Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Handbook of Clinical Neurology, Vol. 123 (3rd series)
Neurovirology
A.C. Tselis and J. Booss, Editors

Chapter 30

Neurologic aspects of influenza viruses

LARRY E. DAVIS[1]*, FREDRICK KOSTER[2], AND ANDREW CAWTHON[3]

[1]*Neurology Service, New Mexico VA Health Care System and Department of Neurology, University of New Mexico School of Medicine, Albuquerque, NM, USA*

[2]*Lovelace Respiratory Research Institute, Albuquerque, NM, USA*

[3]*American Type Culture Collection, Manassas, VA, USA*

INTRODUCTION

This chapter focuses mainly on the neurologic complications associated with human infections with influenza. Where applicable, experimental animal and *in vivo* studies are presented. A brief review of molecular aspects of influenza viruses and how they replicate in respiratory and non-respiratory tissues is followed by a review of the major neurologic syndromes associated with influenza. The syndromes are presented in a historic fashion as the types of neurologic complications have varied in the 20th and 21st centuries.

INFLUENZA VIRUS

Influenza viruses are members of the Orthomyxoviridae family, and are so named from the Greek *orthos*, meaning "straight" and *myxa*, meaning "mucus." The Orthomyoviridae family is composed of five genera: *Influenzavirus A, Influenzavirus B, Influenzavirus C, Thogotovirus*, and *Isavirus* (Fields et al., 2007). The genome of these viruses consists of 7–8 segments of negative-sense single-stranded RNA contained within enveloped virus particles (virions) that are either spherical or filamentous in morphology (Levinson, 2006). The influenza viruses within this genera are categorized as A, B, or C, and differ in host range and severity of disease. Influenza types B and C primarily infect humans; however the severity of illness is relatively mild compared to influenza A viruses. Because influenza B and C remain predominantly within the human population, and neither exchanges genetic material between other influenza types, nor recombines genome segments naturally with viruses from other host species, influenza types B and C do not cause pandemics. In contrast, influenza A viruses infect a wide variety of mammals (including humans, horses, pigs, ferrets, cats, and dogs) as well as avian species. The ability of influenza A viruses to infect such a wide variety of host species that frequently come into close contact with one another permits the occurrence of co-infections with multiple influenza A viruses in permissive hosts that can serve as "mixing vessels." These scenarios can result in the creation of genetic reassortant viruses that express novel antigenic properties, which can cause periodic epidemics in immunologically naïve populations. In some cases these epidemics can spread rapidly and widely enough to be classified as a pandemic. The recent 2009 H1N1 pandemic illustrates the emergence of a highly infectious reassortant strain which resulted when a previous triple reassortment of bird, pig, and human flu viruses further combined with a Eurasian pig flu virus (Trifonov et al., 2009) and rapidly spread across multiple continents.

Influenza A viruses are further divided into subtypes based on the antigenic nature of two important spike glycoproteins found in the host-derived lipid membrane which forms the virus envelope. The hemagglutinin (HA) and neuraminidase (NA) glycoproteins project from the lipid envelope, along with the M2 protein. Influenza A virus subtypes are identified by the serotype of HA and NA expressed on the surface of the virion. There are 16 influenza virus HA types and nine NA subtypes (Fouchier et al., 2005). The HA molecule is involved in the attachment of the virus by binding neuraminic acids (also known as sialic acids) on the surface of host cells. The tropism of influenza A viruses that replicate in different species is at least partially explained by the preferential binding of certain HA molecules with

*Correspondence to: Larry E. Davis, New Mexico VA Health Care System, Neurology Service, 1501 San Pedro Dr. SE, Albuquerque, NM 87108, USA. Tel: +1-505-256-2752, Fax: +1-505-256-5720, E-mail: ledavis@unm.edu

sialic acids with specific linkages found in the penultimate galactose sugar of the sialic acid found on the cell surface. HA from human viruses selectively binds sialic acid residues with an α2,6 linkage, while HA molecules from avian viruses selectively bind sialic acid residues with an α2,3 linkage (Connor et al., 1994). Human tracheal epithelial cells contain a much higher ratio of α2,6-linked sialic acid residues, while the epithelium lining the gut of ducks contains mostly α2,3-linked sialic acid residues (Couceiro et al., 1993; Ito et al., 1998).

The HA glycoprotein exists as a precursor molecule (HA0) that relies on cleavage by cellular proteases in order to become biologically active (HA1 and HA2). Upon binding, influenza virus is internalized via receptor-mediated endocytosis, and the resultant acidification of the endosome induces a conformational change in the HA molecule that triggers fusion of the viral and endosomal membranes, releasing the contents of the virion into the cytoplasm (Klenk et al., 1975; Lazarowitz and Choppin, 1975). This proteolytic activation of HA is essential for viral infectivity and dissemination, and is critical for virus pathogenicity (Webster and Rott, 1987). In many influenza viruses and low pathogenic avian influenza viruses (LPAIV), the cleavage site in the HA0 molecule contains a single basic reside that is cleaved by trypsin-like enzymes found in the respiratory tract and limited organs, resulting in mild or asymptomatic infection. One of the virulence factors distinguishing highly pathogenic avian influenza viruses (HPAIV) from LPAIV is the presence of multiple basic amino acids present at the cleavage site, which allows for cleavage of the HA0 molecule by ubiquitous intracellular proteases. The increased cleavability of the HA molecules of HPAIV in multiple tissue types results in systemic infection in avian species (Stieneke-Grober et al., 1992; Horimoto et al., 1994). These studies suggest that the ability to cleave HA is a determinant of the tissue tropism for avian influenza viruses and the differences in tissue tropism can determine the severity of disease outcome. It has been suggested that the HA molecule may play a role in neurovirulence in mammals (Mori et al., 2002), supported by studies in which a multibasic cleavage site has been cloned into low pathogenic viruses, and increasing virulence (Munster et al., 2010). The acquisition of natural forms of more cleavable HA may occur through polymerase slippage, mutations, reassortant events with coinfections, or nonhomologous recombination events.

Given the role of the HA molecule in the attachment of virus to host cells and potential for increased virulence, the blockade of this interaction by host-derived neutralizing antibodies is considered the gold standard by which influenza vaccine efficacy is currently evaluated.

The NA glycoprotein serves to cleave sialic acid from the cell surface. This function is critical in the release of budding viruses from infected cells, as the HA contained in the lipid membrane of budding viruses is effectively anchored by cell surface sialic acid. The NA molecule cleaves the sialic acid, releasing the virus particle and allowing for virus spread. Studies involving inhibitors of NA or temperature-sensitive NA mutants have demonstrated an accumulation of aggregated virus particles on the infected cell surfaces, which are unable to be fully released (Palese et al., 1974a, b; Palese and Compans, 1976).

INFLUENZA VIRAL REPLICATION

Influenza virus is transmitted primarily by inhalation and by direct contact inoculating the nasal mucosa, infecting epithelial cells throughout the respiratory tract. Tropism for the upper respiratory tract of human seasonal influenza viruses (subtypes H1, H2, and H3) is determined by their preference for the 2,6-galactose-linked sialic acid receptor on ciliated cells. Tropism for the lower respiratory tract among avian strains (H5 and H7 subtypes) stems from preference for binding to the 2,3-gal receptor, particularly on mucin-secreting cells, and explains in part the more common primary viral pneumonia among avian influenza infections (Mastrosovich et al., 2006). Both types of receptor are distributed throughout the respiratory airways, however, and the swine-origin H1N1 pandemic strains are also complicated by primary viral pneumonia more often than seasonal H1N1 viruses. Seasonal, avian, and pandemic strains exhibit different replication efficiencies in airway epithelial cells, explaining in part the different virulence and transmission phenotypes (Mitchell et al., 2011). In uncomplicated influenza infection of nasal and upper-airway epithelial cells results in secretion of virus, cytokine and chemokine secretion, influx of neutrophils, and desquamation of apoptotic cells into the airways (Taubenberger and Morens, 2008). Symptoms are due to both the cytolytic viral infection and the cytokine response, suggested by the coincidence on day 2 of peak viral secretion, peak symptoms, and peak interleukin-6 (IL-6) and interferon-alpha (IFN-α) secretion in volunteers (Hayden et al., 1998). Death is usually due to severe pulmonary infection as acute respiratory distress syndrome or primary viral pneumonia. In primary influenza pneumonia the virus replicates preferentially in ciliated airway epithelial cells, alveolar macrophages, and type I pneumocytes, although replication can occur in type II pneumocytes and non-ciliated epithelial cells (Kuiken and Taubenberger, 2008).

While seasonal strains replicate almost exclusively in the respiratory tract, swine-origin pandemic strains

replicate in some extrapulmonary tissues; avian strain distribution is discussed below. How the virus reaches extrapulmonary tissues is not clear. Viremia has been documented by culture in some studies but a review concludes that viremia is rare and occurs in a narrow window of time (Likos et al., 2007). The sialic acid-decorated glycolipids and glycoproteins that serve as receptors for the HA protein are ubiquitous on the surface of most mammalian cells, providing opportunity for infection, but positive demonstration of infection is rare (Kuiken and Taubenberger, 2008). Because positive culture could arise from blood contamination, *in situ* hybridization and immunohistochemical demonstration of viral antigen in tissue cells are required to prove viral replication and such demonstrations in brain and heart are limited (Kuiken and Taubenberger, 2008).

GENERAL PRINCIPLES OF THE IMMUNE RESPONSE TO INFLUENZA VIRUS

Recovery from primary influenza infection resides in the innate immune response and the development of an adaptive antibody response, particularly in the IgM fraction (Peiris et al., 2009). Although timely diagnosis is usually made by virologic assays, retrospective diagnosis is reliable by serum hemagglutination inhibition antibody specific to the infecting strain appearing 5–10 days after infection. Recovery from a repeated infection with the same or cross-reacting subtype of influenza virus is vested primarily in the CD8+ T-cell memory response. Influenza-specific T cells accumulate in infected lung foci in animal models. The presence of viral antigen directly stimulates the expansion of the influenza-specific T- and B-cell populations, and clearance of the antigen is associated with the disappearance of activated T and B cells in tissue and blood.

PATHOGENESIS OF INFLUENZA INFECTIONS

Since viruses have coevolved with their hosts, influenza virus stimulates a complex array of innate immune responses in the infected cell and the virus counteracts these responses with multiple virulence factors, primarily the viral NS1 protein, targeting specific pathways in the innate response (Hale et al., 2010). Pathogenicity, defined as tissue injury and illness, originates from two interrelated features of the infection, the viral replication itself inducing epithelial cell death through the apoptosis program (Ludwig, 2006) and the subsequent host response with cytokine-driven mucosal and systemic inflammation. For example, the recently described viral protein PB1-F2 is proapoptotic, and the NS1 protein has been shown to have both proapoptotic and antiapoptotic activities. NS1 proteins from different strains antagonize type 1 IFN-α/β with different levels of efficiency, yet type 1 IFNs are also primary inducers of apoptosis. Thus the final consequence of these complex, often opposing, activities in regulating viral replication remains controversial.

Animal models provide some insights into the pathogenesis of influenza (Belser et al., 2009). Epizootic strains infect swine, horses, dogs, cats, domestic poultry, and water birds, but only the avians often exhibit neurovirulent behavior. However, the mouse, ferret, guinea pig, and non-human primate have provided the most insight into pathogenesis. Animal models demonstrate that pulmonary inflammation is a direct consequence of infection of bronchial and bronchiolar epithelial cells, alveolar pneumocytes, and alveolar macrophages. Breakdown of the alveolar barrier function of the pneumocytes leads to alveolar flooding, influx of neutrophils and histiocytes, and plugging of small airways with desquamated cells. Nitric oxide and oxygen radicals play a significant role in pulmonary injury in a murine model of H2N2 infection (Akaike et al., 1996).

In contrast, the contribution of viral replication in brain tissues remains unclear. Mouse microglia and astrocytes can be infected *in vitro* by both H1N1 and H5N1 subtypes and secrete proinflammatory proteins IL-1β, IL-6, and tumor necrosis factor-alpha (TNF-α), with greater induction by H5N1 infection (Wang et al., 2008a). However, a porcine H1N1 virus adapted to a lethal strain for mice did not replicate in any neural or other extrapulmonary tissues (Garigliany et al., 2010). In the murine model of the neurovirulent WSN strain (evolved from the pandemic 1918 strain), it was not clear whether the encephalitis was a result of direct virus-induced apoptosis or was mediated by immunologic or inflammatory responses (Mori et al., 2003). In this model selected brainstem neurons are targeted after injection of virus into the olfactory bulb, and local defense is mediated by activated glial cells and apoptosis of infected neurons (Mori and Kimura, 2001). In the ferret model, the brain is invaded from the olfactory sensory cells in the nasal turbinates through the cribiform plate to the olfactory bulbs and thence to the basal ganglia (Shinya et al., 2011).

Whether cytokines are antiviral, perpetrators of cellular injury, or merely correlates of disease severity is unclear. The cytokines IFN-β and TNF-α have both antiviral and proinflammatory activity. Dysregulation of inflammation induced by the virus is associated with a lethal outcome but depends on the animal model. For example, in mice a lethal HPAI H5N1 strain was more pathogenic, including brain invasion, than the pandemic 1918 strain, and multiorgan dissemination correlated with early and sustained induction of inflammatory genes with active inhibition of the lipoxin-mediated

anti-inflammatory response. In contrast, in the non-human primate, the 1918 strain was more pathogenic with early upregulation of cell death genes, inflammasome genes and IL-1β, whereas the H5N1 strain downregulated these genes. It must be kept in mind that viral replication rate with direct cytolytic injury also determine the clinical outcome and immunopathology in murine H5N1 infection (Hatta et al., 2010). Thus, the role of multiple determinants of pathogenesis remains complex, but the relationship between proinflammatory, cerebral metabolism, and regional brain function may offer future insights into encephalopathy (Semmler et al., 2008).

Pathogenesis of human influenza-associated encephalopathy is hampered of course by the lack of tissue studied during the acute infection, but numerous studies are beginning to suggest the role of systemic inflammation. Seasonal influenza-associated neurologic complications in humans are generally categorized into diagnostic groups, and may represent overlapping pathogenesis and disease severity. These groups include febrile seizures, encephalopathy, encephalitis, Reye's-like syndrome, acute disseminated encephalomyelitis, and acute necrotizing encephalitis (ANE). Details of these types of complications in humans appear later.

In summary, there is a clear hierarchy of influenza A subtypes in the continuum of pathogenesis severity in the lung and likely the brain as well, ordered as follows: seasonal H1N1 < seasonal H3N2 < pandemic 2009 H1N1 < sporadic H5N1 ≤ pandemic 1918. In head-to-head comparison studies, this hierarchy has been demonstrated for viral replication in human and ferret epithelial cells (Mitchell et al., 2011), in disease severity in mice (Kash et al., 2004; Garigliany et al., 2010), in ferret influenza pneumonia (van den Brand et al., 2010), and in lung pathology in animal models and human cases (Guarner and Falcon-Escobedo, 2009).

NEUROLOGIC SYNDROMES ASSOCIATED WITH STANDARD HUMAN INFLUENZA A AND B VIRUS

1918 influenza H1N1 pandemic

The influenza pandemic of 1918–1919 dramatically changed how the world thought about influenza. The previous major pandemic occurred in 1889–1890 and introduced the first important epidemiologic studies through the work of Otto Leichtenstern (1905). Viruses were unknown. The beginnings of virology started in the 1890 s with the study of tobacco mosaic virus. Lessons learned from the 1889 pandemic were that it was communicable and never rose spontaneously. The disease was respiratory and had an explosive onset, with pneumonia as the most serious complication. Most cases occurred in winter and spring months. Deaths in 1889 were uncommon and mainly in the elderly. The influenza pandemic could spread around the world but did not travel faster than humans could travel.

Twenty-eight years later an outbreak of influenza arose in the spring in Spain. However, there is now evidence that the original viral strain likely occurred in another country and spread early to Spain (Taubenberger, 2006). The first wave was relatively benign but a second wave occurring in the fall and winter was much more virulent and rapidly spread around the world, causing many deaths. The third wave occurred in early 1919 and was variable in severity. It is estimated that about one-third of the world's population of 500 million was clinically infected during the pandemic (Burnet and Clark, 1942). The worldwide total number of deaths was estimated to be 40 million (Patterson and Pyle, 1991). In the United States, there were approximately 675 000 deaths (United States Department of Commerce, 1976) (Fig. 30.1). The estimated mortality rate was at least 2.5%, compared with less than 0.1% reported in subsequent influenza epidemics (Marks and Beatty, 1976).

The majority of individuals who died were previously healthy young adults between the ages of 15 and 44 years (Linder and Grove, 1943). In this age group, the influenza death rate was 20 times higher than seen in other influenza epidemics (Simonsen et al., 1998) and not seen in the 1889–1890 pandemic (Erkoreka, 2009). The explanation for the high death rate in these healthy adults remains unexplained. It should be noted that, when deaths are calculated on an age-specific death rate per 100 000, infants less than 1 year and those over 75 years also had elevated mortality rates.

Fig. 30.1. Military personnel hospitalized in makeshift hospital during an outbreak of influenza A 1918 at Camp Funston, Kansas. (Courtesy of Armed Forces Institute of Pathology library.)

The 1918 pandemic occurred before influenza virus was recognized. It was not until 1930 when the first human and swine influenza viruses were isolated (Shope and Lewis, 1931) and Smith et al. reported the isolation of human influenza in viruses in ferrets in 1933. However, using modern polymerase chain reaction (PCR) techniques, Taubenberger and others have now sequenced the entire virus using frozen and formalin-fixed lung tissue of patients who died during the pandemic (Taubenberger et al., 2005; Taubenberger, 2006). The virus sequencing and analyses of antibody titers of 1918 influenza survivors (Philip and Lackman, 1962; Dowdle, 1999) demonstrated that the virus was a novel H1N1 virus. Reassortment involving genes encoding surface proteins (HA and NA) appeared critical for the production of a pandemic virus allowing the new virus strain to spread and replicate efficiently in humans (Taubenberger, 2006). Current evidence suggests that the prior circulating influenza virus had an H3 subtype (Dowdle, 1999) and that likely both the NA and HA viral proteins were new. However, neither the 1918 HA nor the 1918 NA genes have obvious genetic features that can be directly related to virulence (Taubenberger, 2006). Recent interest has focused on the novel non-structural protein NS1. The NS1 protein is effective in blocking type 1 IFN and may have allowed the 1918 influenza to replicate rapidly and spread quickly throughout the upper and lower respiratory tract (Talon et al., 2000; Wang et al., 2000).

The majority of deaths were pulmonary and many patients succumbed to secondary bacterial pneumonia since antibiotics were not available in 1918 (LeCount, 1919; Wolbach, 1919; Winternitz et al., 1920). However, others died within a few days of the onset of respiratory symptoms from either massive pulmonary edema or acute pulmonary hemorrhage (LeCount, 1919; Wolbach, 1919). At death, there was remarkably little other organ pathology, including the brain (Taubenberger and Morens, 2008).

Although the deaths have been mainly attributed to respiratory causes, this pandemic has been associated with a number of unique neurologic illnesses that are discussed below.

Encephalitis lethargica

Encephalitis lethargica (EL), von Economo's encephalitis, epidemic encephalitis, or brainstem encephalitis is covered in detail in Chapter 36. The etiology of EL is unknown but it has a controversial association with the 1918 influenza pandemic. It is clear that an epidemic of what is now usually termed brainstem encephalitis did develop mainly from 1918 through about 1924. Sporadic cases of brainstem encephalitis were reported by von Economo in a Viennese clinic in 1917 and 1918 (von Economo, 1917, 1931). Similar cases were soon reported around the world with the peaks during 1919 and 1920.

Many of the reported cases had signs and symptoms typical of brainstem encephalitis. Prodromal signs and symptoms often included lethargy, insomnia, sleep reversal, headache, vomiting, vertigo, dry mouth, hiccups, dysuria, tremors, and diplopia and lasted 3–21 days. A mild to moderate fever was common. Some patients never progressed. In general, two forms of EL were subsequently described. Until about 1920, a somnolent-ophthalmoplegic form was the most common. Patients developed progressive somnolence until they became stuporous or comatose (von Economo, 1917). The face was characteristically impassive and mask-like. The somnolence lasted 1–2 weeks and gradually diminished or progressed to coma (Reid et al., 2001). Patients when somnolent were noted to have ocular abnormalities that ranged from ophthalmoplegia to ptosis, diplopia, and pupillary irregularities. Facial palsy, hemiparesis, and cerebellar ataxia could develop. The death rate was higher in the somnolent-ophthalmoplegic form and ranged up to 50%, but severe neurologic sequelae were uncommon in survivors.

In the years from 1920 to 1924, a hyperkinetic form was recognized with restlessness, tics, myoclonus, chorea, disturbances of intraocular muscles, and frenetic psychiatric disturbances (Reid et al., 2001). This form had a more rapid onset and often was accompanied by limb weakness, insomnia, and sleep reversal. The hyperkinetic form could also progress to the somnolent form. Other clinical pictures of what was called EL were reported. The mortality rate of the hyperkinetic form was up to 40% but neurologic sequelae were more common than in the somnolent form (Reid et al., 2001).

In the first years of EL, most of the cases were reported in the winter months (November to March) (Darrach et al., 1929). In later years more cases were reported in summer months. The majority of patients were from 10 to 40 years and the gender ratio was about equal.

Lumbar punctures were occasionally performed during the acute phase. Opening pressure, when recorded, was elevated (von Economo, 1917). A mild lymphocytic pleocytosis was not infrequent, with cells seldom exceeding 30/mm^3. There was often a slight increase in total protein but the glucose level was normal. In rare cases the cerebrospinal fluid (CSF) was highly suggestive of bacterial meningitis.

Calhoun (1920) in Iowa reported a 37-year-old man who in January 1919 developed influenza with secondary pneumonia and recovered. In March he developed the somnolent form of EL and died 2 weeks later. His brain

showed brainstem encephalitis and vascular congestion. Anderson and others (2009) reviewed 112 brain autopsies of EL. They found the median age to be 29 years, with the majority occurring between 10 and 40 years. The median duration of the illness was 10 days but the majority were less than 5 days. The neuropathology usually demonstrated inflammation in the brainstem ranging from the midbrain to the medulla. There was lymphocytic perivascular cuffing, foci of parenchymal lymphocytes, foci of glial nodules, and vascular congestion. The third-nerve nucleus showed focal pathology in half the patients along with midbrain pathology but the substantia nigra had lesions in only 12%. In the cerebral cortex, vascular congestion, cerebral edema, glial cell proliferation, foci of inflammation, and focal hemorrhages were often seen. Thirty-six percent of patients exhibited pathology in the basal ganglia characterized by infiltration of mononuclear cells and congestion. The meninges had vascular congestion but seldom white-cell infiltration. Thus, most patients who died demonstrated evidence of inflammation in the brainstem and occasionally in the cortex plus vascular congestion with evidence of increased intracranial pressure.

There continues to be considerable controversy regarding the role the 1918 influenza virus played in causing EL. The underlying problems include the lack of a clear, clean definition of EL. The term encephalitis was poorly defined in that era and the many arboviruses and other viruses that are now recognized to cause encephalitis were not known. In addition, many physicians during this period were untrained in neurologic diseases and how to perform a careful neurologic exam. As such, many of the clinical descriptions of EL are vague. This wide variation in clinical features suggests that several different etiologies of illnesses were lumped together as EL.

In spite of these problems, there is evidence both clinically and neuropathologically that a unique form of brainstem encephalitis did develop and peaked during the 1918 influenza pandemic and slowly disappeared by the end of the 1920s. What is less clear is when it first appeared and disappeared and how many cases actually occurred. Sporadic reports of "encephalitis" appear as early as 1915 and continue well into the late 1920s but without obvious clustering.

von Economo is credited with the first comprehensive description based on cases he saw in 1916 in Vienna (von Economo, 1917). However, many countries, including the United Kingdom and the United States, were describing similar cases in the fall of 1918 and in 1919. Reports from New York City noted the cases paralleled the 1918 influenza pandemic. The most careful study came from a review of cases reported in Seattle, Washington, and in Samoa (Ravenholt and Foege, 1982). The authors identified 142 EL deaths as well as deaths related to influenza/pneumonia during 1918 through 1926. There was an association with the 1918 influenza but the EL cases clustered about 12 months after each of three waves. The hospital death records of the EL cases did not mention whether the individuals had experienced infection from the 1918 influenza months earlier. The authors also reviewed death records from both Western Samoa and American Samoa. In Western Samoa, the 1918 influenza hit the island in November 1918 and cases of EL appeared over the next few years and disappeared. However, American Samoa had a quarantine and developed no cases of influenza or EL. Finally, the authors presented reported cases of EL from Sweden and Switzerland that clearly demonstrated high peaks of EL that correspond to late 1919 or 1920 and followed shortly after their peaks of influenza.

All reports of EL note that the disease is not transmissible to others, consistent with EL being a consequence of another illness such as influenza or an infection that required a vector. Attempts to pass EL brains into many experimental animals failed and pathologic studies failed to identify any obvious bacteria, parasites, or specific types of inclusion bodies. The peak number of cases almost always occurred in the winter and not in the summer, when arboviruses could be a cause. The peak age distribution of 864 cases of EL was 10–50 years in previously healthy adults and matches closely the attack rate of the 1918 strain of influenza (Marmot, 1980).

There are many arguments against the association of EL with the 1918 influenza virus. EL-like illness has not been associated with other human strains of influenza virus. Experimental with strains of human influenza virus, pathology identical to EL has not been seen in experimental animals. However, some of the highly pathogenic avian influenza strains demonstrate somewhat similar brain pathology in animals (see end of chapter). The unusually long delay of 6 months or more for the appearance of EL after the 1918 influenza hit a city is difficult to explain. Many reports of acute EL patients did not report that the patients previously experienced influenza. However, the lack of a clear association of EL with a prior influenza infection may be due to the fact that patients rarely sought medical attention for influenza and may not have suffered a severe case of influenza. Nevertheless, there is considerable evidence that EL never developed in patients during their acute influenza infection. Finally, McCall and others (2001) failed to detect influenza RNA in archival brain tissues from acute EL.

In summary, clusters of EL appeared around the world about the same time as the 1918 influenza pandemic and disappeared as the 1918 virus pandemic waned and disappeared. Subsequently, only rare cases

of brainstem encephalitis have developed and most have been proven due to non-influenza viruses. It is unlikely that EL occurred as a direct complication in a patient with the 1918 influenza. However, a postinfectious influenza complication has not been ruled out. If EL was not due to the 1918 influenza virus, then the etiology must have been an agent closely associated with the 1918 influenza as it spread around the world beginning and disappearing about the same time.

Postencephalitic parkinsonism (PEP)

A large cluster of young adults developed parkinsonism from 1918 into the 1930s that were associated with previously having EL. It was recognized that these postencephalitic patients had many features of typical Parkinson's disease but differed in several aspects. First, they were much younger at the age of onset. In a series by Duvoisin and Yahr (1965) from New York City, the mean age of onset of 31 patients who had a reliable history of EL was 29 years, compared to 57 years for cases of classical Parkinson's disease. Similarly, Dimsdale (1946) reviewed 320 cases of parkinsonism diagnosed in the United Kingdom from 1900 to 1942. Of the 100 cases from 1920 to 1930, two-thirds appeared to follow EL. The modal age of onset was in the third decade. The PEP cases could immediately follow EL or develop up to 19 years later but most sought medical attention within 2 years of EL. In both series, atypical features for Parkinson's disease were common and included oculogyric crises, ocular nerve abnormalities (abnormal external ocular movement, pupillary irregularities, poor accommodation), excessive salivation, and marked somnolence. Some patients also had hemiparesis, dystonia, chorea, tics, bulbar palsies, and behavioral disturbances.

Various series have estimated that, of survivors of EL, one-third developed PEP by 3 years and one-half after 5 years (Duvoisin and Yahr, 1965). One epidemiologic study even argued that all Parkinson's disease could be attributed to a cohort that developed the illness around 1920 (Poskanzer and Schwab, 1963). However, Parkinson's disease had been recognized long before 1920. Charcot noted that Parkinson's disease was the fifth most common disease treated at the Salpetrière and the disease was well recognized in New York City when studied from 1888 to 1904 (Hart, 1904).

The neuropathology of PEP has generally shown features consistent to EL but with marked degeneration of the substantia nigra. McKinley (1923) reported a 51-year-old Minnesota farmer who developed EL in 1920 and survived with improvement over 2 years. He continued to have increased somnolence but then developed a pill-rolling tremor, masked facies, bradykinesia, and rigidity consistent with Parkinson's disease. He died several months later. His brain showed persistence or residuals of a brainstem encephalitis with some perivascular cuffing of lymphocytes in the midbrain and elsewhere. There was marked loss of substantia nigra neurons and early gliosis. Other reported cases found similar pathology with persistent inflammation of lymphocytes and plasma cells around blood vessels months to years after the EL subsided, widespread distribution of lesions throughout the brain but mainly the brainstem, profound degeneration on neurons in the substantia nigra, and degeneration of neurons also in the striatum, pallidum, cortex, and midbrain tegmentum (Elizan and Casals, 1983).

There have been several attempts to identify or isolate influenza virus from the brains of PEP patients. Influenza virus antigen was identified in the midbrain and hypothalamus of frozen sections by immunofluorescence using fluorescein-conjugated globulin directed against several strains of influenza A (H1N1) virus (Gamboa et al., 1974). However, others have questioned this study and similar immunofluorescent studies have been negative (Elizan and Casals, 1983). No evidence of influenza RNA was detected using PCR studies of formalin-fixed tissues (McCall et al., 2001). Similarly, no differences were found in antibody distribution or titers to several influenza A (H1N1) strains between PEP patients and matched controls (Marttila et al., 1977; Elizan et al., 1979).

Subsequently rare cases of parkinsonism have been reported in patients with viral encephalitis due to arboviruses (Japanese B, West Nile, and St. Louis) and coxsackievirus (Walters, 1960; Pradhan et al., 1999; Robinson et al., 2003). In many of these cases, the parkinsonism was transient and resolved.

In summary, there is considerable evidence that PEP could develop rapidly or later as sequelae of EL. PEP developed in a much younger age than classical Parkinson's disease, began during the period when the 1918 strain of H1N1 influenza was pandemic, and has not reappeared since that cohort. However, there is no evidence for persistence of influenza virus in the brains of these patients. If EL was a sequela of the pandemic virus, then PEP was likely also. Although the Spanish 1918 influenza H1N1 strain has now been sequenced, it has not been assembled into an infectious virion. As such, the full biology of the virus remains incomplete. To date, however, there is no evidence that the 1918 strain during the pandemic directly infected and replicated in the brain of patients.

Reye's syndrome

In 1963 Reye and others described both the clinical and pathologic features of 21 children who died with a severe

encephalopathy and fatty degeneration of the liver. Johnson and others (1963) reported an association with what was soon called Reye's syndrome (RS) and influenza B viral infections. Although occasional patients were reported earlier who in retrospect may have had RS, after 1963 cases were soon recognized around the world (Utian et al., 1964; Golden and Duffell, 1965; Dvorackova et al., 1966; Norman et al., 1968).

By the 1970s, RS had become the most common hepatic cause of death in children and the second most common cause of death among virus-related diseases of the central nervous system (CNS) in children (Rogers et al., 1985). During the peak years of the 1970s, RS was commonly occurring worldwide. In the United States, the attack rate ranged from 30 to 60 cases per 100 000 influenza B infections (Corey et al., 1977b) and RS occurred from 0.3 to 0.4 cases per 100 000 influenza A infections. The influenza A infection could be associated with either the A H3N2 or H1N1 strain. Temporal and geographic associations between influenza B and RS outbreaks were repeatedly described (Johnson et al., 1963; Glick et al., 1970; Reynolds et al., 1972; Linnemann et al., 1975; Corey et al., 1976, Nelson et al., 1979).

The clinical features of RS are fairly characteristic (Davis and Woodfin, 1989). The syndrome developed primarily in children with the peak between the ages of 5 and 14 years (Rogers et al., 1985). However, histologically confirmed cases have occurred in neonates and adults (Huttenlocher and Trauner, 1978; Davis and Kornfeld, 1980). The clinical manifestations can be broadly divided into a prodrome and RS. The most commonly used staging system has been based on the system of Lovejoy et al. (1974). Individuals can progress relentlessly from stage I through stage V or stop at any stage and recover. The factors that govern progression of the disease through the stages are unknown.

A prodrome has been reported in over 90% of well-studied cases. In all, 60–87% of cases have been associated with an upper respiratory disease, 20–30% have been associated with chickenpox, and 5–15% with diarrhea (Corey et al., 1976). The large majority of cases have been associated with preceding infections of either influenza B or A viruses (Sullivan-Bolyai and Corey, 1981). A variety of other viruses have had one or a few cases of RS (Davis and Woodfin, 1989).

Vomiting is the cardinal feature of stage I. The vomiting is abrupt in onset and is repetitive, lasting hours to several days. The patient is lethargic and irritable. Fever may be present but jaundice is not. Individuals have normal strength, sensation, cranial nerves, and reflexes. Many patients in stage I do not progress further and recover (Heubi et al., 1984). In stage II the child is stuporous, may have a non-purposeful response to pain, show sluggish pupillary reactions, and demonstrate conjugate eye deviation to the oculovestibular reflex. In stage III the patient is comatose and shows decorticate posturing to pain. In stage IV the posturing is decerebrate, breathing is disorganized, and the oculovestibular reflex may be absent. In stage V, the patient is deeply comatose without spontaneous respirations, muscle tone is flaccid without posturing, and pupillary reflexes are absent. Few patients in stage V survive.

There is no single diagnostic laboratory test for RS. Arterial blood ammonia concentrations are usually at least threefold elevated and may exceed 1000 μg/dL (Huttenlocher et al., 1969; Haller, 1975). Other biochemical changes involving the liver are always present. Serum transaminases (alanine transaminase and aspartate transaminase) are typically elevated 20-fold above normal. Prothrombin times are often prolonged but hemorrhages are rare. A variety of other serum abnormalities may be present (Davis and Woodfin, 1989).

The CSF may have a normal opening pressure early in the illness but soon becomes highly elevated (Mickell et al., 1976). The CSF is acellular and has normal glucose and protein levels. The electroencephalogram (EEG) is always abnormal, showing slowing of background activity, seizures, burst suppression activity, and electrocerebral silence in stage V (Aoki and Lombroso, 1973). Neuroimaging is often normal in the early stages but in later stages demonstrates diffuse cerebral edema and possibly brain herniation (Russell et al., 1979).

The differential diagnosis of a Reye's-like syndrome in the absence of an outbreak of influenza A or B or chickenpox is long and includes acute generalized diseases, toxins, drugs, and genetic diseases (Davis and Woodfin, 1989). The diagnosis of RS is epidemiologically defined by the Centers for Disease Control and Prevention (CDC) as an acute, non-inflammatory encephalopathy documented by the clinical picture of alterations in the level of consciousness and liver dysfunction (Rogers et al., 1985).

The dominant brain pathology in RS is moderate to severe brain swelling due to cerebral cytotoxic edema rather than vasogenic edema (Reye et al., 1963; Evans et al., 1970; Davis and Kornfeld, 1980). In severe cases, widespread cortical neuronal degeneration and large myelin blebs occur. Inflammation is absent and viral particles or inclusion bodies are not seen. The liver in all stages is slightly swollen and increased in weight for the age of the patient. Liver biopsies show several characteristic changes. On frozen histologic sections, lipid is abundant and uniformly distributed. Hepatocyte cytoplasm is distended by microvesicular fat droplets (Schubert et al., 1972; Svoboda and Reddy, 1975). On paraffin-embedded sections stained with hemotoxylin and eosin, there is little cytoplasmic vacuolation early

but later there is a uniform foaminess of the cytoplasm. Inflammation is rare. By electron microscopy, hepatocytes show microvesicular fat droplets and prominent morphologic changes in mitochondria (Partin et al., 1971; Bove et al., 1975). The mitochondria often measured 2–3 μm in diameter with the outer membrane deformed by deep cytoplasmic invaginations and normal-appearing cristae. Liver biopsies obtained weeks to months after recovery appear almost normal. The kidney may also demonstrate lipid droplets within the cytoplasm of cells of the loop of Henle and proximal convoluted tubules. The myocardium occasionally also demonstrates lipid accumulation and abnormal mitochondria.

Management of children with RS has been primarily through attempts to control increased intracranial pressure (Corey et al., 1977a; DeVivo, 1985). Intracranial pressure monitors were often placed with a goal of maintaining the pressure below 20 mmHg (Ropper, 1984). Hyperventilation was a common method and often continued for days. It was often successful in controlling the intracranial pressure. However, the long-term consequences of brain ischemia produced neurologic sequelae. The risk of long periods of cerebral vasoconstriction were not recognized then. Use of mannitol intravenously was beneficial for 1–2 days but the serum osmolality level needed to be kept below 320 mOsmol/L. Even removal of parts of the calvarium and hypothermia were attempted as heroic methods. Treatment of the hyperammonemia was difficult. Use of peritoneal dialysis, hemodialysis, or plasma exchange did not appear to improve survival (Corey et al., 1977a). Vitamin K was usually administered. Anti-influenza drugs available at the time did not made a difference in outcome.

The early mortality rate in the United States was 40% but then fell to between 30 and 35% due to better intensive care and earlier detection of mild cases (Rogers et al., 1985). In the United Kingdom, the mortality rate was 41% (Communicable Disease Surveillance Center, 1985). In survivors, the sequelae were mainly neurologic, with over one-third having various aspects of mental retardation, hemiparesis, seizures, cortical blindness, and apraxia (Brunner et al., 1979; Shaywitz et al., 1982).

The pathogenesis of RS remains a mystery. There is overwhelming evidence that outbreaks and individual infections with influenza B virus were associated with developing the syndrome. Infections with influenza A virus and varicella-zoster virus also were associated with the syndrome. In addition to the acute influenza viral infection, there is strong epidemiologic evidence that taking aspirin (acetylsalicylic acid) early in the influenza predisposed to developing RS (Hurwitz et al., 1985, 1987). There was no evidence that these children were given excessive amounts of aspirin as the trigger. However, the aspirin and influenza correlation with RS was not close to one to one. Many children were reported who developed RS associated with influenza but had no exposure to aspirin. Two retrospective studies found that aspirin was given to the majority of children with flu symptoms that did not develop RS (71% and 74%) (Halpin et al., 1982; Waldman et al., 1982). Nevertheless, when warnings against children taking aspirin when developing a flu-like symptoms were widely circulated in the mid-1980s, the incidence of RS dramatically fell (Remington et al., 1986). By the early 1990s, RS around the world was rare.

There are several unexplained questions regarding the association of aspirin and RS. First, for aspirin alone to cause microvesicular steatosis of the liver, it requires high overdose intoxication. Second, acetylsalicylic acid was widely administered to children with fevers and flu symptoms since the early 1900s and was widely used even during the 1918, 1958, and 1964 influenza pandemics. Third, acetaminophen was marketed in 1956 and ibuprofen marketed in 1969 (just before the RS epidemic) and given to children with influenza, but neither has been associated with RS. Fourth, clear dose–response curves for aspirin have not been established for RS. The current argument is that any aspirin consumption can trigger RS in susceptible individuals. Fifth, cases of RS fell simultaneously around the world, although warnings about aspirin were publicized mainly in developed countries.

In favor of the association, there are strong epidemiologic arguments that aspirin was associated with RS if the child was also infected with influenza (Glasgow, 2006). Studies have demonstrated that salicylate inhibits β-oxidation of long-chain fatty acids in rodent liver mitochondria, leading to a possible explanation of why susceptible patients with RS have abnormal liver mitochondria and increased hepatic triglycerides (Deschamps et al., 1991).

Numerous attempts have been made to create a good animal model for RS. In general, animal models have focused on chemicals, infectious agents, or combinations of the two (reviewed by DeVivo, 1984; Deshmukh, 1985). Mouse models similar to RS have been developed in which juvenile mice given intravenous influenza B virus develop many of the clinical, laboratory, and pathologic features of RS 1–3 days later (Henle and Henle, 1946; Davis et al., 1983, 1993; Davis and Kornfeld, 1986). The mice developed elevated arterial serum ammonia, transaminase elevated levels, and hypoglycemia. The animals became lethargic, often developed seizures, and died. Microvesicular fatty degeneration was present throughout the liver with mitochondrial abnormalities seen on electron microscopy that was similar to that seen in human RS livers. The brain demonstrated cerebral edema by light and electron microscopy as well as biochemical studies. No

inflammation was seen in the liver or brain but was present in the trachea. No virus was isolated in the liver or brain but virus could be isolated from the respiratory tract. However, viral antigens by immunoperoxidase staining were detected in liver hepatocytes and cerebral endothelial cells. Influenza RNA was also detected in the brain and liver. Thus the liver and brain were nonpermissive influenza viral infections while the trachea infection was permissive and produced virions. The addition of aspirin to the mouse model did not increase mortality (Davis et al., 1985).

Young ferrets administered intranasal influenza virus and placed on an arginine-deficient diet developed severe hyperammonemia, serum transaminase elevations and an encephalopathy and fatty degeneration of the liver (Deshmukh and Thomas, 1985). Unfortunately, normal ferrets placed on an arginine-deficient diet also develop severe hyperammonemia and encephalopathy (Deshmukh and Shope, 1983). Finally, a spontaneous Reye's-like disease has been recognized to occur in Balb/c by J mice in which the mice become lethargic and stuporous and die (Brownstein et al., 1984). No viruses or other infectious agents have been isolated from the mice but serologic studies have suggested an infection with a coronavirus.

Leaving the questions about the association with aspirin aside, it still remains unclear how influenza B or A can cause RS. Clinically, RS does not occur at the peak of the influenza but rather as the patient is beginning to recover. Although influenza virus can be isolated often from other tissues such as the nasopharynx or lungs, it is rare for the virus to be isolated from blood, liver, or brain by conventional techniques (Noble et al., 1975; LaMontagne, 1980). Liver and brain biopsies examined by electron microscopy have not identified any budding influenza virus-like particles. Unfortunately, PCR techniques and other nucleic acid technology were not available then that would have been more sensitive. There have been no subsequent reports studying stored RS tissues using these technologies. Limited clinical laboratory studies indicated that no particular strain of influenza virus caused RS. The pathologic findings in the liver and brain do not suggest viral encephalitis or hepatitis. Thus, how influenza virus may have caused RS remains a mystery. In a later section, current theories of the pathogenesis of many of the neurologic complications of influenza will be discussed.

INFLUENZA, INFLUENZA VACCINE, AND GUILLAIN–BARRE SYNDROME

Guillain–Barré syndrome (GBS) is a transient monophasic, rapidly evolving polyradiculoneuropathy with symmetric motor weakness and variable autonomic features (Ropper, 1992). Currently there is no specific diagnostic test but patients usually have flaccid limb weakness that may progress to paralysis, weakness of respiratory muscles requiring mechanical ventilation, and cranial motor nerve palsies. Initially the patient is afebrile and the CSF is acellular and otherwise normal. Delayed motor nerve conduction velocities in peripheral nerves are usually seen by electromyography beginning after 1 week. The peripheral nerve pathology shows inflammation in the nerve with lymphocytes and macrophages surrounding endoneural blood vessels and causing adjacent segmental demyelination (Ropper, 1992). Acute treatment has either been plasma exchanges or intravenous pooled immunoglobulin. Both have been shown to shorten the time on a respirator and time to walk again (Ropper, 1992).

The syndrome has three different clinical patterns but all are likely to have an autoimmune basis. The strongest associations with GBS have been with preceding infections of *Campylobacter jejuni* and cytomegalovirus. However, both influenza viral infections and vaccinations with both live and killed influenza viruses have been associated with GBS. Currently there is no evidence that patients with acute influenza are at risk of developing GBS during their respiratory infection. However, there are epidemiologic associations with a preceding influenza-like infection. These associations date at least to 1946 when five cases of GBS developed after an influenza-like illness (Leigh, 1946). In 1959 two fatal cases of GBS were reported in patients who had serologic evidence of a recent influenza B viral infection (Wells et al., 1959). Fifty-two cases of GBS in the United Kingdom were serologically examined for evidence of a preceding viral infection (Melnick and Flewett, 1964). They reported a high incidence of upper respiratory tract infections occurring within 1 month of onset of the GBS but serologic evidence of true influenza was uncommon.

Epidemiologic studies generally have confirmed that preceding influenza-like respiratory illnesses are commonly associated with GBS but clear evidence that the respiratory illness was influenza has been lacking. An epidemiologic study of GBS in the greater Paris area from 1996 to 2001 found that 22% were associated with *C. jejuni* infections and 15% were associated with a preceding infection with cytomegalovirus (Sivadon-Tardy et al., 2006). However, 60% of the GBS cases peaked in the winter and half were preceded by a vague respiratory infection, influenza-like syndrome, or gastrointestinal illness.

A second study from UK National Health Service hospitals reporting cases of GBS from 1993 to 2002 found an association between the numbers of reports of laboratory-confirmed influenza A in any given week and GBS hospitalization in the same week (Tam et al., 2006). A regression analysis for an expected delay between the influenza infection and GBS also showed a

significant association for proven infections of influenza A and influenza B for individuals over the age of 35 years. However, they were not able to link the actual influenza virus infection to the individual with GBS.

The third epidemiologic study was a case-controlled study using data from the UK General Practice Research Database between 1991 and 2001 (Tam et al., 2007). The authors reported positive associations between GBS and infection with *Campylobacter*, Epstein–Barr virus, and influenza-like illnesses in the previous 2 months. There data provide evidence for patients with influenza-like illnesses having an 18-fold increased risk of GBS.

Unfortunately, not all epidemiologic studies have found an association between influenza infections and GBS. Two US studies failed to find any significant association between antecedent influenza and GBS (Kennedy et al., 1978; Alter, 1990). A third Netherlands age- and sex-matched study of 154 GBS patients found significant serologic evidence of preceding infections of *C. jejuni*, cytomegalovirus, and Epstein–Barr viruses but only 3 patients (2%) had serologic evidence of a preceding infection with influenza A or B viruses (Jacobs et al., 1998).

If there is a true association between influenza and GBS, it must be weak and GBS does not occur during the acute influenza illness but within the month afterwards.

The association between influenza vaccination and GBS began in 1976 with the occurrence at Fort Dix, New Jersey, of human infections with a swine influenza A strain (Hsw1 N1 or A/NJ/1976/H1N1). Before then, no causal relationship between GBS and influenza vaccination had been epidemiologically documented and few cases after vaccination had been reported (Hurwitz et al., 1981). In response to a perceived threat that the Hsw1N1 strain was similar to the 1918 pandemic strain, 40 million adults were vaccinated with a rapidly produced killed swine influenza vaccine. As the vaccination program proceeded, it became recognized that cases of GBS started appearing. Beginning about the second week after vaccination, a sharp rise in GBS cases occurred that peaked in the third week, followed by a fairly rapid decline that extended a total of 6 weeks (Langmuir, 1979, Schonberger et al., 1979; Marks and Halpin, 1980). Since children under the age of 18 were not recommended for vaccination, few GBS cases developed in that age group. Compared to unvaccinated individuals who developed GBS, the increased relative risk rose to 12.7 per 1000 vaccinees for ages 25–44 years, 7.1 for ages 45–64, and 5.6 for ages over age 65 years (Langmuir, 1979). In all, there were 500 cases of GBS occurring among vaccinated persons, with 25 deaths. For all age groups, the rate for vaccinated cases was 7.3 and for unvaccinated cases 0.77, giving a ratio or relative risk of 9.5 to 1 or an increase of one case of GBS for every 100 000 adult vaccinations (Haber et al., 2009).

Beginning with the 1978 influenza vaccine program, active surveillance for GBS following vaccination has occurred. Most published reports have not found a statistically significant association between vaccination and GBS (Hurwitz et al., 1981; Kaplan et al., 1982; Lasky et al., 1998). In addition, a US Vaccine Adverse Event Reporting System (VAERS) supported by the CDC was established (CDC, 2009). VAERS is a voluntary reporting system for adverse events to all vaccines. VAERS and a similar UK reporting system have reported either no increased risk or a minimal increased risk of about one GBS case per million persons vaccinated associated with previous influenza vaccines (CDC, 2010a). Regarding the 2009 H1N1 vaccine, as of April 2010, VAERS reported nearly 127 million doses of the 2009 vaccine being shipped to vaccination providers and having received only 136 GBS reports, which can be compared to a predicted 80–160 cases of GBS per week regardless of vaccination (CDC, 2010a).

Currently, the CDC also conducts active GBS surveillance in 10 states in its Emerging Infections Program. As of March 31, 2010, individuals who received the 2009 influenza A vaccine had an estimated incidence of 1.92 cases of GBS per 100 000 person-years compared to an estimated incidence for non-vaccinated individuals of 1.21 GBS cases per 100 000 person-years (CDC, 2010b). This significant excess risk relates to 0.8 cases per one million vaccinations.

At the moment, there is no satisfactory explanation why the 1976 swine influenza vaccine caused a much higher rate of associated GBS cases following vaccination compared to all subsequent influenza vaccine strains. One explanation given by the CDC is that the Fort Dix strain contained a "trigger element" (Langmuir, 1979). What the trigger element was is unclear despite considerable research. One possibility is that of molecular mimicry, with the vaccine triggering the production of antiganglioside antibodies in selected recipients which produced the GBS peripheral neuropathy (Nachamkin et al., 2008).

MYALGIA AND MYOSITIS ASSOCIATED WITH INFLUENZA

Patients developing influenza A or B infections commonly experience diffuse myalgias or muscle aches and pains early in the illness (Nicholson, 1992). The myalgias seldom interfere with muscle strength but can be associated with transient serum elevations of creatine kinase (Friman, 1976). The myalgias correlate with the severity of the influenza, last several days, and resolve along with the other symptoms during recovery. Muscle biopsies have not been done on these patients so the pathogenesis and pathology are unknown.

In a much smaller percentage of patients with influenza, the individual develops focal muscle aches and swelling later in the illness. The association of influenza and myositis was first described in 1957 with a series of 74 cases (Lundberg, 1957). Since then benign acute myositis has been reported in many epidemics of influenza A and B (Middleton et al., 1970; Gamboa et al., 1979; Farrell et al., 1980; Ruff and Secrist, 1982; Hu et al., 2004). In a series of 316 cases reviewed from the literature, the myositis usually developed in school-aged children (mean age of 8 years) with a 2:1 male predominance (Agyeman et al., 2004). About three-quarters of the infections were attributed to influenza B virus. The mean interval of myositis from onset of influenza symptoms was 3 days. The calf muscles were usually involved, with 69% being the only muscle group involved and 31% having calf and other muscles involved. The gastrocnemius is commonly tender to palpation (75%) and could have a mild swelling but the overlying skin was seldom warm to the touch or red. Walking is difficult and usually done with a limp. If both calves are involved, the child often refuses to walk. Serum creatine kinase is always elevated but rhabdomyolysis and renal failure occur in only 3%. The outcome is excellent, with symptoms of focal pain resolving in a median of 3 days. No studies have demonstrated that administration of anti-influenza drugs is effective in shortening the duration of the myopathy.

The muscle pathology of the involved muscles typically demonstrates segmental degeneration or rhabdomyolysis with or without accompanying inflammation (Mejlszenkier et al., 1973; Gamboa et al., 1979; Congy et al., 1980; Farrell et al., 1980; Bove et al., 1983). In a summary of 28 biopsy specimens, all showed degeneration and necrosis but six specimens showed no inflammation (Agyeman et al., 2004). The degeneration was quite focal and patchy. Frank hemorrhages did not develop. Attempts to isolate influenza virus from the muscle biopsy have varied. Often the isolation attempt was unsuccessful (Greco et al., 1977; Schlesinger et al., 1978) but influenza A or B virus has been isolated from several patients (Partin et al., 1976; Gamboa et al., 1979; Kessler et al., 1980, 1983). In addition, an immunohistochemical study from a muscle biopsy of a symptomatic patient demonstrated influenza viral antigen within myofibers often in a segmental pattern (Gamboa et al., 1979). Muscle fibers at the periphery of a bundle appeared to have more viral antigen than those that were central.

Experimental animal studies have also demonstrated that influenza virus can cause a focal infection of skeletal muscle. Influenza B/Lee virus inoculated into mouse thigh muscle caused a non-permissive or poorly permissive localized infection of muscle fibers (Davis and Kornfeld, 2001). Serum creatine kinase levels became transiently elevated. Microscopic studies demonstrated segments of the muscle fiber with degeneration within the fiber and inflammation in the perimysium surrounding muscle fascicles. Immunohistochemistry and PCR assays confirmed the localized viral infection into specific nuclear domains of the muscle fiber consistent with the human biopsies. Virus was poorly isolated from the muscle and quantitative data suggested it was only residual virus from the inoculum.

In vitro studies of muscle cells from muscle biopsies infected with influenza virus have demonstrated viral replication with production of virions if the cultures were held at 36–37°C (Klavinskis et al., 1985; Servidei et al., 1987). However, if the culture temperature was raised to a higher temperature, the infection was non-permissive (Cox et al., 1977).

In summary, viral myalgias are common with influenza but the pathology and pathogenesis for the diffuse muscle discomfort are unknown. Currently elevated serum cytokines are postulated to be the cause. The severity of the myalgia correlates with the severity of the influenza respiratory symptoms and with the titer of influenza virus shed from the nasopharynx (Hall et al., 1979). Children and occasional adults can develop a focal degeneration of mainly leg muscles that often demonstrates segmental involvement in muscle fibers. It is postulated that the respiratory infection results in a transient viremia (Naficy, 1963; Stanley and Jackson, 1966) that somehow localizes to calf muscles, producing mainly a non-permissive localized myopathy with limited inflammation. However, the occurrence of myositis did not correlate with the quantities of virus shed in the nasopharynx (Hall et al., 1979).

MYOCARDITIS ASSOCIATED WITH INFLUENZA

Cardiac dysfunction associated with influenza ranges from 0% to 10% depending on the methods used to detect myocardial involvement and occurs through direct effects of the virus on the myocardium or through exacerbation of existing cardiovascular disease (Mamas et al., 2008). In general, the incidence of myocarditis is highest in hospitalized patients, in older adults, and in individuals with pre-existing pulmonary or cardiac disease. In spite of that, a series of 67 healthy Finnish conscripts hospitalized with influenza A were reported to have electrocardiac and echocardiologic evidence of myocarditis in 9% (Karjalainen et al., 1980).

When acute myocarditis presents in a patient with influenza, the symptoms include chest pains or dyspnea. However, these same symptoms may also suggest the patient has congestive heart failure or pericardial

effusion, making a clinical diagnosis more difficult. The cardiac symptoms usually develop within the first week of influenza onset. The electrocardiogram demonstrates non-specific tachycardia (also common in uncomplicated influenza) plus ST elevation associated with Q waves or occasionally left bundle branch block (Weiss et al., 2010). Echocardiography usually shows left ventricular dysfunction with wall motion abnormalities and reduced ejection fractions (Erden et al., 2010; Weiss et al., 2010). Cardiac magnetic resonance imaging (MRI) has shown focal left ventricle edema on T2-weighted images, increased global relative enhancement on the T1-weighted gradient inversion recovery sequence, and epicardial late gadolinium enhancement (Weiss et al., 2010).

Endomyocardial biopsies or myocardial examination at autopsy usually demonstrate multiple foci of active inflammation, focal edema, and varying degrees of myocyte degeneration or necrosis (Engblom et al., 1983; Bratincsak et al., 2010; Frank et al., 2010). Influenza virus occasionally is recovered from heart muscle or by PCR assays for influenza RNA of cardiac muscle but careful blood controls to rule out a viremic or nearby infected lung contamination are lacking (Kaji et al., 1959; Engblom et al., 1983; Bratincsak et al., 2010; Frank et al., 2010). Four children aged 3–9 years have been reported with myocarditis associated with 2009 influenza A (El-Said et al., 2010). Three had fulminant myocarditis with full recovery but one died. This fatal case and one other had severe myocardial damage characterized by mononuclear infiltration. Reverse transcriptase-PCR (RT-PCR) assay for influenza viral RNA was positive in cardiac tissue.

Experimental mice were administered an aerosol of influenza A/PR/8/34 virus. Virus was isolated from cardiac tissue on days 3–7. Microscopic examination of the tissue demonstrated small necrotic foci with inflammatory cell infiltration spreading in the myocardium of days 3–7. The necrotic tissue was phagocytosed by macrophages and degenerating cardiocytes, macrophages, and lymphocytes were in close contact (Kotaka et al., 1990). Immunofluorescent studies demonstrated viral antigen in endothelial cells and cardiocytes until day 7. Cultured neonatal primary rat heart muscle infected with influenza virus demonstrated viral antigen in the nuclei and cytoplasm of the muscle cells but no virion production was observed, suggesting the infection was non-permissive (Suciu et al., 1985).

Epidemics of influenza also are associated with an increased risk of autopsy-proven myocardial infarctions, which in one study rose 30% when compared to those in non-influenza winters (Madjid et al., 2007). During periods of influenza, the risk of a cardiovascular death increases considerably in the elderly (Barker and Mullooly, 1980; Alling et al., 1981). It is possible that myocarditis developing in a patient with impaired cardiac ejection fraction from pre-existing cardiac disease could lead to developing frank congestive heart failure from the influenza myocarditis.

In summary, influenza virus-associated myocarditis is more common than generally appreciated. When the myocarditis develops, other skeletal muscle pain may mask the chest pains (Verel et al., 1976; Tabbutt et al., 2004). In young patients, the myocarditis is usually non-fatal and reversible but the elderly may experience serious cardiac disease. Like the myositis considered above, it is unclear whether the pathogenesis of the myocarditis is secondary to direct virus infection of cardiac muscle fibers or to an indirect toxic effect such as elevated levels of serum cytokines.

FEBRILE SEIZURES ASSOCIATED WITH INFLUENZA

Febrile seizures are a common cause of childhood seizures. Febrile seizures are defined as a seizure in children aged 6 months to 5 years associated with fever but without evidence of intracranial infection or other definable cause (Chiu et al., 2001). In one series of 73 children hospitalized for febrile seizures, a viral cause was thought to be responsible in 86% (Lewis et al., 1979). Published series have determined that several common viruses are associated with febrile seizures and include influenza, adenovirus, parainfluenza, respiratory syncytial virus, and rotavirus (Chung and Wong, 2007). In series of hospital visits for febrile seizures, about 20% are associated with influenza (Chiu et al., 2001; Chung and Wong, 2007). The majority had a single uncomplicated partial or generalized seizure but 20–33% had more complex seizures that could be prolonged for more than 15 minutes, multiple seizures occurring within 24 hours, or postictal impairment of consciousness lasting for more than 30 minutes (Chung and Wong, 2007). Patients with febrile seizure should not have abnormalities on their EEG or neuroimaging and at discharge should be normal. In a series of 842 patients hospitalized with laboratory-confirmed influenza, 72 (0.9%) developed neurologic complications (Newland et al., 2007). Seizures were the reason for admission in 56 (58%) and febrile seizures in 27 of the 56 (48%). Whether influenza virus triggers a seizure simply by causing a childhood fever or whether there are other factors involved is unclear.

ENCEPHALOPATHY WITH OR WITHOUT SEIZURES ASSOCIATED WITH INFLUENZA

Encephalopathy with or without seizures appears to be the most common major neurologic association with

influenza. The term encephalopathy implies a change in mental status lasting more than 24 hours that may be associated with seizures and occasionally focal neurologic signs but lacks evidence of inflammation of the brain or meninges. For epidemiologic purposes, the CDC defines influenza-related encephalopathy as patients who had altered mental status or personality changes lasting >24 hours and occurring within 5 days of an acute febrile respiratory illness that was proven subsequently to be laboratory-confirmed influenza (Newland et al., 2007).

The term encephalitis implies inflammation of the brain. Clinically the two conditions may be difficult to distinguish without a CSF examination, brain biopsy/autopsy, or good neuroimaging (Davis, 2000).

Influenza-associated encephalopathy has been described almost every year and was well recognized as far back as the 1918 influenza pandemic (Jelliffe, 1918). The encephalopathy has been associated with influenza H1, H2, and H3 viral strains as well as influenza B strains (Paisley et al., 1978; Steininger et al., 2003; Lin et al., 2006; Ekstrand et al., 2010). It has been difficult to determine whether particular strains of influenza A or B have a higher incidence of encephalopathy.

Children with influenza-associated encephalopathy likely have been underdiagnosed as just very sick kids with the flu that were not hospitalized (Toovey, 2008). As such, the true incidence is unknown. One study of 842 patients hospitalized with proven influenza from 2000 to 2004 reported that 10% developed neurologic symptoms and estimated the incidence as four cases per 100 000 person-years (Newland et al., 2007). Some series have reported that the risk of encephalopathy is higher in children with pre-existing neurologic problems. Another study evaluated children hospitalized with encephalitis or encephalopathy over an 11-year period (Amin et al., 2008). Of the 311 children identified, they found evidence of influenza viral infection in 5%.

Children under the age of 6 years have the highest risk of developing encephalopathy but it clearly can occur in adults (Steininger et al., 2003; Newland et al., 2007). Children and adults usually develop a non-productive cough, sore throat, and nasal congestion accompanied by a fever, headache, and myalgias (Maricich et al., 2004). Diarrhea, nausea and vomiting may also occur in children. Beginning on the same day or within a few days, the individual becomes confused and may be delirious (Wang et al., 2010). In some individuals, the delirium can persist and patients develop hallucinations, inappropriate emotional outbursts of laughter or fear, mumbling and incoherent speech, or even psychosis (Huang et al., 2003; Lin et al., 2006; Toovey, 2008; Takanashi et al., 2009; German-Diaz et al., 2010). MRI scans in a few of these individuals, especially in Japan, who do not progress to coma show a reversible splenial lesion (Takanashi et al., 2009).

Generalized or complex partial seizures occur in about one-half of patients (Maricich et al., 2004). Often the seizures are repetitive, may progress to status epilepticus, and are difficult to control with anticonvulsants (Sugaya, 2002). Within a few hours to a few days, the encephalopathy may worsen to where the patient becomes semicomatose or comatose. Some patients develop focal neurologic signs such as hemiparesis, aphasia, torticollis, and opisthotonus (Amin et al., 2008).

The large majority of individuals have a CSF that may be under increased opening pressure, lack a white blood cell (WBC) pleocytosis, and have normal CSF protein and glucose levels (Studahl, 2003; Amin et al., 2008; Okumura et al., 2009; Ekstrand et al., 2010). If the CSF contains many WBCs, the diagnosis is usually switched to encephalitis or to bacterial meningitis or aseptic meningitis (Newland et al., 2007). The blood seldom demonstrates characteristic abnormalities. The WBC may be normal or slightly elevated. Liver function studies usually are normal. However, occasional cases, especially from Japan, describe liver transaminase elevations and even arterial ammonia elevations that are very similar to RS (Sugaya, 2002). These cases are often described as Reye's-like, since in general these patients have not consumed aspirin or similar compounds.

The EEG may be normal, or demonstrate diffuse slowing, focal areas of slowing, epileptiform spikes, or seizures (Steininger et al., 2003; Maricich et al., 2004; Baltagi et al., 2010).

Neuroimaging by MRI is the most sensitive for detecting abnormalities. Many cases of encephalopathy have normal neuroimaging (Baltagi et al., 2010). Radiologists have divided the types of MRI images into several categories: normal, diffuse involvement with cerebral edema of the cerebral cortex, symmetric involvement of the thalami, basal ganglia and brainstem (ANE), and a postinfectious or acute disseminated encephalomyelitis category with multiple abnormal foci, mainly in the white matter (Kimura et al., 1998; Studahl, 2003) (Fig. 30.2). Occasionally the MRI may be normal early but develop abnormalities within a few days.

Fortunately, individuals with only encephalopathy seldom die. The few autopsies of these patients have either been normal or demonstrate varying degrees of cerebral edema, usually without inflammation. The pathology of ANE is much different and is described below.

The majority of patients with only encephalopathy have a good prognosis but up to 30% may be discharged with neurologic sequelae that include hemiparesis, aphasia, cognitive loss, developmental delay, dysarthria, abnormal tremor or posturing, ataxia, and epilepsy (Steininger et al., 2003; Amin et al., 2008).

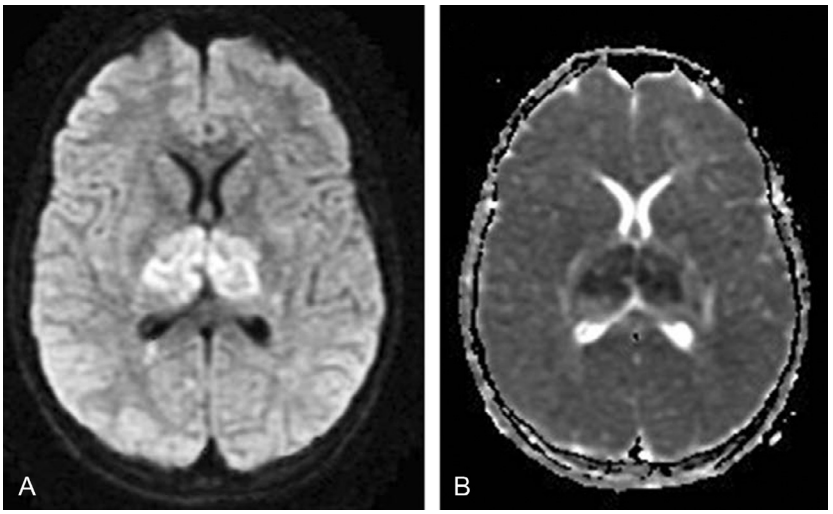

Fig. 30.2. A 12-year-old girl developed influenza encephalopathy. (**A**) Axial diffusion-weighted image magnetic resonance imaging with restricted diffusion in thalami bilaterally. (**B**) Accompanying apparent diffusion coefficient map. (Reproduced with permission from Lyon et al., 2010.)

In addition to the typical encephalopathy associated with influenza, influenza has been associated with a variety of other neurologic signs or symptoms. They include vertigo lasting about a week (Walford, 1949), movement disorders such as choreoathetosis (Ryan et al., 1999), and strokes (Newland et al., 2007).

ACUTE NECROTIZING ENCEPHALOPATHY ASSOCIATED WITH INFLUENZA

Beginning about 1994, some cases of encephalopathy associated with influenza have been much more severe, with very abnormal neuroimaging, coma, and >30% deaths (Togashi et al., 2004). These patients are now described as having ANE. Although most of the cases have come from Japan, cases are now occasionally recognized around the world, including the United States (Lyon et al., 2010). The majority of cases have been associated with influenza A (H3N2 or H1N1), but cases from influenza B virus are recognized (Sazgar et al., 2003).

Most cases are children under age 6 years with the neurologic symptoms beginning within 1–3 days of the onset of respiratory signs (Morishima et al., 2002; Togashi et al., 2004). Adults can also develop ANE (Morishima et al., 2002). Often the children become lethargic, experience single or multiple seizures, and lapse into a coma. The coma often is deep, requiring mechanical ventilation. The development of hypotension is not uncommon.

Individuals may have thrombocytopenia, elevated liver transaminases, and elevated ammonia levels (Morishima et al., 2002; Togashi et al., 2004). The CSF usually has an elevated opening pressure when measured, lacks pleocytosis, has normal glucose, and only occasionally has an elevated protein (Fujimoto et al., 2000; Ormitti et al., 2010). The MRI may be normal but often demonstrates areas of T2-weighted enhancement in both basal ganglia, thalami, brainstem, cerebellar white matter, and cerebral white matter (Lyon et al., 2010). Computed tomography shows hypointense lesions in the same regions (Sazgar et al., 2003). Depending on the Japanese series, deaths range from 30 to 40%, and 40% of survivors have neurologic sequelae with hemiparesis, paraplegia, choreoathetosis, parkinsonism, or dementia (Fujimoto et al., 2000).

Autopsies have demonstrated diffuse cerebral edema with focal areas of necrosis in the same areas identified by MRI in life. These foci have necrotic cells, localized edema, congestion and hemorrhages, but have little inflammation in the lesions or meninges (Yagishita et al., 1995; Sazgar et al., 2003; Togashi et al., 2004; Kirton et al., 2005; Lyon et al., 2010). One study reported histologic markers of apoptosis occurring in neurons and glia (Takahashi et al., 2000; Nakai et al., 2003). The cerebral blood vessels are not occluded by inflammatory cells or other debris but often had dilated Virchow–Robin spaces containing clear fluid (Ishigami et al., 2004). Many autopsy reports noted histologic evidence of vascular endothelial pathology with surrounding vasogenic edema (Sugaya, 2002; Mizuguchi et al., 2007).

To date a wide variety of treatments have been tried, including anti-influenza drugs, steroids, plasmapheresis, intravenous immunoglobulin, hypothermia, anticonvulsants, and antibiotics, but none has been proven as being very helpful in preventing death or neurologic sequelae.

The precise incidence of neurologic complications during any year has been difficult to determine (Newland et al., 2007). However, since a large majority of individuals with influenza never seek medical attention or are hospitalized, the risk must be less than 1% of those infected. Most individuals with the encephalopathy do not have pre-existing neurologic illness or have a chronic immunosuppression, but clearly some do. In the past two decades, children less than 6 years appear to be at a greater risk than adults for developing ANE from the influenza A H3 and H1 strains. Uncomplicated encephalopathy occurred more often in children during the influenza A (H1N1) pandemic but that may have reflected that mainly children developed the H1N1 infection.

The pathogenesis of both encephalopathy and ANE associated with influenza are poorly understood. Two theories have been put forth but neither is proven.

There is increasing interest that the encephalopathy associated with the respiratory influenza infection may be due to several cytokines. However, production of proinflammatory cytokines is a normal defense mechanism in an influenza infection. A comprehensive study of 20 normal volunteers who were nasally infected with influenza A Texas/36/91 (H1N1) virus were serially followed with nasal and serum cytokine levels which correlated with symptoms and nasal viral titers (Hayden et al., 1998). Influenza virus infection and replication in the respiratory tract directly injure the nasal and tracheobronchial epithelium. The resulting loss of respiratory epithelial cells is a major reason for several symptoms accompanying the infection, such as cough, depressed tracheobronchial clearance, and altered pulmonary function. Influenza virus induces a cascade of host immune responses leading to mucosal inflammation and the influx of polymorphonuclear cells, lymphocytes, and macrophages into the respiratory tract. It is this immune response that is responsible for resolution of the infection and possibly the clinical systemic symptoms. In the volunteer study, virus was recovered from nasal washes beginning on day 1, peaking on day 2 and persisting up to day 7. Peak influenza virus titers on day 2 were about $10^{3.7}$ 50% tissue culture infectious doses per mL. The patient temperature also peaked on day 2. Respiratory and systemic symptoms, such as fever, headache, and myalgias, also peaked on day 2 and persisted to about day 6. Two cytokines, IL-6 and IFN-α, peaked in the nasal washes and serum on day 2 but serum TNF-α peaked on day 4. Serum IL-6 levels were about fourfold above normal. Plasma and serum IL-6 levels nicely correlated with total systemic symptoms on days 2–4. Considerable evidence finds that the cytokines studied were produced locally in the respiratory tract by both infected respiratory epithelial cells and immune invading cells. Another study reported similar findings (Kaiser et al., 2001). Thus, several cytokines appear responsible for both clearance of the respiratory infection and production of common influenza systemic symptoms.

Recent studies of serum and cytokine levels from patients with influenza who developed an encephalopathy have suggested that very elevated cytokine levels may be in part responsible for the encephalopathy. Studies of patients with encephalopathy have reported very elevated serum and/or CSF elevated levels of IL-1α, IL-6, IL-8, IL-10, IL-15, and TNF-α, and soluble TNF receptor (Ichiyama et al., 2003b; To et al., 2010). Furthermore, when patients were divided into categories ranging from simple respiratory illness, to febrile seizures, and encephalopathy, those with the encephalopathy generally had the highest serum levels (Ichiyama et al., 1998, 2004; Kawada et al., 2003; Ito et al., 1999; Fukumoto et al., 2007). Individuals with ANE often, but not always, had extremely elevated serum and CSF levels of IL-6 (Yoshikawa et al., 2001; Ichiyama et al., 2003a; Okumura et al., 2009). Thus, there was a correlation between very elevated serum cytokine levels and poor outcome from death or neurologic sequelae. The viral pneumonia complicating the pandemic 2009 H1N1 infection is a primary source of elevated cytokine production (To et al., 2010).

Complicating the analysis is that many patients with ANE also had a viral pneumonia that could have contributed to the elevated cytokine levels (To et al., 2010).

In addition, very elevated CSF cytokine levels have been reported in other illnesses, including other viral encephalitis (Ichiyama et al., 2009). Finally, the mechanism by which elevated serum or CSF cytokine levels actually cause the cerebral edema or focal areas of necrosis in selected areas of the brain is unclear. However, it has been postulated that several cytokines, including IL-6, TNF- α, and IL-1, can induce disruption of the blood–brain barrier in animals and *in vitro* (Saija et al., 1995; deVires et al., 1996).

An alternative theory is that influenza virus directly plays a role in the encephalopathy. This hypothesis is complicated as there is almost no evidence that influenza virus fully replicates in the brain, causing encephalitis. Isolation of influenza virus from brain lesions or CSF is unusual (Frankova et al., 1977) and evidence of influenza replications in organs outside the respiratory tract is uncommon. The histopathology of the encephalitis does not show inflammation, as would be expected from most forms of encephalitis.

There is some evidence supporting some direct role of influenza virus in the encephalopathy. The hypothesis would be that a non-permissive or abortive influenza virus infection of the brain or cerebral blood vessels is the cause. The influenza virus is normal but the cell that the virus infects is non-permissive for a full cycle of replication. A non-permissive infection of many

non-respiratory cells in humans and animals has been demonstrated. In these cells the virus starts the replication cycle in the cell, causes dysfunction of the cell, but fails to produce progeny virions that can produce additional cycles of replication or be isolated from the cells.

Influenza virus can cause a viremia in humans, particularly early in the infection and before clinical symptoms (Naficy, 1963; Stanley and Jackson, 1966; Khakpour et al., 1969; Lehmann and Gust, 1971; Xu et al., 1998). The incidence of the viremia appears low based on blood PCR assays of patients with influenza respiratory symptoms (Mori et al., 1997) and blood isolation attempts in larger series of patients (Khakpour et al., 1969).

The non-permissive theory argues that the initial respiratory influenza viral infection produces an early viremia that secondarily infects brain endothelial cells (producing cerebral edema with headache or encephalopathy), myocytes (producing myalgia or myositis), myocardium (producing myocardopathy), and hepatocytes (producing liver enzyme dysfunction and RS).

In a few autopsies, influenza viral antigen has been detected in brain ependymal cells (Frankova et al., 1977), in Purkinje cells and some pontine nuclei (Takahashi et al., 2000), and within capillary vessel walls of the basal ganglia (Ishigami et al., 2004). Detection of influenza RNA by RT-PCR assays has been reported to be positive in both brain tissue and CSF (Fujimoto et al., 1998; Morishima et al., 2002; Steininger et al., 2003; Togashi et al., 2004; Ekstrand et al., 2010). However, other studies using PCR assays have been negative in single case reports or reported as positive in less than half of attempts in their series (Fujimoto et al., 2000; Shinjoh et al., 2000; Morishima et al., 2002; Steininger et al., 2003; Togashi et al., 2004; Lyon et al., 2010).

Support for the non-permissive theory exists in experimental animals. Following intranasal inoculation, intravenous inoculation, or direct muscle injection, human influenza virus in mice or hamsters produces a non-permissive viral infection in cerebral endothelial cells causing cerebral edema, in muscle myofibrils causing myositis, in myocardium causing myocarditis, and in hepatocytes causing a fatty steatosis similar to that seen in RS (Davis, 1987; Davis et al., 2000). The non-permissive viral infection transiently produces viral nucleic acid and viral antigens for 1–3 days but produces very little, if any, infectious virions and results in little tissue inflammation.

NEUROLOGIC SYNDROMES ASSOCIATED WITH AVIAN INFLUENZA H5N1

Avian influenza is different from seasonal and pandemic strains in three respects.

First, although less than 500 human cases of avian H5N1 influenza have been recorded, the high mortality rate of approximately 60% (WHO, 2008) has raised the fear that a future highly pathogenic H5N1 strain acquiring human transmissibility will produce the greatest worldwide pandemic. Second, avian influenza strains of subtype H5 were never recognized in humans until 1997 during a small outbreak in Hong Kong. Evolution of these strains through mutation resulted in greater viral replication efficiency in mammalian cells (Twu et al., 2007). Subsequently explosive spread of avian influenza began in 2004 and within 2 years had spread throughout Asia with extension to Europe and Africa. Multiple clades of H5N1 viruses have evolved over the last dozen years (Chen et al., 2006), complicating the prediction of suitable vaccines. Although the immediate source of infection is usually not identified, contact with domestic poultry has been a constant association with human infection and epizootics of avian flu in domestic fowl have led to the destruction of millions of birds. Low pathogenic influenza viruses are enzootic in feral water fowl but introduction into domestic poultry appears to accelerate adaptation, virulence, and high levels of aerosol transmission among crowded flocks (Lebarbenchon et al., 2010). H7 and H9 subtypes have also infected humans but the disease is in general mild and not thought to represent a pandemic threat.

Population-based surveys of farmers, merchants, and cooks in close contact with poultry production and preparation find a low seroprevalence of antibody to the H5 HA. Human-to-human transmission of avian influenza is rare (Wang et al., 2008b), so it appears that very close contact with infected fowl is required for infection. Underlying disease does not predispose to death, but children and adolescents are overrepresented among death statistics (Kandun et al., 2008). Although most infecting strains are resistant to amantadine but sensitive to oseltamivir, treatment with NA inhibitors or ribavirin does not seem to alter the disease course.

The third reason that avian influenza is unique among the influenza viruses is its multiorgan dissemination of infection seen in both animal models and humans.

The sialic acid-decorated glycolipids and glycoproteins that serve as receptors for the HA protein are ubiquitous on the surface of most avian and mammalian cells. In most avian species influenza is primarily an enteric infection, with highest titer of virus found in the cloaca. Intestinal infection following intranasal inoculation in the ferret has been documented and results in diarrhea. CNS infection is well described in many bird species, with infection of neurons and microglial cells documented (Vascellari et al., 2007). Mouse microglia and astrocytes bear both the α-2,3-gal and α-2,6-gal receptors and are productively infected *in vitro* by both human and avian viruses (Wang et al., 2008b).

Extrapulmonary dissemination is characteristic of H5N1 infection in mice (Gao et al., 1999). Note that H5N1 viruses display a predilection for binding to the α-2,3-galactose-linked sialic acid receptors found predominantly in human lower respiratory tract mucosal epithelial cells (Shinya et al., 2006). Thus it is recommended that in early infection diagnosis is better achieved from specimens taken from the lower respiratory tract (Zhang et al., 2010).

The anatomic routes of entry from the initial mucosal infection to non-mucosal tissues are not yet clear. Viremia has been documented but appears to be rare. In a murine model of an H5N3 virus inoculated intranasally, viral antigen was detected initially in vagal and trigeminal ganglia but not in the blood (Shinya et al., 2000). In the mouse model several routes of entry of the virus into the brain have been suggested. Intranasal inoculation of highly pathogenic H5N1 virus appeared to enter via the mesenteric and myenteric plexi of the enteric nervous system prior to appearing in the brainstem nuclei (Jang et al., 2009). Inoculation with a dose lethal to half the mice resulted in large weight loss, ataxia, tremor, and bradykinesia in all the animals. This study also found that, among survivors examined 90 days after infection, neuronal loss, abnormal protein aggregations, and microglial activation were prominent, all hallmarks of the neurodegenerative diseases, including Parkinson's and Alzheimer's diseases.

In ferrets inoculated intranasally with the highly pathogenic HPAI H5N1 virus, high titers of virus appeared in the periglomerular and mitral cells of the olfactory bulb within 24 hours of inoculation, with later spread to neurons and microglial cells in the brainstem and all other lobes. CNS lesions were focal non-suppurative collections of karyorrhectic cells and influenza antigen concentrated in cellular nuclei and surrounding debris, with scattered regions of purulent meningitis. This sequence suggests that entry was from the sensory epithelial cells in the dorsal turbinates through the cribiform plate to neuronal tracts throughout the CNS (F. Koster, unpublished data).

Ferrets infected with HPAI in the respiratory tract exhibit replication to high titers in multiple systemic organs, including the spleen, liver, bone marrow, intestine, and brain (Zitzow et al., 2002; Maines et al., 2005). The majority of ferrets exhibit severe neurologic signs, including hemiparesis, convulsions, torticollis, and spasticity prior to death (Rowe et al., 2003). High levels of cytokine secretion are found in mouse (Lipatov et al., 2005; Szretter et al., 2007) and ferret (Cameron et al., 2008) models. However, in view of the extensive regions of necrosis in all lobes of the ferret brain in sites of replicating virus, it is difficult to escape the conclusion that the meningoencephalitis is due primarily to the cytolytic viral replication.

Human neurologic sequelae of H5N1 HPAI infections are clearly different from that in the ferret model. The few postmortem studies have not yet been able to elucidate thoroughly the pathogenesis of this severe disease, but available data have been summarized in detail (Gambotto et al., 2008; Korteweg and Gu, 2008). Most deaths have occurred in China, Vietnam, and Indonesia and are usually due to acute respiratory death syndrome (Kawachi et al., 2009) and well-described cases do not include neurologic symptoms and signs (Hien et al., 2004). In a study of a 6-year-old boy who died of acute respiratory distress syndrome on the 17th day of illness, viral RNA and antigen were not detected in the brain or trachea but were detected in spleen, large and small intestine, and lung tissue, where it was restricted to the type II alveolar pneumocyte (Uiprasertkul et al., 2005). Positive-strand viral RNA was restricted to the lung and intestine, indicating that viral replication was occurring in only these two organs. Viral dissemination was found in another patient by immunohistochemical demonstration of viral antigen in bone marrow, glial cells, and neurons in the brain and in lymphocytes, but viral replication by culture was found only in the lung and upper respiratory tract (Zhang et al., 2009). In a careful study of two adults and a fetus, viral antigen and viral RNA by *in situ* hybridization with sense and antisense probes was detected in type II alveolar epithelial cells, ciliated and non-ciliated tracheal cells, T cells of the lymph node, neurons in the brain, and cytotrophoblasts of the placenta (Gu et al., 2007). This widespread dissemination of replicating virus was confirmed by strand-specific RT-PCR, real-time RT-PCR, and nucleic acid sequence-based amplification H5 detection assays, yet despite the evidence for viral replication in the brain, there was no histopathologic evidence for inflammation in the brain.

Viral replication may not be specifically pathogenic in the brain. The alternative explanation is indicated by the numerous studies finding hyperinduction of cytokines and chemokines associated with multiorgan failure and death (Cheung et al., 2002; Peiris et al., 2004; de Jong et al., 2005, 2006; Uiprasertkul et al., 2005; To et al., 2010). In 18 individuals with H5N1 infection the low blood T lymphocyte counts and high levels of proinflammatory cytokines and chemokines were correlated with high pharyngeal viral loads and detection of viral RNA in blood and rectum, particularly in fatal cases (de Jong et al., 2006). Although suppression of the host inflammatory response may confer some therapeutic benefit, anecdotal experience with corticosteroids did not improve the clinical outcome in H5N1 infection (Oner et al., 2006). In a murine model study anti-TNF-α antibodies reduced illness severity (Hussell et al., 2001), suggesting more exploration of this strategy.

CONCLUSION AND FUTURE OF INFLUENZA INFECTIONS OF HUMANS

Human and animal influenza viral infections have been present for centuries. Influenza virus has the ability to mutate frequently to a new strain as well as reassort some of its eight RNA segments when two strains are co-infected in the same cell. The result is that every year slightly different strains appear in the population, allowing for it to have a widespread circulation. Every decade or so a major change occurs in the HA or NA outer protein coat that enables the virus to become virulent to most of the world's population, setting forth a pandemic. The recent pandemic 2009 H1N1 means the prediction of future pandemics remains uncertain (Taubenberger et al., 2007).

As the human population becomes denser and the citizens of many countries live in close proximity to either pigs or birds, the risk of a virulent avian influenza strain mutating to enable both infection of humans and spread between humans is very real. Currently uncertain is whether the sporadic spread of avian H5N1 infection, which is very virulent in humans, will evolve to a highly pathogenic strain capable of human-to-human transmission. If so, we could face an influenza pandemic that carries a mortality rate as high as or higher than the 1918 influenza pandemic.

To date, the major approach of managing influenza infections is via prevention through yearly vaccination programs. While this is highly effective in either preventing or lessening the severity of the influenza, production of a new vaccine requires months, is expensive, and is hard to distribute quickly around the world, let alone in developed countries. However, the incubation period of influenza is only a few days and in the world of airplane travel could spread around the world in weeks before any vaccine could be developed. On the positive side, there are several new approaches in development toward producing influenza vaccines rapidly (Lambert and Fauci, 2010).

At present, we lack highly effective anti-influenza drugs. With respect to the neurologic complications of the latest influenza A H1N1 pandemic, there is no strong evidence that any of the existing anti-influenza drugs, including oseltamivir, were beneficial in treating the encephalopathy. There is a need to develop more potent anti-influenza medications that have application for a wide range of influenza strains and cross the blood–brain barrier.

Finally, we need a better understanding of how influenza virus causes the occasional neurologic complications. At present, evidence suggests that there may be several pathogenic mechanisms involved. If elevated blood or CSF cytokine levels are proven to be the cause, better agents to block the key cytokines are needed.

References

Agyeman P, Duppenthaler A, Heininger U et al. (2004). Influenza-associated myositis in children. Infection 32: 199–203.

Akaike T, Noguchi Y, Ijiri S et al. (1996). Pathogenesis of influenza virus-induced pneumonia: involvement of both nitric oxide and oxygen radicals. Proc Natl Acad Sci 93: 2448–2453.

Alling DW, Blackwelder WC, Stuart-Harris CH (1981). A study of excess mortality during influenza epidemics in the United States, 1968–1976. Am J Epidemiol 113: 30–42.

Alter M (1990). The epidemiology of Guillain–Barré syndrome. Ann Neurol 27 (suppl): S7–S12.

Amin R, Ford-Jones E, Richardson SE et al. (2008). Acute childhood encephalitis and encephalopathy associated with influenza. Pediatr Infect Dis J 27: 390–395.

Anderson LL, Vilensky JA, Duvoisin RC (2009). Review: Neuropathology of acute phase encephalitis lethargica: a review of cases from the epidemic period. Neuropathol Appl Neurobiol 35: 462–472.

Aoki Y, Lombroso CT (1973). Prognostic value of electroencephalography in Reye's syndrome. Neurology 23: 333–343.

Baltagi SA, Shoykhet M, Felmet K et al. (2010). Neurological sequelae of 2009 influenza A (H1N1) in children: a case series observed during a pandemic. Pediatr Crit Care Med 11: 179–184.

Barker WH, Mullooly JP (1980). Impact of epidemic type A influenza in a defined adult population. Am J Epidemiol 112: 798–811.

Belser JA, Szretter KJ, Katz JM et al. (2009). Use of animal models to understand the pandemic potential of highly pathogenic avian influenza viruses. Adv Virus Res 73: 56–97.

Bove KE, McAdams AJ, Partin JC et al. (1975). The hepatic lesion in Reye's syndrome. Gastroenterology 69: 685–697.

Bove KE, Hilton PK, Partin J et al. (1983). Morphology of acute myopathy associated with influenza B infection. Pediatr Pathol 1: 51–66.

Bratincsak A, El-Said HG, Bradley JS et al. (2010). Fulminant myocarditis associated with pandemic H1N1 influenza A virus in children. J Am Coll Cardiol 55: 928–929.

Brownstein DG, Johnson EA, Smith AL (1984). Spontaneous Reye's-like syndrome in Balb/c by J mice. Lab Invest 51: 386–395.

Brunner RL, O'Grady DJ, Partin JC et al. (1979). Neuropsychologic consequences of Reye's syndrome. J Pediatr 95: 706–711.

Burnet F, Clark E (1942). Influenza: a survey of the last 50 years in the light of modern work on the virus of epidemic influenza. Macmillan, Melbourne, pp. 188–200.

Calhoun HA (1920). Histopathology of the brain and spinal cord in a case presenting a postinfluenzal lethargica encephalitis syndrome. Arch Neurol Psychiatry 3: 1–16.

Cameron CM, Cameron MJ, Bermejo-Martin JF et al. (2008). Gene expression analysis of host innate immune responses during lethal H5N1 infection in ferrets. J Virol 82: 11308–11317.

Centers for Disease Control and Prevention (2009). Neurologic complications associated with novel influenza A (H1N1) virus infection in children – Dallas, Texas, May 2009. MMWR Morb Mortal Wkly Rep 58: 773–778.

Centers for Disease Control, Prevention (2010a). Summary of 2009 monovalent H1N1 influenza vaccine data – vaccine adverse event reporting system. Available at, http://VAERS.hhs.gov/resources/2010flu/vaccinesummary_May07.pdf, Accessed May 2010.

Centers for Disease Control and Prevention (2010b). Preliminary results: surveillance for Guillain–Barré syndrome after receipt of influenza A (H1N1) 2009 monovalent vaccine – United States, 2009–2010. MMWR Morb Mortal Wkly Rep 59: 657–661.

Chen H, Smith GJD, Li KS et al. (2006). Establishment of multiple sublineages of H5N1 influenza virus in Asia: implications for pandemic control. Proc Natl Acad Sci U S A 103: 2845–2850.

Cheung CY, Poon LL, Lau AS et al. (2002). Induction of proinflammatory cyokines in human macrophages by influenza A (H5N1) viruses: a mechanism for the unusual severity of human disease? Lancet 360: 1831–1837.

Chiu SS, Tse CYC, Lau YL et al. (2001). Influenza A infection is an important cause of febrile seizures. Pediatrics 108: 1004–1005.

Chung B, Wong V (2007). Relationship between five common viruses and febrile seizures. Arch Dis Child 92: 589–593.

Communicable Disease Surveillance Center (1985). Reye's syndrome surveillance scheme: third annual summary report. Br Med J 291: 329–330.

Congy F, Hauw J, Wang A et al. (1980). Influenza acute myositis in the elderly. Neurology 30: 877–878.

Connor RJ, Kawaoka Y, Webster RG et al. (1994). Receptor specificity in human, avian, and equine H2 and H3 influenza virus isolates. Virology 205: 17–23.

Corey L, Rubin RJ, Hattwick MAW et al. (1976). A nationwide outbreak of Reye's syndrome. Am J Med 61: 615–625.

Corey LR, Rubin RJ, Hattwick MAW et al. (1977a). Reye's syndrome. clinical progression and evaluation of therapy. Pediatrics 60: 708–714.

Corey L, Rubin RJ, Thompson TR et al. (1977b). Influenza B-associated Reye's syndrome: incidence in Michigan and potential for prevention. J Infect Dis 135: 398–407.

Couceiro JN, Paulson JC, Baum LG et al. (1993). Influenza virus strains selectively recognize sialyloligosaccharides on human respiratory epithelium; the role of the host cell in selection of hemagglutinin receptor specificity. Virus Res 29: 155–165.

Cox NJ, O'Neil MC, Kendal AP (1977). Replication of animal viruses in differentiating muscle cells: influenza virus A. J Gen Virol 37: 161–173.

Darrach W, Emerson H, Stockard CR (1929). Epidemic encephalitis. Etiology, epidemiology, treatment. Columbia University Press, New York.

Davis LE (1987). Influenza B virus model of Reye's syndrome. Evidence for a nonpermissive infection of liver and brain. Lab Invest 32: 32–36.

Davis LE (2000). Diagnosis and treatment of acute encephalitis. Neurologist 6: 145–159.

Davis LE, Kornfeld M (1980). Influenza A virus and Reye's syndrome in adults. J Neurol Neurosurg Psychiatry 43: 516–521.

Davis LE, Kornfeld M (1986). Mouse influenza B virus model of Reye's syndrome: encephalopathy and microvesicular fatty metamorphosis of the liver by influenza B virus following intravenous administration in mice. Am J Pathol 122: 190–192.

Davis LE, Kornfeld M (2001). Experimental influenza B viral myositis. J Neurol Sci 187: 61–67.

Davis LE, Woodfin BM (1989). Reye's syndrome. In: RR McKendall (Ed.), Handbook of clinical neurology. Elsevier Science, Amsterdam, pp. 267–298.

Davis LE, Cole LL, Lockwood SJ et al. (1983). Experimental influenza B virus toxicity in mice. Lab Invest 48: 140–147.

Davis LE, Green CL, Wallace JM (1985). Influenza B virus of Reye's syndrome in mice: the effect of aspirin. Ann Neurol 18: 556–559.

Davis LE, Woodfin BM, Tran TQ et al. (1993). The influenza B virus mouse model of Reye's syndrome: Pathogenesis of the hypoglycemia. Int J Exp Pathol 74: 251–258.

Davis LE, Kornfeld M, Daniels RS et al. (2000). Experimental influenza causes a non-permissive viral infection of brain, liver and muscle. J Neurovirol 6: 529–536.

de Jong MD, Bach VC, Phan TQ et al. (2005). Fatal avian influenza A (H5N1) in a child presenting with diarrhea followed by coma. N Engl J Med 353: 686–691.

de Jong MD, Simmons CP, Thanh TT et al. (2006). Fatal outcome of human influenza A (H5N1) is associated with high viral load and hypercytokinemia. Nat Med 12: 1203–1207.

Deschamps D, Fisch C, Fromenty B et al. (1991). Inhibition by salicylic acid of the activation and thus oxidation of long chain fatty acids. Possible role in the development of Reye's syndrome. J Pharmacol Exp Ther 259: 894–904.

Deshmukh DR (1985). Animal models of Reye's syndrome. Rev Infect Dis 7: 31–40.

Deshmukh DR, Shope TC (1983). Arginine requirement and ammonia toxicity in ferrets. J Nutr 113: 1664–1667.

Deshmukh DR, Thomas PE (1985). Arginine deficiency, hyperammonemia and Reye's syndrome in ferrets. Lab Anim Sci 35: 242–245.

deVires HE, Blom-Roosemalen MC, van Oosten M et al. (1996). The influence of cytokines on the integrity of the blood–brain barrier in vitro. J Neuroimmunol 64: 37–43.

DeVivo DC (1984). Do animals develop Reye syndrome? Lab Invest 51: 367–372.

DeVivo DC (1985). Reye syndrome. Neurol Clin 3: 95–115.

Dimsdale H (1946). Changes in the Parkinsonian syndrome in the twentieth century. Q J Med 15: 155–170.

Dowdle WR (1999). Influenza A virus recycling revisited. Bull World Health Organ 77: 820–828.

Duvoisin RC, Yahr MD (1965). Encephalitis and Parkinsonism. Arch Neurol 12: 227–239.

Dvorackova I, Vortel V, Hroch M (1966). Encephalitic syndrome with fatty degeneration of viscera. Arch Pathol 81: 240–246.

Ekstrand JJ, Herbener A, Rawlings J et al. (2010). Heightened neurologic complications of children with pandemic H1N1 influenza. Ann Neurol 68: 762–766.

Elizan TS, Casals J (1983). The viral hypothesis in Parkinsonism. J Neural Transm 19 (suppl): 75–88.

Elizan TS, Madden DL, Noble GR et al. (1979). Viral antibodies in serum and CSF of Parkinsonism patients and controls. Arch Neurol 36: 529–534.

El-Said HG, Bradley JS, Shayan K et al. (2010). Fulminant myocarditis associated with pandemic H1N1 influenza A virus in children. J Am Coll Cardiol 55: 928–929.

Engblom E, Ekfors TO, Meurman OH et al. (1983). Fatal influenza A myocarditis with isolation of virus from the myocardium. Acta Med Scand 213: 75–78.

Erden I, Erden EC, Ozhan H et al. (2010). Echocardiolgraphic manifestations of pandemic 2009 (H1N1) influenza A virus infection. J Infect xx: 1–6.

Erkoreka A (2009). Origins of the Spanish influenza pandemic (1918–1920) and its relation to the first World War. J Mol Gen Med 3: 190–194.

Evans H, Bourgeois CH, Comer DS et al. (1970). Brain lesions in Reye's syndrome. Arch Pathol 90: 543–546.

Farrell MK, Partin JC, Bove KE et al. (1980). Epidemic influenza myopathy in Cincinnati in 1977. J Pediatr 96: 545–551.

Fields BN, Knipe DM, Howley PM et al. (2007). Fields' virology. Wolters Kluwer Health/Lippincott Williams & Wilkins, Philadelphia.

Fouchier RA, Munster V, Wallensten A et al. (2005). Characterization of a novel influenza A virus hemagglutinin subtype (H16) obtained from black-headed gulls. J Virol 79: 2814–2822.

Frank H, Wittekind C, Liebert UG et al. (2010). Lethal influenza B myocarditis in a child and review of the literature for pediatric age groups. Infection 38: 231–235.

Frankova V, Jirasek A, Tumova B (1977). Type A influenza: postmortem virus isolations from different organs in human lethal cases. Arch Virol 53: 265–268.

Friman G (1976). Serum creatine phosphokinase in epidemic influenza. Scand J Infect Dis 8: 13–20.

Fujimoto S, Kobayashi M, Uemura O (1998). PCR on cerebrospinal fluid to show influenza-associated acute encephalopathy or encephalitis. Lancet 352: 873–875.

Fujimoto Y, Shibata M, Tsuyuki M et al. (2000). Influenza A virus encephalopathy with symmetrical thalamic lesions. Eur J Pediatr 159: 319–321.

Fukumoto Y, Okumura A, Hayakawa F et al. (2007). Serum levels of cytokines and EEG findings in children with influenza associated with mild neurological complications. Brain Dev 29: 425–430.

Gamboa ET, Wolf A, Yahr MD et al. (1974). Influenza virus antigen in postencephalitic Parkinsonism brain. Detection by immunofluorescence. Arch Neurol 31: 228–232.

Gamboa ET, Eastwood AB, Hays AP et al. (1979). Isolation of influenza virus from muscle in myoglobinuric polymyositis. Neurology 29: 1323–1335.

Gambotto A, Barratt-Boyes SM, de Jong MD et al. (2008). Human infection with highly pathogenic H5N1 influenza virus. Lancet 371: 1464–1475.

Gao P, Watanabe S, Ito T et al. (1999). Biological heterogeneity, including systemic replication in mice, of H5N1 influenza A virus isolates from humans in Hong Kong. J Virol 73: 3184–3189.

Garigliany M-M, Habyarimana A, Lambrecht B et al. (2010). Influenza A strain-dependent pathogenesis in fatal H1N1 and H5N1 subtype infections in mice. Emerg Infect Dis 16: 595–603.

German-Diaz M, Pavo-Garcia R, Diaz-Diaz J et al. (2010). Adolescent with neuropsychiatric symptoms associated with novel influenza A (H1N1) virus infection. Pediatr Infect Dis J 29: 1–2.

Glasgow JFT (2006). Reye's syndrome. The case for a causal link with aspirin. Drug Saf 29: 1111–1121.

Glick TH, Ditchek NT, Salitsky S et al. (1970). Acute encephalopathy and hepatic dysfunction. Am J Dis Child 119: 68–71.

Golden GS, Duffell D (1965). Encephalopathy and fatty change in the liver and kidney. Pediatrics 36: 67–74.

Greco TP, Askenase PW, Kashgarian M (1977). Post-viral myositis: myxovirus-like structures in affected muscle. Ann Intern Med 86: 193–194.

Gu J, Xie Z, Gao Z et al. (2007). H5N1 infection of the respiratory tract and beyond: a molecular pathology study. Lancet 370: 1137–1145.

Guarner J, Falcon-Escobedo R (2009). Comparison of the pathology caused by H1N1, H5N1, and H3N2 influenza viruses. Arch Med Res 40: 655–661.

Haber P, Sejvar J, Mikaeloff Y et al. (2009). Vaccines and Guillain–Barré syndrome. Drug Saf 32: 309–323.

Hale BG, Albrecht RA, Garcia-Sastre A (2010). Innate immune evasion strategies of influenza viruses. Future Microbiol 5: 23–41.

Hall CB, Douglas RG, Geiman JM et al. (1979). Viral shedding patterns of children with influenza B infection. J Infect Dis 140: 610–613.

Haller JS (1975). Clinical experience with Reye's syndrome. In: JD Pollack (Ed.), Reye's syndrome. Grune and Stratton, New York, pp. 2–14.

Halpin TJ, Holtzhaur FJ, Campbell RJ et al. (1982). Reye's syndrome and medication use. JAMA 248: 687–691.

Hart TS (1904). Paralysis agitans: some clinical observations based on the study of 219 cases seen at the clinic of Professor M. Allen Starr. J Nerv Ment Dis 31: 177–178.

Hatta Y, Hershberger K, Shinya K et al. (2010). Viral replication rate regulates clinical outcome and CD8 T cell responses during highly pathogenic H5N1 influenza virus infection in mice. PLoS Pathog e1001139.

Hayden FG, Fritz RS, Lobo MC et al. (1998). Local and systemic cytokine responses during experimental human influenza A virus infection. J Clin Invest 101: 643–649.

Henle W, Henle G (1946). Studies on the toxicity of influenza viruses. II. The effect of intra-abdominal and intravenous injection of influenza viruses. J Exp Med 84: 639–660.

Heubi JE, Daugherty CC, Partin JS et al. (1984). Grade I Reye's syndrome – outcome and predictors of progression to deeper coma grades. N Engl J Med 311: 1539–1542.

Hien TT, Liem NT, Dung NT et al. (2004). Avian influenza A (H5N1) in 10 patients in Vietnam. N Engl J Med 350: 1179–1188.

Horimoto T, Nakayama K, Smeekens SP et al. (1994). Proprotein-processing endoproteases PC6 and furin both activate hemagglutinin of virulent avian influenza viruses. J Virol 68: 6074–6078.

Hu JJ, Kao CL, Lee PI et al. (2004). Clinical features of influenza A and B in children and association with myositis. J Microbiol Immunol Infect 37: 95–98.

Huang YC, Lin TY, Wu SL et al. (2003). Influenza A-associated central nervous system dysfunction in children presenting as transient visual hallucination. Pediatr Infect Dis J 22: 366–368.

Hurwitz ES, Schonberger LB, Nelson DB et al. (1981). Guillain–Barré syndrome and the 1978–1979 influenza vaccine. N Engl J Med 304: 1557–1561.

Hurwitz ES, Barrett MJ, Bregman D et al. (1985). Public Health Service study on Reye's syndrome and medications. N Engl J Med 313: 849–857.

Hurwitz ES, Barrett MJ, Bregman D et al. (1987). Public Health Service study on Reye's syndrome and medications. Report of the main study. JAMA 257: 1905–1911.

Hussell T, Pennycook A, Openshaw PJ (2001). Inhibition of tumor necrosis factor reduces the severity of virus-specific lung immunopathology. Eur J Immunol 31: 2566–2573.

Huttenlocher PR, Trauner DA (1978). Reye's syndrome in infancy. Pediatrics 62: 62–84.

Huttenlocher PR, Schwartz AD, Klatskin G (1969). Reye's syndrome: ammonia intoxication as a possible factor in the encephalopathy. Pediatrics 43: 443–454.

Ichiyama T, Nishikawa M, Yoshitomi T et al. (1998). Tumor necrosis factor-α, interleukin-1β, and interleukin-6 in cerebrospinal fluid from children with prolonged febrile seizures: comparison with acute encephalitis/encephalopathy. Neurology 50: 407–411.

Ichiyama T, Endo S, Kaneko M et al. (2003a). Serum cytokine concentrations of influenza-associated acute necrotizing encephalopathy. Pediatr Int 45: 734–736.

Ichiyama T, Isumi H, Ozawa H et al. (2003b). Cerebrospinal fluid and serum levels of cytokines and soluble tumor necrosis factor receptor in influenza virus-associated encephalopathy. Scand J Infect Dis 35: 59–61.

Ichiyama T, Morishima T, Isumi H et al. (2004). Analysis of cytokine levels and NF-κB activation in peripheral blood mononuclear cells in influenza-associated encephalopathy. Cytokine 27: 31–37.

Ichiyama T, Ito Y, Kubota M et al. (2009). Serum and cerebrospinal fluid levels of cytokines in acute encephalopathy associated with human herpesvirus-6 infection. Brain Dev 31: 731–738.

Ishigami A, Kubo SI, Ikematsu K et al. (2004). An adult autopsy case of acute encephalopathy associated with influenza A virus. Leg Med 6: 252–255.

Ito T, Couceiro JN, Kelm S et al. (1998). Molecular basis for the generation in pigs of influenza A viruses with pandemic potential. J Virol 72: 7367–7373.

Ito Y, Ichiyama T, Kimura H et al. (1999). Detection of influenza virus RNA by reverse transcriptase-PCR and proinflammatory cytokines in influenza-virus-associated encephalopathy. J Med Virol 58: 420–425.

Jacobs BC, Rothbarth PH, van der Meche FGA et al. (1998). The spectrum of antecedent infections in Guillain–Barré syndrome. Neurology 51: 1110–1115.

Jang H, Boltz D, Sturm-Ramirez K et al. (2009). Highly pathogenic H5N1 influenza virus can enter the central nervous system and induce neuroinflammation and neurodegeneration. Proc Natl Acad Sci U S A 106: 14063–14068.

Jelliffe S (1918). Nervous and mental disturbances of influenza. N Y Med J 108: 725–728, 755–757, 807–811.

Johnson GM, Scurletis TD, Carroll NB (1963). A study of sixteen fatal cases of encephalitis-like disease in North Carolina children. N C Med J 24: 464–473.

Kaiser L, Fritz RS, Strauss SE et al. (2001). Symptom pathogenesis during acute influenza: interleukin-6 and other cytokine responses. J Med Virol 64: 262–268.

Kaji M, Oseasohn R, Jordan WS et al. (1959). Isolation of Asian Virus from extrapulmonary tissues in fatal human influenza. Proc Soc Exp Biol Med 100: 272–275.

Kandun IN, Tresnaningsih E, Purba WH et al. (2008). Factors associated with case fatality of human H5N1 virus infections in Indonesia: a case series. Lancet 372: 744–749.

Kaplan JE, Katona P, Hurwitz ES et al. (1982). Guillain–Barré syndrome in the United States, 1979–1980 and 1980–1981. Lack of association with influenza vaccination. JAMA 248: 698–700.

Karjalainen J, Markku S, Heikkila N et al. (1980). Influenza A1 myocarditis in conscripts. Acta Med Scand 207: 27–30.

Kash JC, Basler CF, Garcia-Sastre A et al. (2004). Global host immune response: pathogenesis and transcriptional profiling of type A influenza viruses expressing the hemagglutinin and neuraminidase genes from the 1918 pandemic virus. J Virol 78: 9499–9511.

Kawachi S, Luong ST, Shigematsu M et al. (2009). Risk parameters of fulminant acute respiratory distress syndrome and avian influenza (H5N1) infection in Vietnamese children. J Infect Dis 200: 510–515.

Kawada JI, Kimura H, Ito Y et al. (2003). Systemic cytokine responses in patients with influenza-associated encephalopathy. J Infect Dis 188: 690–698.

Kennedy RH, Danielson MS, Mulder DW et al. (1978). Guillain–Barré syndrome: a 42-year epidemiologic and clinical study. Mayo Clin Proc 53: 93–99.

Kessler HA, Trenholme GM, Harris AA et al. (1980). Acute myopathy associated with influenza A/Texas/1/77 infection. Isolation of virus from a muscle biopsy specimen. JAMA 243: 461–462.

Kessler HA, Trenholme GM, Vogelzang NJ et al. (1983). Elevated creatine phosphokinase levels associated with influenza A/Texas/1/77 infection. Scand J Infect Dis 15: 7–10.

Khakpour M, Saidi A, Naficy K (1969). Proved Viremia in Asian influenza (Hong Kong variant) during incubation period. Br Med J 4: 208–209.

Kimura S, Ohtuki N, Nezu A et al. (1998). Clinical and radiological variability of influenza-related encephalopathy. Acta Paediatr Jpn 40: 264–270.

Kirton A, Busche K, Ross C et al. (2005). Acute necrotizing encephalopathy in Caucasian children: two cases and review of the literature. J Child Neurol 20: 527–532.

Klavinskis LS, Patterson S, Whiting PJ et al. (1985). Infection of cultured human muscle cells by influenza virus. J Gen Virol 66: 2335–2345.

Klenk HD, Rott R, Orlich M et al. (1975). Activation of influenza A viruses by trypsin treatment. Virology 68: 426–439.

Korteweg C, Gu J (2008). Pathology, molecular biology, and pathogenesis of avian influenza A (H5N1) infection in humans. Am J Pathol 172: 1155–1170.

Kotaka M, Kitaura Y, Deguchi H et al. (1990). Experimental influenza A virus myocarditis in mice. Light and electron microscopic, virologic and hemodynamic study. Am J Pathol 136: 409–419.

Kuiken T, Taubenberger JK (2008). Pathology of human influenza revisited. Vaccine 26 (Suppl 4): D59–D66.

Lambert LC, Fauci AS (2010). Influenza vaccines for the future. N Engl J Med 363: 2036–2044.

LaMontagne JR (1980). Summary of a workshop on influenza B viruses and Reye's syndrome. J Infect Dis 142: 452–465.

Langmuir AD (1979). Guillain–Barré syndrome: the swine influenza virus vaccine incident in the United States of America, 1976–77: preliminary communication. J R Soc Med 72: 660–669.

Lasky T, Terracciano GJ, Magder L et al. (1998). The Guillain-Barre Syndrome and the 1992–1993 and 1993–1994 influenza vaccines. N Engl J Med 339: 1797–1802.

Lazarowitz SG, Choppin PW (1975). Enhancement of the infectivity of influenza A and B viruses by proteolytic cleavage of the hemagglutinin polypeptide. Virology 68: 440–454.

Lebarbenchon C, Feare CJ, Renaud F et al. (2010). Persistence of highly pathogenic avian influenza viruses in natural ecosystems. Emerg Infect Dis 16: 1057–1062.

LeCount ER (1919). The pathologic anatomy of influenzal bronchopneumonia. JAMA 72: 650–652.

Lehmann NI, Gust ID (1971). Viraemia in influenza. A report of two cases. Med J Aust 2: 1166–1169.

Leichtenstern OML (1905). Influenza. In: J Mannaberg, OML Leichtenstern, R Ross et al. (Eds.), Malaria, influenza and dengue. WB Saunders, Philadelphia, pp. 523–719.

Leigh AD (1946). Infections of the nervous system occurring during an epidemic of influenza B. Br Med J 2: 936–938.

Levinson W (2006). Review of medical microbiology and immunology. Lange Medical Books/McGraw-Hill, New York.

Lewis HM, Parry JV, Parry RP et al. (1979). Role of viruses in febrile convulsions. Arch Dis Child 54: 869–875.

Likos AM, Kelvin DJ, Cameron CM et al. (2007). Influenza viremia and the potential for blood-borne transmission. Transfusion 47: 1080–1088.

Lin CH, Huang YC, Chiu CH et al. (2006). Neurologic manifestations in children with influenza B virus infection. Pediatr Infect Dis J 25: 1081–1083.

Linder FE, Grove RD (1943). Vital statistics rates in the United States, 1900–1940. Government Printing Office, Washington DC.

Linnemann CC, Shea L, Partin LC et al. (1975). Reye's syndrome: epidemiologic and viral studies, 1963–1974. Am J Epidemiol 101: 517–526.

Lipatov AS, Andreansky S, Webby RJ et al. (2005). Pathogenesis of Hong Kong H5N1 influenza virus NS gene reassortants in mice: the role of cytokines and B- and T-cell responses. J Gen Virol 86: 1121–1130.

Lovejoy Jr FH, Smith AL, Bresnan MJ et al. (1974). Clinical staging in Reye's syndrome. Am J Dis Child 128: 36–41.

Ludwig S (2006). Signaling and apoptosis in influenza virus-infected cells. In: Y Kawaoka (Ed.), Influenza virology: current topics. Vol. 12. Caister Academic Press, Norfolk, UK, pp. 323–340.

Lundberg A (1957). Myalgia cruris epidemica. Acta Paediatr 46: 18–31.

Lyon JB, Remigio C, Milligan T et al. (2010). Acute necrotizing encephalopathy in a child with H1N1 influenza infection. Pediatr Radiol 40: 200–205.

Madjid M, Miller CC, Zarubaev VV et al. (2007). Influenza epidemics and acute respiratory disease activity are associated with a surge in autopsy-confirmed coronary heart disease deaths: results from 8 years of autopsies in 34,892 subjects. Eur Heart J 28: 1205–1210.

Maines TR, Lu XH, Erb SM et al. (2005). Avian influenza (H5N1) viruses isolated from humans in Asia in 2004 exhibit increased virulence in mammals. J Virol 79: 11788–11800.

Mamas MA, Fraser D, Neyses L (2008). Cardiovascular manifestations associated with influenza virus infection. Int J Cardiol 130: 304–309.

Maricich SM, Neuol JL, Lotze TE et al. (2004). Neurologic complications associated with influenza A in children during the 2003–2004 influenza season in Houston, Texas. Pediatrics 114: e626–e633.

Marks G, Beatty WK (1976). Epidemics. Scribner, New York.

Marks JS, Halpin TJ (1980). Guillain–Barré syndrome in recipients of A/New Jersey influenza vaccine. JAMA 243: 2490–2494.

Marmot MG (1980). Parkinson's disease and encephalitis: the cohort hypothesis re-examined. In: FC Rose (Ed.), Clinical neuroepidemiology. University Park Press, New York, pp. 391–400.

Marttila RJ, Halonen P, Rinne UK (1977). Influenza virus antibodies in Parkinsonism. Comparison of postencephalitic and idiopathic Parkinson patients and matched controls. Arch Neurol 34: 99–100.

Mastrosovich MN, Klenk H-D, Kawaoka Y (2006). Receptor specificity, host-range, and pathogenicity of influenza viruses. In: Y Kawaoka (Ed.), Influenza virology: current topics. Vol. 4. Caister Academic Press, Norfolk, UK, pp. 95–137.

McCall S, Henry JM, Reid AH et al. (2001). Influenza RNA not detected in archival brain tissues from acute encephalitis lethargica or in postencephalitic Parkinson cases. J Neuropathol Exp Neurol 60: 696–704.

McKinley JC (1923). Lesions in the brain of a patient with postencephalitic paralysis agitans. Arch Neurol Psychiatry 9: 47–58.

Mejlszenkier JD, Safran AP, Healy JJ et al. (1973). The myositis of influenza. Arch Neurol 29: 441–443.

Melnick SC, Flewett TH (1964). Role of infection in the Guillain–Barré syndrome. J Neurol Neurosurg Psychiatry 27: 395–406.

Mickell JJ, Cook DR, Reigel DH et al. (1976). Intracranial pressure monitoring in Reye-Johnson syndrome. Crit Care Med 4: 1–7.

Middleton PJ, Alexander RM, Szymanski MT (1970). Severe myositis during recovery from influenza. Lancet 2: 533–535.

Mitchell H, Levin D, Forrest S et al. (2011). Higher replication efficiency of 2009 (H1N1) pandemic influenza than seasonal and avian strains: kinetics from epithelial cell culture and computational modeling. J Virol 85: 1125–1135.

Mizuguchi M, Yamanouchi H, Ichiyama T et al. (2007). Acute encephalopathy associated with influenza and other viral infections. Acta Neurol Scand 115: 45–56.

Mori I, Kimura Y (2001). Neuropathogenesis of influenza virus infection in mice. Microbes Infect 3: 475–479.

Mori I, Nagafuji H, Matsumoto K et al. (1997). Use of the polymerase chain reaction for demonstration of influenza virus dissemination in children. Clin Infect Dis 24: 736–737.

Mori I, Yokochi T, Kimura Y (2002). Role of influenza A virus hemagglutinin in neurovirulence for mammalians. Med Microbiol Immunol 191: 1–4.

Mori I, Goshima F, Koshizuka T et al. (2003). Differential activation of the c-Jun N-terminal kinase/stress-activated protein kinase and p38 mitogen-activated protein kinase signal transduction pathways in the mouse brain upon infection with neurovirulent influenza A virus. J Gen Virol 84: 2401–2408.

Morishima T, Togashi T, Yokota S et al. (2002). Encephalitis and encephalopathy associated with an influenza epidemic in Japan. Clin Infect Dis 35: 512–517.

Munster VJ, Schrauwen EJ, de Witt E et al. (2010). Insertion of a multibasic cleavage motif into the hemagglutinin of a low-pathogenic avian influenza H6N1 virus induces a highly pathogenic phenotype. J Virol 84: 7953–7960.

Nachamkin I, Shadomy SV, Moran AP et al. (2008). Anti-ganglioside antibody induction by swine (A/NJ/1976/H1N1) and other influenza vaccines: insights into vaccine-associated Guillain–Barré syndrome. J Infect Dis 198: 226–233.

Naficy K (1963). Human influenza infection with proved viremia. Report of a case. N Engl J Med 269: 964–966.

Nakai Y, Itoh M, Mizuguchi M et al. (2003). Apoptosis and microglial activation in influenza encephalopathy. Acta Neuropathol 105: 233–239.

Nelson DB, Sullivan-Bolyai JS, Marks JS et al. (1979). Reye syndrome: an epidemiologic assessment based on national surveillance 1977–1978 and a population based study in Ohio 1973–1977. In: JFS Crocker (Ed.), Reye's syndrome II. Grune and Stratton, New York, pp. 33–46.

Newland JG, Laurich M, Rosenquist AW et al. (2007). Neurologic complications in children hospitalized with influenza: Characteristics, incidence and risk factors. J Pediatr 150: 306–310.

Nicholson KG (1992). Clinical features of influenza. Semin Respir Infect 7: 26–37.

Noble GR, Corey L, Rubin RJ (1975). Virologic components of Reye's syndrome. In: JD Pollack (Ed.), Reye's syndrome. Grune and Stratton, New York, pp. 189–197.

Norman MG, Lowden JA, Hill DE et al. (1968). Encephalopathy and fatty degeneration of the viscera in childhood. II. Report of a case with isolation of influenza B virus. Can Med Assoc J 99: 549–554.

Okumura A, Abe S, Kidokoro H et al. (2009). Acute necrotizing encephalopathy: a comparison between influenza and non-influenza cases. Microbiol Immunol 53: 277–280.

Oner AF, Bay A, Arslan S et al. (2006). Avian influenza A (H5N1) infection in eastern Turkey in 2006. N Engl J Med 355: 2179–2185.

Ormitti F, Ventura E, Summa A et al. (2010). Acute necrotizing encephalopathy in a child during the 2009 influenza A (H1N1) pandemic: MR imaging in diagnosis and follow-up. AJNR Am J Neuroradiol 31: 396–400.

Paisley JW, Bruhn W, Lauer BA et al. (1978). Type A2 influenza viral infections in children. Am J Dis Child 132: 34–36.

Palese P, Compans RW (1976). Inhibition of influenza virus replication in tissue culture by 2-deoxy-2,3-dehydro-*N*-trifluoroacetylneuraminic acid (FANA): mechanism of action. J Gen Virol 33: 159–163.

Palese P, Schulman JL, Bodo G et al. (1974a). Inhibition of influenza and parainfluenza virus replication in tissue culture by 2-deoxy-2,3-dehydro-*N*-trifluoroacetylneuraminic acid (FANA). Virology 59: 490–498.

Palese P, Tobita K, Ueda M et al. (1974b). Characterization of temperature sensitive influenza virus mutants defective in neuraminidase. Virology 61: 397–410.

Partin JC, Schubert WK, Partin JS (1971). Mitochondrial ultrastructure in Reye's syndrome (encephalopathy and fatty degeneration of the viscera). N Engl J Med 285: 1339–1343.

Partin JC, Schubert WK, Partin JS et al. (1976). Isolation of influenza virus from liver and muscle biopsy, specimens from a surviving case of Reye's syndrome. Lancet 2: 599–602.

Patterson KD, Pyle GF (1991). The geography and mortality of the 1918–1919 influenza pandemic. Bull Hist Med 65: 4–21.

Peiris JS, Yu WC, Leung CW et al. (2004). Re-emergence of fatal influenza A subtype H5N1 disease. Lancet 363: 617–619.

Peiris JS, Cheung CY, Leung CY et al. (2009). Innate immune responses to influenza A H5N1: friend or foe? Trends Immunol 30: 574–584.

Philip RN, Lackman DB (1962). Observations on the present distribution of influenza A/swine antibodies among Alaskan natives relative to the occurrence of influenza in 1918–1919. Am J Hygiene 75: 322–334.

Poskanzer DC, Schwab RS (1963). Cohort analysis of Parkinson's syndrome. Evidence for a single etiology

related to subclinical infection about 1920. J Chronic Dis 16: 961–973.
Pradhan S, Pandey N, Shashank S et al. (1999). Parkinsonism due to predominant involvement of substantia nigra in Japanese encephalitis. Neurology 53: 1781–1786.
Ravenholt RT, Foege WH (1982). 1918 influenza, encephalitis lethargica, Parkinsonism. Lancet 2: 860–864.
Reid AH, McCall S, Henry JM et al. (2001). Experimenting on the past: The enigma of von Ecomono's encephalitis lethargica. J Neuropathol Exp Neurol 60: 663–670.
Remington PL, Rowley D, McGee H et al. (1986). Decreasing trends in Reye syndrome and aspirin use in Michigan, 1979 to 1984. Pediatrics 77: 93–98.
Reye RDK, Morgan G, Baral J (1963). Encephalopathy and fatty degeneration of the viscera: a disease entity of childhood. Lancet 2: 749–752.
Reynolds DW, Riley HD, LaFont DS et al. (1972). An outbreak of Reye's syndrome associated with influenza B. J Pediatr 80: 429–432.
Robinson RL, Shabida S, Madan N et al. (2003). Transient Parkinsonism in West Nile Encephalitis. Am J Med 115: 252–253.
Rogers MF, Schonberger LB, Hurwitz ES et al. (1985). National Reye syndrome surveillance, 1982. Pediatrics 75: 260–264.
Ropper AH (1984). Raised intracranial pressure in neurologic disease. Semin Neurol 4: 397–407.
Ropper AH (1992). The Guillain–Barré Syndrome. N Engl J Med 326: 1130–1136.
Rowe T, Cho DS, Bright RA et al. (2003). Neurological manifestations of avian influenza viruses in mammals. Avian Dis 47 (Suppl): 1122–1126.
Ruff RL, Secrist D (1982). Viral studies in benign acute childhood myositis. Arch Neurol 39: 261–263.
Russell EJ, Zimmerman RD, Leeds NE et al. (1979). Reye syndrome: computed tomographic documentation of disordered intracerebral structure. J Comput Assist Tomogr 3: 217–220.
Ryan MM, Procopis PG, Ouvrier RA (1999). Influenza A encephalitis with a movement disorder. Pediatr Neurol 21: 669–673.
Saija A, Princi P, Lanza M et al. (1995). Systemic cytokine administration can affect blood–brain barrier permeability in the rat. Life Sci 56: 775–784.
Sazgar M, Robinson JL, Chan AKJ et al. (2003). Influenza B acute necrotizing encephalopathy: a case report and literature review. Pediatr Neurol 28: 396–399.
Schlesinger JJ, Gandara D, Bensch KG (1978). Myoglobinuria associated with herpes-group viral infections. Arch Intern Med 138: 422–424.
Schonberger LB, Bregman DEJ, Sullivan-Bolyai JZ et al. (1979). Guillain–Barré syndrome following vaccination in the National Influenza Immunization Program, United States, 1976–1977. Am J Epidemiol 110: 105–123.
Schubert WK, Partin JC, Partin JS (1972). Encephalopathy and fatty liver (Reye's syndrome). In: H Popper (Ed.), Progress in liver diseases. Grune and Stratton, New York, pp. 489–510.
Semmler A, Hermann S, Mormann F et al. (2008). Sepsis causes neuroinflammation and concomitant decrease of cerebral metabolism. J Neuroinflammation 5: 38.
Servidei S, Miranda AF, Gamboa ET (1987). Infectivity of influenza B virus in cultured human muscle. Acta Neuropathol 73: 67–76.
Shaywitz SE, Cohen PM, Cohen DJ et al. (1982). Long-term consequences of Reye syndrome: a sibling-matched, controlled study of neurologic, cognitive, academic and psychiatric function. J Pediatr 100: 41–46.
Shinjoh M, Bamba M, Jozaki K et al. (2000). Influenza A-associated encephalopathy with bilateral thalamic necrosis in Japan. Clin Infect Dis 31: 611–613.
Shinya K, Shimada A, Ito T et al. (2000). Avian influenza virus intranasally inoculated infects the central nervous system of mice through the general visceral afferent nerve. Arch Virol 145: 187–195.
Shinya K, Ebina M, Yamada S et al. (2006). Avian flu: influenza virus receptors in the human airway. Nature 440: 435–436.
Shinya K, Makino A, Hatta M et al. (2011). Subclinical brain injury caused by H5N1 influenza virus infection. J Virol 85: 5202–5207.
Shope RE, Lewis PA (1931). Swine influenza. Experimental transmission and pathology. J Exp Med 54: 349–359.
Simonsen L, Clarke MJ, Schonberger LB et al. (1998). Pandemic versus epidemic influenza mortality: a pattern of changing age distribution. J Infect Dis 178: 53–60.
Sivadon-Tardy V, Orlikowski D, Rozenberg F et al. (2006). Guillain–Barré syndrome, greater Paris area. Emerg Infect Dis 12: 990–993.
Smith W, Andrewes CH, Laidlaw PP (1933). A virus obtained from influenza patients. Lancet 1: 66–68.
Stanley ED, Jackson GG (1966). Viremia in Asian influenza. Trans Assoc Am Physicians 79: 376–387.
Steininger C, Popow-Kraupp T, Laferi H et al. (2003). Acute encephalopathy associated with influenza A virus infection. Clin Infect Dis 36: 567–574.
Stieneke-Grober A, Vey M, Angliker H et al. (1992). Influenza virus hemagglutinin with multibasic cleavage site is activated by furin, a subtilisin-like endoprotease. EMBO J 11: 407–414.
Studahl M (2003). Influenza virus and CNS manifestations. J Clin Virol 28: 225–232.
Suciu EM, Muschner K, Witzleb W (1985). Cytotoxicity of influenza A virus for cultured heart muscle cells. Acta Virol 29: 487–492.
Sugaya N (2002). Influenza-associated encephalopathy in Japan. Semin Pediatr Infect Dis 13: 79–84.
Sullivan-Bolyai JZ, Corey L (1981). Epidemiology of Reye-syndrome. Epidemiol Rev 3: 1–26.
Svoboda DJ, Reddy JK (1975). Pathology of the liver in Reye's syndrome. Lab Invest 32: 571–579.
Szretter KJ, Gangappa S, Lu X et al. (2007). Role of host cytokine responses in the pathogenesis of avian H5N1 influenza viruses in mice. J Virol 81: 2736–2744.
Tabbutt S, Leonard M, Godinez RI et al. (2004). Severe influenza B myocarditis and myositis. Pediatr Crit Care Med 5: 403–406.

Takahashi M, Yamada T, Nakashita Y et al. (2000). Influenza virus -induced encephalopathy: clinicopathologic study of an autopsied case. Pediatr Int 42: 204–214.

Takanashi JI, Tada H, Kuroki H et al. (2009). Delirious behavior in influenza is associated with reversible splenial lesion. Brain Dev 31: 423–426.

Talon J, Horvath CM, Polley R et al. (2000). Activation of interferon regulatory factor 3 is inhibited by the influenza A virus NS1 protein. J Virol 74: 7989–7996.

Tam CC, O'Brien SJ, Rodrigues LC (2006). Influenza, *Campylobacter* and *Mycoplasma* infections, and hospital admissions for Guillain–Barré syndrome, England. Emerg Infect Dis 12: 1880–1887.

Tam CC, O'Brien SJ, Peterson I et al. (2007). Guillain–Barré syndrome and preceding infection with *Campylobacter*, influenza and Epstein–Barr virus in the general practice research database. Plos One 2: e344.

Taubenberger JK (2006). The origin and virulence of the 1918 "Spanish" influenza virus. Proc Am Philos Soc 150: 86–112.

Taubenberger J, Morens DM (2008). The pathology of influenza virus infections. Annu Rev Pathol 3: 499–522.

Taubenberger JK, Reid AH, Lourgens RM et al. (2005). Characterization of the 1918 influenza virus polymerase genes. Nature 437: 889–893.

Taubenberger JK, Morens DM, Fauci AS (2007). The next influenza pandemic. Can it be predicted? JAMA 297: 2025–2027.

To KKW, Hung IFN, Li IWS et al. (2010). Delayed clearance of viral load and marked cytokine activation in severe cases of pandemic H1N1 2009 influenza virus infection. Clin Infect Dis 50: 850–859.

Togashi T, Matsuzono Y, Narita M et al. (2004). Influenza-associated acute encephalopathy in Japanese children in 1994–2002. Virus Res 103: 75–78.

Toovey S (2008). Influenza-associated central nervous system dysfunction: a literature review. Travel Med Infect Dis 6: 114–124.

Trifonov V, Khiabanian H, Rabadan R et al. (2009). Geographic dependence, surveillance, and origins of the 2009 influenza A (H1N1) virus. N Engl J Med 361: 115–119.

Twu KY, Kuo R-L, Marklund J et al. (2007). The H5N1 influenza virus NS genes selected after 1998 enhance virus replication in mammalian cells. J Virol 81: 8112–8121.

Uiprasertkul M, Puthavathana P, Sangsiriwut K et al. (2005). Influenza A H5N1 replication sites in humans. Emerg Infect Dis 11: 1036–1041.

United States Department of Commerce (1976). Historical statistics of the United States: Colonial times to 1970. Government Printing Office, Washington DC.

Utian HL, Wagner JM, Sichel RJS (1964). "White liver" disease. Lancet 2: 1964–1965.

van den Brand JMA, Stittelaar KJ, van Amerongen G et al. (2010). Severity of pneumonia due to new H1N1 influenza virus in ferrets is intermediate between that due to seasonal H1N1 virus and highly pathogenic avian influenza H5N1 virus. J Infect Dis 201: 993–999.

Vascellari M, Granato A, Trevisan L et al. (2007). Pathologic findings of highly pathogenic avian influenza virus A/duck/Vietnam/12/05 (H5N1) in experimentally infected Pekin ducks, based on immunohistochemistry and in situ hybridization. Vet Pathol 44: 635–642.

Verel D, Warrack AJN, Potter CW et al. (1976). Observations on the A2 England influenza epidemic: a clinicopathological study. Am Heart J 92: 290–296.

von Economo C (1917). Encephalitis lethargica. Wien Klin Wochenschr 30: 581–583.

von Economo C (1931). Encephalitis lethargica: Its sequelae and treatment. Oxford University Press, London.

Waldman RH, Hall WN, McGee H et al. (1982). Aspirin as a risk factor in Reye's syndrome. JAMA 247: 3089–3094.

Walford PA (1949). Vertigo and influenza. Br Med J 1: 821–822.

Walters JH (1960). Postencephalitic Parkinson syndrome after meningoencephalitis due to coxsackie virus group B, type 2. N Engl J Med 263: 744–747.

Wang X, Li M, Zheng H et al. (2000). Influenza A virus NS1 protein prevents activation of NF-kappa B and induction of alpha/beta interferon. J Virol 74: 11566–11573.

Wang G, Zhang J, Li W et al. (2008a). Apoptosis and proinflammatory cytokine responses of primary mouse microglia and astrocytes induced by human H1N1 and avian H5N1 influenza viruses. Cell Mol Immunol 5: 113–116.

Wang H, Feng Z, Shu Y et al. (2008b). Probable limited person-to-person transmission of highly pathogenic avian influenza A (H5N1) virus in China. Lancet 371: 1427–1434.

Wang GF, Li W, Li K (2010). Acute encephalopathy and encephalitis caused by influenza virus infection. Curr Opin Neurol 23: 305–311.

Webster RG, Rott R (1987). Influenza virus A pathogenicity: the pivotal role of hemagglutinin. Cell 50: 665–666.

Weiss TW, Stensaeth KH, Eritsland J (2010). Myocarditis in a juvenile patient with influenza A virus infection. Eur Heart J 31: 277.

Wells CE, James WR, Evans AD (1959). Guillain–Barré syndrome and virus of infleunza A (Asian strain); report of two fatal cases during the 1957 epidemic in Wales. AMA Arch Neurol Psychiatry 81: 699–705.

Winternitz MC, Wason IM, McNamara FP (1920). The pathology of influenza. Yale University Press, New Haven, CT.

Wolbach SB (1919). Comments on the pathology and bacteriology of fatal influenza cases, as observed at Camp Devens, Mass. Johns Hopkins Hospital Bull 30: 104.

World Health Organization (2008). Cumulative number of confirmed human cases of avian influenza A/H5N1 reported to WHO. WHO, Geneva.

Xu H, Yasui O, Tsuruoka H et al. (1998). Isolation of type B influenza virus from the blood of children. Clin Infect Dis 27: 654–655.

Yagishita A, Nakano I, Ushioda T et al. (1995). Acute encephalopathy with bilateral thalmotegmental involvement in infants and children: imaging and pathology changes. AJNR Am J Neuroradiol 16: 439–447.

Yoshikawa H, Yamazaki S, Watanabe T et al. (2001). Study of influenza-associated encephalitis/encephalopathy in children during the 1997 to 2001 influenza seasons. J Child Neurol 16: 885–890.

Zhang Z, Zhang J, Huang K et al. (2009). Systemic infection of avian influenza A virus H5N1 subtype in humans. Hum Pathol 40: 735–739.

Zhang J, Geng X, Ma Y et al. (2010). Fatal avian influenza (H5N1) infection in human, China. Emerg Infect Dis 16: 1797–1799.

Zitzow LA, Rowe T, Morken T et al. (2002). Pathogenesis of avian influenza A (H5N1) viruses in ferrets. J Virol 76: 4420–4429.