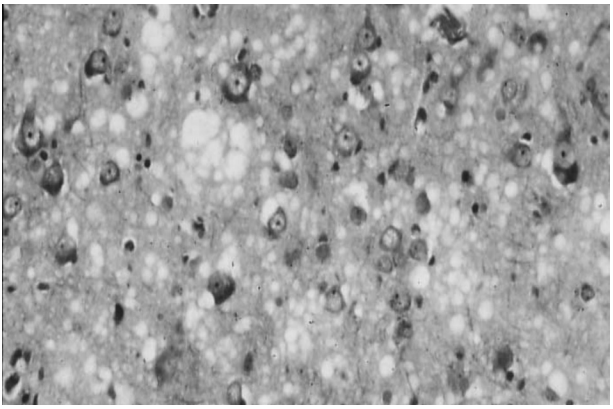

FIGURE 1.6 **(See color insert.)** Creutzfeldt–Jakob disease. Spongiform change in the cerebral cortex. Luxol stain.

PrP with pathological conformation may induce normal cellular PrPs to take over a similar one. Mutations of the PRNP gene and structural peculiarities in various PrPs explain that certain types of prion diseases may have an infectious, that is, transmissible, sporadic, or genetically transmitted nature (Dearmond and Prusiner 1997). For the discovery of the transmissible character of spongiform encephalopathies, Carleton Gajdusek received the Nobel Prize in Physiology or Medicine in 1976, and for the discovery of the PrP, Stanley Prusiner received the Nobel Prize in Physiology or Medicine in 1997.

The clinical, virological, epidemiological, and neuropathological research of viral infections of the nervous system has greatly contributed to the therapy and prophylaxis of these diseases. The second half of the past century excelled particularly in the introduction and performance of vaccinations against poliomyelitis, measles/SSPE, rabies, and Japanese encephalitis. That these neuroviral infections have been only partially eradicated worldwide has no scientific reasons, only organizational and financial ones. The production of antiviral pharmaceutics has significantly improved the therapeutic perspectives particularly of herpesvirus and HIV infections. Neuroviral research, however, has to fulfill many other tasks, including increasing the awareness to newly emerging viral pathogens, mutations, and new recombinations of already known agents.

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2 Neuroviral Infections and Immunity

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CONTENTS

2.1 INTRODUCTION

Viral infection of the brain frequently results in development of severe disease including meningitis or encephalitis. Once disease has developed, there are few therapeutic interventions available for most viral infections. Subsequently, recovery from neuroviral infections is largely dependent upon supportive medical care and the host immune response. However, this response can come at a cost, including long-term