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MOVEMENT DISORDERS - ORIGINAL ARTICLE

Encephalitis lethargica and the influenza virus. II. The influenza pandemic of 1918/19 and encephalitis lethargica: epidemiology and symptoms

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Abstract This is the first of two papers which critically examine the relationship between the 1918/19 influenza pandemic and encephalitis lethargica (EL). The role of influenza in the etiology of EL was vigorously debated until 1924. It is notable, however, that the unitarian camp were largely reactive in their argumentation; while the influenza skeptics provided detail descriptions of EL and the features they argued to be unique or at least unusual, influenza supporters focused on sequentially refuting the evidence of their opponents. The impression which emerges from this debate is that the individual features identified by the skeptics were not absolutely pathognomic for EL, but, on the other hand, their combination in one disorder had not previously been described for any other disease.

Keywords Encephalitis lethargica · Epidemic encephalitis · Influenza · History of the neurosciences

Encephalitis lethargica (EL) is a neuropsychiatric disorder which in recent times has occurred only once in epidemic form: Between 1917 and 1930 it was reported from around the world, but was most prominent in Europe, North America and the Soviet Union. Despite intensive investigations throughout the 1920s, the etiology of the disorder was never conclusively determined. Even in its time, EL was remarkable in this obdurate refusal to divulge its origins. The Austrian pathologist Karl Landsteiner had demonstrated in 1908 that poliomyelitis, another prominent infectious neurological disease of the early 20th century, was transmissible in the form of a "filterable virus." The Viennese bacteriologist Anton Weichselbaum had in the late nineteenth century discovered *Diplococcus* (now *Streptococcus*) *pneumoniae*, which played an important role in the 1918/19 influenza pandemic, and the meningococcus (*Neisseria meningitides*), the pathogen of a third epidemic neurological disorder, cerebrospinal fever (meningococcal disease). By the 1930s, the influenza virus had been discovered and was being investigated, as were the arthropod-borne viruses (arboviruses) responsible for other encephalitides first described in the wake of the EL epidemic.

EL, however, defied elucidation. By the time EL began to fade from public consciousness, two major etiological theories had established themselves, without either being able to claim victory in what was at times as much a nationalistic as a scientific controversy: those who regarded the *herpes virus* as the major pathogen of EL, and those who assigned this role to *streptococcal infection*. Ironically, it would be a third position which gained ascendency in the post-EL years, although by 1930 it was regarded as the least likely explanation: that EL was essentially the outcome of infection with a particularly neurotropic form of the influenza "virus."

Background

Two distinct but related questions are being addressed in these papers:

(1) is the *influenza virus* a good candidate for the role of pathogen in EL?

The three papers of this series are based on a presentation by the author on June 21, 2007 at the annual meeting of the International Society for the History of the Neurosciences in Los Angeles.

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(2) was EL etiologically related to the historical disorder *influenza*?

Prior to 1930 "influenza" did not necessarily mean infection with the as yet undiscovered *influenza A virus*, and often explicitly referred to the presence in bodily fluids or tissues of one of the bacterial pathogens then implicated in the etiology of influenza: usually Pfeiffer's bacillus (*Haemophilus influenzae*), but also *Moraxella catarrhalis* or *Bacterium (Dialister) pneumosintes* (Jordan 1927a; Thomson et al. 1933).

From the outset, the relationship between EL and pandemic influenza had been subject to lively discussion. Constantin von Economo (1876–1931), author of the first paper on EL, was convinced that EL was a disorder *sui generis*, a distinct condition and not simply a neurological response to influenza (Economo 1917a; 1919; 1929a, pp. 138–146). Some who shared his view nevertheless suspected that EL and influenza might be somehow related, just as measles and whooping cough were then regarded as allied disorders as they often occurred together in a population. At the other extreme, the controversial British epidemiologist Francis Crookshank (1873–1933) argued that influenza, EL, poliomyelitis and a host of other disorders observed in the past few centuries were variant forms of a single disease, "epidemic encephalomyelitis" (Crookshank 1922, pp. 64–102).

More common in the "unitarian camp" were those who interpreted EL either as a neurologic form of influenza (*Kopfgrippe*: 'head' or 'brain influenza'), or as the pathologic expression of a normally benign infection exulted by pre- or co-infection with influenza. The unitarian hypothesis was most popular during the early years of the EL epidemic, primarily on the basis that both EL and pandemic influenza first came to prominence in 1917/18. This approximate contemporaneity, together with the unsettled definition of "influenza," resulted in the intuitively attractive linking of the two diseases during the first half of the 1920s. But as fresh EL cases continued to be diagnosed despite the passing of the influenza pandemic, the unitarian position lost ground, and was revived only after EL itself appeared to have vanished.

What was the epidemiologic relationship between the 1918/19 influenza pandemic and EL?

In 1982, Ravenholt and Foege (Centers for Disease Control, USA) discussed two sets of epidemiological data which supported the etiological significance of influenza in EL. In the first, the distributions of influenza–pneumonia deaths (by month of death) and of 142 EL deaths (by month of illness onset) in Seattle-King County (northwest USA) between 1918 and 1926 were compared. Peaks in the onset of fatal EL (winters of 1919/20, 1920/21, 1922/23) trailed by about 12 months peaks in influenza deaths, while the winter of 1920/21, with few influenza deaths, was associated with a dearth of EL deaths the following winter. The EL peaks, on the other hand, were not correlated with the regular seasonal pattern of "other pneumonia/bronchitis deaths." The second dataset was even clearer: the rise and fall of an EL-like disorder in Western Samoa paralleled that of influenza during the 1918/19 pandemic, whereas in neighboring American Samoa the maritime quarantine which prevented importation of influenza apparently also excluded EL (Ravenholt and Foege 1982).

The Ravenholt–Foege data are cogent, but not compelling. The Western Samoan "EL cases," for example, were actually described in death records as *fa-aniniva*, or 'fatal disease of the head.' Given the difficulties associated with establishing what constituted authentic EL in western countries, it would be speculative to interpret all *fa-aniniva* as genuine EL, particularly in the absence of neuropathological data. The data for Seattle are stronger in this respect, but are nevertheless subject to a problem recognized by the authors: the data include only a subset of all EL cases, those with a fatal outcome. The correlation established by these authors would be more convincing had the number of *cases* of each disease, rather than *deaths*, been analyzed. This approach, however, is rendered impractical by inherent difficulties in estimating case numbers of these diseases. EL might be reported early in its course by an informed physician, but more frequently following the later presentation of post-encephalitic sequelae, or even *post mortem* on the basis of neuropathology. In Australia, for example, the *reported EL deaths* for a given period often exceeded the number of *reported cases* (Foley, unpublished data). It was also generally recognized that a proportion—perhaps the majority—of EL infections were undiagnosed or unreported (see, for example, Neel 1927; Amsel 1931).

Timing of the influenza and EL epidemics

The Ravenholt–Foege data are thus interesting, but not conclusive. This is especially the case as the literature of the 1920s is replete with reports in which a discernible link between EL and influenza had been explicitly excluded.

There is, however, even stronger evidence for an etiological distinction: the long-term dissonance between the rhythms of EL and influenza epidemiology. Particularly significant is that EL cases were reported in numbers *before* pandemic influenza cast its shade over Europe. Leaving aside putative individual cases prior to the First World War, the first major appearance of what would later be termed "EL" was in 1915 in France (Cruchet 1928; Cruchet et al. 1917). Economo's cases were described in early 1917 (Economo

1917a, b), the first English cases were recorded in early 1918 (as "botulism"; Hall 1918; Harris 1918). Further cases from 1915 to 1917 had been unrecognized and were only diagnosed retrospectively (for example, Hall 1924, p. 7). Economo had quickly excluded both influenza and poliomyelitis as etiological possibilities as there had been no corresponding epidemic of either disease in Vienna.

These early EL reports all pre-date the arrival in Europe of the first wave of pandemic influenza in May 1918, and occurred long before the deadly second wave of August–November 1918. The third and final wave of the influenza pandemic receded from Europe in early 1919, before EL had achieved its peak in most countries. This disjuncture is difficult to reconcile with EL and pandemic influenza sharing a common etiology. The Berlin physician Werner Gottstein argued in his doctoral thesis (published: 1922) that influenza had been present in Europe prior to 1918, that it was indeed impossible to determine the beginning or end of an epidemic, and upon this basis asserted that no EL cases had been described in a authentically "influenza-free" period. Even should one accept his argument, some alignment between the rise and fall of influenza and EL would be expected; it was the lack of such a correlation between EL and poliomyelitis data that an etiologic link between these two considerably more similar disorders had been rejected.

The *peak year for EL* differed from place to place. For most European countries it occurred in 1920/1921, but there were significant exceptions, the most prominent being the dramatic 1924 outbreak in Great Britain (British Medical Association 1926). Influenza throughout the period in question, however, was more consistent in its ebb and flow across Europe, with the consequence that no correlation between occurrences of the two disorders is evident.

These epidemiological discrepancies cannot be ascribed to an *interval between infection with influenza and the development of EL*. There was typically a symptom-free interval between the acute and chronic stages of EL, but proposing that a similar interval existed between influenza infection and symptomatic EL is purely speculative. This is particularly true in light of the common finding that post-influenzal nervous symptoms manifested themselves within a few weeks of the onset of influenza (for example, Marcus 1920). Finally, while recidivism was a noted feature of influenza, relapses generally involved the return of catarrhal symptoms and prostration, not the evolution of a completely new clinical picture (Jordan 1927c, pp. 286f; Thomson et al. 1933, pp. 225–227).

Evidence for the independence of EL from influenza outbreaks increased through the 1920s. The American epidemiologist Edwin Oakes Jordan (1866–1936) analyzed published data for various American cities between 1918 and 1923 and could discover no consistent relationship (Jordan 1927b). Similarly, the course of the major British epidemic of 1924, the greatest single outbreak in the history of EL, was not paralleled by changes in influenza statistics:

> In some places the peak of influenza (measured by reported mortality) anticipates that of encephalitis (reported cases) by many weeks, as in London, while in others, as in Manchester, encephalitis begins to wane before influenza reaches its highest point. (Jordan 1927b; see also Health Section (League of Nations) 1922–1936, July 1924)

There were also areas where the rise and fall of EL and influenza were inversely related, and the case of Portugal where EL *preceded* influenza (Jorge 1924). Similar disconnectedness was reported elsewhere (Jorge 1920; Lafora 1920; Strümpell 1920; Micheli 1921; Pecori 1921; Reys 1922; Stallybrass 1923; Sterling 1923; British Medical Association 1926). In the United States, the influenza pandemic moved with incredible speed from east to west, whereas EL required almost a year to cover the same distance. The difference was even more frappant in Europe, as the sluggish spread of EL during the 1919/1920 epidemics was generally from east to west, whereas the lightning propagation of influenza pursued the opposite direction (Jordan 1927c, pp. 334f).

The epidemiological situation was nicely encapsulated by David and Robert Thomson (Pickett-Thomson Research Laboratory, London), who concluded their discussion of EL in an encyclopedic review of influenza thus:

> No doubt in a disease like influenza, which is characterised by an enormous high attack rate in which during pandemic periods anything up to 50 per cent or more of the population is attacked, a certain number of nervous diseases which occur during or following an epidemic are almost certain to be attributed directly or indirectly to the influenza attack, although doubtlessly they would have appeared sooner or later in any case. In this respect, it has often been observed that the first symptoms of general paralysis of the insane appeared to follow an attack of influenza (Thomson et al. 1934, pp. 848f).

In summary, the temporal overlap between pandemic influenza and EL was limited to the height of the influenza pandemic; EL was extant in parts of Europe both before and long after this window. Further, there is no evidence to suggest that EL occurred in North America before it appeared in Europe, but this may well have been the case for influenza (Barry 2004; but see Oxford et al. 2006). Finally, acute EL cases continued to be reported in sizeable numbers until the 1930s, long after the end of the 1918/19 influenza pandemic, and following marked changes in the epidemiologic and clinical characteristics of influenza itself

(reports and statistics published regularly in Office International D'hygiène Publique 1920–1936; Health Section (League of Nations) 1922–1926, 1922–1936).

Comparative severity of influenza and EL epidemics

Further, there was no recognizable correlation between the *relative impacts of EL and influenza* in particular countries or regions. In the most populous regions on Earth, researchers identified only a handful of EL cases, and in neither India nor China did the distribution of cases concord with the course of the influenza pandemic (for example Malone and Maitra 1919/20; Pfister 1926, 1929; Dhunjibhoy 1929). British India bore the brunt of global mortality associated with the 1918/19 influenza pandemic, accounting for about half of all lives lost (and equivalent to almost 9% of the Indian population: Mills 1989; Johnson and Mueller 2002), but here EL was a comparative rarity throughout the 1920s. This cannot be attributed to poor record-keeping, as investigators diligently sought cases in non-western countries in the hope that they might illuminate the EL problem.

Communicability

A further objection to the unitarian position is that the 1918/19 influenza was highly *contagious* (to a greater extent than the 1890s pandemic), whereas EL seemed extremely difficult to transmit. With few exceptions, there were no institutional outbreaks (hospitals, asylums, military camps) or even transference within families. The Prague pathologist Franz Lucksch (1872–1952) reported that there was no evidence in Germany for even a single person-to-person transmission of EL (Lucksch 1928). Silent carriers may have played a role in its dissemination, as in poliomyelitis, but would still not entirely overcome the epidemiological difficulties which encumbered the unitarian position (see, for example, Levaditi 1922; Stiefler 1922, pp. 201–213). On the other hand, mortality in EL appeared to be much greater (as high as 40% in Europe during its early years, compared with 1–2% for influenza), although the possibility of *formes frustes* (cases of infection where no or only rudimentary symptoms developed) might have confounded estimates of the death rate (for example, Netter 1920a; Alexander 1921; Levaditi et al. 1921; Roger and Blanchard 1921; Stern 1926). Even transplacental transmission was more the exception than the rule, and the few cases reported impressed some observers as evidence for the specificity of the EL virus (Jorge 1920). Influenza was a very public invader, while EL was much stealthier; those who contracted influenza generally returned to full health within months, whereas survival of the acute phase of EL was often the segue to lifelong debility.

Age and gender

The preferred *age of onset* by EL did not vary significantly throughout the 1920s, with those aged 12–35 years most at risk. While this age range also figured prominently in the mortality statistics for the 1918/19 influenza, lending the mortality curve its atypical W-shape, it is notable that the curves for succeeding influenza epidemics (some of which involved local mortality rates higher than those of the "great influenza") had by 1920 resumed the usual U-shape (Collins 1945; Crome 1954). EL generally spared infants to a greater extent than did influenza (Almasio 1921).

Finally, influenza played no favorites with respect to *gender*, but it was widely reported that there were up to twice as many male as female EL cases, although the prognosis in the latter tended to be worse (Stern 1936). On the other hand, the analysis of 122 United States EL cases indicated that 54% occurred without preceding influenza—but that 71% of EL cases *with* preceding influenza were male, while the numbers of cases without influenza were evenly divided between the genders. Curiously, the influenza attack rate in EL patients (46%) was higher than for the general American population (c. 30%; Smith 1921).

Were EL-like disorders reported during other influenza epidemics?

The second major argument for the unitarian hypothesis is that EL-like disorders had been reported during previous influenza epidemics. Historically minded authors pointed to episodes of "sleeping sickness" in the wake of previous influenza epidemics, most famously those of 1580, 1712 and 1831–1833, as well as the *nona* of the 1890s pandemic (reviewed: Crookshank 1918/1919; Ebstein 1921; Kayser-Petersen 1923).

Medical journals of the late nineteenth century teemed with cases of influenza sufferers reportedly crippled physically or psychiatrically by the disorder. More recently, influenza-associated encephalopathy (largely restricted to younger persons, as was EL) and a variety of neurological sequelae of influenza have been described, including Guillain-Barré and Reye's syndromes (Toovey 2008). It might therefore seem reasonable to suppose that EL was simply chronic influenza in yet another nervous guise.

The 1889–1892 influenza pandemic and influenza encephalitis

The 1889–1892 influenza pandemic, initially recognized as such in St. Petersburg (for which reason it was dubbed the "Russian influenza"; the Russians themselves traced it to Bukhara in Uzbekistan), swept the world in a series of

annual waves for four winters. It was vigorously investigated by scientific investigators and government enquêtes, and remained the yardstick for assessing the impact of influenza until the 1918/1919 pandemic (reviewed: Leyden and Guttmann 1892; Thompson 1892; Wolff 1892; Parsons 1893).

The 1889–1892 influenza pandemic was strongly associated with neurological and psychiatric symptoms, to such an extent that the German-English neurologist Julius Althaus (1833–1900) characterized the infection, returning after several decades' absence from Europe, as primarily a disorder of the central nervous system. He described three major forms of influenza—nervous, gastro-intestinal and catarrhal, according to their most prominent features—and noted that, in any particular epidemic year, one of these forms tended to dominanate to the relative exclusion of the others (Althaus 1892). Nervous symptoms linked to influenza ranged from headache, muscular pain and weariness to paralyses of varying degree, as well as conditions resembling fully elaborated psychoses. Kraepelin (1890), for example, remarked that he had "the opportunity during the recent influenza epidemic to observe a great series of psychiatric disturbances which could be linked with various degrees of confidence to the prevailing epidemic." Indeed, "post-influenzal psychoses" provided impetus to investigation of exogenous factors in the etiology of psychoses in general, one of the most vigorously debated topics in neurology and psychiatry until the Second World War (see, for example, Bonhoeffer 1912; Krisch 1930).

Post-influenzal encephalitis was described in detail at this time by the respected German clinician Otto Leichtenstern (1845–1900) in his monograph on the pandemic (1896, 1912). Leichtenstern characterized this encephalitis as:

> beginning in an abrupt, apoplectiform manner, either at the very beginning or at the height of the influenza, with high fever and grave central brain symptoms (delirium, sometimes unconsciousness, coma, epileptoid cramps, Jacksonian epilepsy, etc.). The clinical picture is often so similar to apoplexy caused by brain hemorrhage or embolism with obligate hemiplegia that it is only the usually young age of the patient, the acute onset with chills, the concomitant high fever and the occurrence of such cases during an influenza epidemic which permits distinction from a normal case of apoplexy (Leichtenstern 1912, p. 157).

Leichtenstern's encephalitis was thus an extremely violent assault upon the victim and their nervous system; in some cases, it *preceded* the onset of the catarrhal symptoms. He specifically noted that *encephalitis grippalis* often attacked the cerebral motor zone, and that there had been no confirmed cases in which:

> localization on the floor of the third or fourth ventricles led to an acute hemorrhagic polioencephalitis superior or inferior. All reported cases of nuclear oculomotor paralysis had developed after the influenza had run its course, usually a considerable period afterward, without fever or notable cerebral symptoms, and thus along the lines of a degenerative neuritis or neuronucleitis (Leichtenstern 1912, p. 160f).

The onset of EL, in contrast, was usually less tempestuous, and EL rarely developed *during* a well-defined bout of influenza (or pneumonia). The German neurologist and leading EL expert Felix Stern (1884–1941) addressed this difference in 1936, attaching a brief discussion of influenza encephalitis as an appendix to his comprehensive depiction of EL:

> Influenza or epidemic encephalitis? *The difficulty is relatively small if significant encephalitic symptoms are presented in the course of influenza or of an influenza-like disease. Influenza encephalitis is, in any case, now quite rare; otherwise one can orient oneself diagnostically according to the two poles: Where the symptoms, frequently apoplectic in intensity, erupt suddenly at the height of severe catarrhal influenza, where Jacksonian fits and gross focal losses, such as hemiplegia, aphasia and even hemicerebellar disturbances develop, and the cerebrospinal fluid is clear or contains blood; then one thinks of focal influenza encephalitis. When the ailment commences with what is usually milder influenza or only after an influenza-like complaint, the onset is less abrupt and primarily in the form of brainstem symptoms, then one should suspect epidemic encephalitis* (Stern 1936, p. 456).

The "comatose form of influenza" and *la nona*

But Leichtenstern had also described a "comatose form of influenza," the discussion of which he separated from that of influenza encephalitis, attributing it to influenzal meningo-encephalitis (Leichtenstern 1912, pp. 166–168). He regarded it as less common but nonetheless well documented, in which a degree of somnolence approaching full coma, in the absence of other cerebral signs, supervened upon a period of high fever, "distinguishing it from other forms." The somnolence persisted for a period of hours to weeks, and could be associated with cataleptic or catatonic symptoms. It is notable that in his discussion of historical precedents for comatose influenza ("sleeping sickness" in Tübingen, 1712; the "cephalitis epidemica" of Sauvages) Leichtenstern expressed doubt that these earlier events were really cases of influenza, specifically because "it would not occur to any observer to apply similar names to the current epidemic [of influenza]."

Leichtenstern's comatose form of influenza was exceptional, and its neuropathology unknown. Nevertheless, it was often invoked by later proponents of the unitarian position, who, however, often confused this form with the more common influenza encephalitis. Significantly, Leichtenstern's much cited reference to "paralysis agitans" (parkinsonism) as a post-influenza complication was not part of his description of comatose influenza, but was rather included as an aside under "influenza epilepsy and other irritative motor signs," which also included chorea, hiccough and other phenomena as after-effects of influenza (Leichtenstern 1912, p. 169). Stern regarded these latter cases as "undoubtedly" being EL cases, while at the same time not committing himself to a direct causal relationship between influenza and EL (Stern 1928, p. 353).

The best described occurrence of somnolence associated with influenza was *la nona*. This mysterious disorder was initially described in northern Italy and adjacent areas of central Europe in the winter of 1889/1890, although (albeit dubious) cases were subsequently reported from as far away as Portsmouth and New York. The origin of the term *nona* (Italian = "nine") is obscure; it has been suggested that it referred to the number of days its victims might hope to survive. Some writers proposed the unlikely corruption of the word "coma" as its origin, while others related it to "nonna" ("grandmother"); it may simply refer to the year 1890 (*nonagesimo* = 90th). Whatever the truth, the disease caused anxious excitement in affected areas and in the popular press, where it was described as an extreme somnolence which often terminated in death (review: Longuet 1892).

Official investigations by the Italian and Austrian governments concluded that *nona* was simply a form of meningo-encephalitis associated with the then prevalent influenza. After 1890 the disorder was gradually forgotten by the medical community, but it survived in the memories of those who had experienced it; Economo, for example, was reminded by his initial EL cases of tales of the *nona* related by his grandmother. In the United Kingdom and United States, *nona* was briefly employed as a synonym for EL (Dragotti 1918; Anonymous 1919; Bassoe 1919; Smith 1921).

Too little was known about the *nona* to validly infer its identity with EL. The published medical literature was limited to a few cases; official circles dismissed it entirely. The only specific link between this curiosity and EL was the deep somnolence which drew puzzled attention, and even this similarity was more misleading than enlightening: it was very difficult to rouse a *nona* patient from sleep, whereas this was remarkably easy in EL. None of the other features associated with acute EL, most notably the ocular symptoms, were described in the scant literature devoted to the *nona*.

The ascertainable situation regarding EL-like disorders during the 1890s influenza pandemic was later summarized by Edwin Jordan:

> In point of fact, no unusual prevalence of encephalitis appears to have been noted in the United States or in Northern Europe during the influenza pandemic of 1889–1890, and the form of encephalitis that was occasionally observed seems to have been different clinically and anatomically from the present epidemic disease (Jordan 1927b).

Pre-1890 somnolent disorders

The dubiousness of the attempt to identify historical disorders with EL applies even more to proposed links between earlier "influenza"-related phenomena and EL, such as the "sleeping sickness" (*Schlafkrankheit*) of Tübingen in 1712. This event was much cited by many during the EL period, but few appear to have noticed that Economo had been quick to correct his own early reference to this episode. He admitted that his source had misconstrued the Latin original, in which the author noted that he himself had *not* seen evidence of the somnolence apparently reported elsewhere (cf. Economo 1929a, p. 13 and Camerarius 1715(1712)). The British epidemiologist Crookshank (1918/1919) argued that *Schlafkrankheit* had been in any case an erroneous transcription of *Schafkrankheit* or 'sheep disease'; similar terms were used throughout Europe until the early 1700s to refer to the barking cough of influenza and (probably) pertussis (see Glorez 1701, II, p. 128; Höfler 1899, p. 321).

In contrast, Economo (1929a, p. 13) regarded the 1695 description by Albrecht of Hildesheim of a "lethargic fever ending with bilateral strabismus" as being "obviously" a sporadic case of EL, but here there was no clear link with influenza. "Lethargic fevers" were periodically reported until the mid-nineteenth century, some of which were associated with "influenza" epidemics, but the term was used in connection with a range of infectious diseases, particularly abdominal typhus and scarlet fever, so that the connection with EL is tenuous at best. While respecting appreciation of historical antecedents, past epidemics can only be handled with great caution, especially where concepts as vaguely defined as "influenza" and "somnolence" are central to the discussion.

Post-1930 links between influenza and EL symptoms

Although isolated cases of parkinsonism attributed to influenza have been described since the 1920s pandemic, and despite the fact that the influenza A virus exhibits a certain tropism for the substantia nigra in laboratory

animals (Mattock et al. 1988; Takahashi et al. 1995; Yamada et al. 1996; Casals et al. 1998; Mihara et al. 2001; Takahashi and Yamada 2001), EL-like symptoms have not been associated to any degree with influenza. A causal association between the two disorders must therefore implicitly suggests that influenza between the World Wars was uniquely capable of eliciting EL in humans.

Has direct evidence of influenza infection in EL cases been forthcoming?

Attempts to find evidence in EL brains of infection with the influenza virus (such as the presence of specific nucleic acid) have generally met with negative results (review: McCall et al. 2008). It would be surprising, however, to find in a living person such evidence of an infection which had occurred several decades ago, and the chances of finding viral nucleic acid in archival brain material is even slimmer: one need only consider the efforts required by Taubenberger's group to find fragments of influenza nucleic acid material in the bodies of influenza victims (Taubenberger 2005). Even today, influenza virus and genetic material can only rarely be isolated from cerebrospinal fluid (CSF) or autopsied brain material in cases of presumed influenza CNS infection (Johnson 1998, pp. 214f; Toovey 2008). An Austrian study of influenza encephalopathy found that even highly sensitive PCR techniques could ascertain its presence in CSF in only 1 of 18 cases (Steininger et al. 2003).

The identification of a specific pathogen in *post mortem* brain tissue was also attempted during the 1890s and 1918/1919 influenza pandemics, with similarly limited success. Both Pfuhl (Kassel) and Nauwerck (Königsberg) identified the recently discovered Pfeiffer's bacillus (see Pfeiffer 1893) in hemorrhagic brain foci of influenza encephalitis cases (Pfuhl 1892; Nauwerck 1895; Pfuhl 1897), but these results were more frequently cited than replicated. Others isolated a variety of cocci, but could not be certain that their presence was not the result of secondary infection (Ribbert 1892; Parsons 1893).

The first organism isolated from an EL brain was Viennese pathologist Richard Wiesner's (1875–1954) diplostreptococcus (Wiesner 1917), and his findings were confirmed by others without clarifying their significance. Some of the most adamant supporters of the unitarian hypothesis supported their position by reference to the demonstration of Pfeiffer's bacillus in patients' body fluids or tissue; the Dublin physician Crofton (1925a, b), for example, reported success in the treatment of EL by administration of Pfeiffer's bacillus antigen prepared from the patients' urine or sputum. In Philadelphia, Stewart and Evans (1930) isolated the bacterium from nasopharyngeal washings of all 114 of their EL cases, most of whom were parkinsonian, and the sera of chronic EL patients agglutinated the Hammett strain of the Pfeiffer bacillus in all cases; the corresponding figures for 37 controls were 46 and 2%. On the basis of this work, the authors trialled the employment of soluble Pfeiffer bacillus antigen (at a dose of 10 pg!), and claimed to have achieved significant reduction of rigidity in their patients. The authors interpreted their results as indicating that chronic infection of the nasal sinuses with Pfeiffer's bacillus underlay the chronic symptoms of EL.

In his detailed 1920 study of EL, neuropathologist Herbert Siegmund (Cologne; 1893–1954) recorded the results of bacteriological examinations undertaken in 15 cases:

> In ten the result was totally negative, in five cases streptococci could be cultivated, which the bacteriological institute identified as small gram-positive diplostreptococci… In these same cases … streptococci could be demonstrated … in the subarachnoid fluid, the ventricle contents and … within vascular infiltrates and between the ependymal cells on the floor of the 4th ventricle. … Numerous bioassays in which we attempted to transmit the disease to guinea pigs, mice and rabbits by means of intradural, intraperitoneal and endocardial injection of ventricular fluid and brain tissue were unsuccessful (Siegmund 1920).

Several authors isolated various streptococci (Bernhardt and Simons 1919; Economo 1920a; House 1920; Reichert 1920; Bastai 1921; Dieckmann 1921; Reinhart 1922; Rosenow 1924; Jahnel 1925; Evans and Freeman 1926), but, as Bernhardt (1918) early opined, "[the] microorganism found in encephalitis lethargica is in any case not a specific pathogen, as it is also found in many cases of influenza in a broad range of organs as well as in influenza encephalitis". Groß (1923) commented that the isolated bacteria could induce the most serious hemorrhagic, purulent inflammations, so that it would be remarkable should the same organism cause only the circumscribed, microscopic changes observed in the EL brain.

The French medical bacteriologist and leading EL investigator Arnold Netter (1855–1936) argued that if one were to nominate a disorder with which EL might be related it would be poliomyelitis rather than influenza (in discussion to: Achard 1920; see also Bernard and Renault 1920; Netter 1920b). French authors, in fact, were generally skeptical from the beginning. The short review of the issue by the author of the most comprehensive of the early French EL monographs, Charles Achard (1866–1944)—a brevity reflecting his own skeptical position—included reference to a number of French instances of EL in the

absence of influenza. He suggested that distinct influenza and encephalitis "viruses" were each found in the nasopharynx, from where they spread to the entire body (Achard 1921, p. 189).

Contemporary assessment of blood and CSF pathology

Where significant hematological changes were reported, they were generally in the direction of leucocytosis in acute EL versus leucopenia in influenza (Vaidya 1918; Géronne 1920; Kraus and Pardee 1921; Berger and Untersteiner 1924; Model and Wolf 1925; Dobreff and Saprjanoff 1937). CSF findings offered nothing which alone could secure an EL diagnosis—increased sugar levels, weak pleocytosis, slight protein increase, a colloid pattern reminiscent of weak to moderate lues (but with a negative Wassermann reaction)—but they did aid differential diagnosis with respect to influenza, where CSF findings were generally negative (Grosz and Pappenheim 1919; Boveri 1920; Barré and Reys 1921; Eskuchen 1922; see also Rietti 1935, pp. 136–138; Achard 1921, pp. 70–83; Stern 1928, pp. 231–248).

The pathogen issue inevitably remained unresolved, as the etiology of neither influenza nor EL had been clarified by the time the EL epidemic had subsided. Ivy Mackenzie (Glasgow) succinctly expressed the consensus: "while nothing is known of the toxic agent except that it produces encephalitis, it is not the toxic agent of influenza or of poliomyelitis or of herpes" (Mackenzie 1927).

Were there symptoms common to both EL and influenza?

Early EL cases were characterized by the "classic triad" of moderate to high fever, somnolence and diplopia. In later cases, these acute symptoms were less marked, and the acute stage might even pass unnoticed; EL was often diagnosed retrospectively on the basis of "post-encephalitic symptoms," including behavioral problems in younger victims and neurological symptoms (parkinsonism, oculogyria) in older patients. It was only with the emergence of the chronic symptoms—despite clinical variability in the acute phase, the chronic phase was depressingly consistent—that many cases were recognized as EL; at least 30% of diagnosed cases included no suggestion of encephalitis in the patient's history (Achard 1921; Economo 1929a; Guillain and Mollaret 1932; Rietti 1935; Stern 1936). The diagnosis "EL" was eventually expanded to include cases which with the benefit of hindsight were dubious, but the fact remains that physicians, neurologists and psychiatrists were confident that EL cases could be distinguished from other possibilities on the basis of symptomatology and course.

Although differential diagnosis in living patients could be difficult (Baumann and de Leeuw 1933), the opposite was more frequently asserted. Even physicians who declared that they had never seen an EL patient without recent influenza regarded the two disorders as clinically distinguishable. Hall (1866–1951), Professor of Medicine in Sheffield and author of the most comprehensive monograph on EL to be published in England, was unequivocal: "If there is any connection between epidemic encephalitis and influenza it is unusually well concealed from the physician" (Hall 1924, p. 39). Sheffield was perhaps the city hardest hit by EL in England, particularly during the great epidemic of 1924, so that there was no shortage of case material upon which Hall could base his conclusion that neither in the acute nor in the chronic phase of the disorder was there a degree of similarity with influenza which would confuse a careful physician.

Influenza-like symptoms and EL

Reports of "influenza-like symptoms" early in the histories of patients diagnosed with EL, particularly where an acute encephalitic stage could not be identified, have often been interpreted as evidence for a causal relationship between EL and influenza. Although some patients retrospectively recalled "flu-like symptoms" as presaging the onset of their disorder, this by no means establishes that they had suffered influenza. "Flu-like symptoms" were also regarded, for instance, as typical for acute poliomyelitis. Both this phrase and "grippe" were often used, even in scientific publications, to indicate something closer to the meaning today associated by the general public with "flu"—a vague and undiagnosed feeling of ill-health and lethargy—rather than influenza *sensu strictu*. The reporting of such symptoms might also occur in response to prompting from the physician, as in this EL case:

> Nothing is known with certainty concerning infectious diseases, particularly influenza. After repeated questioning, the patient says that it is possible that he had experienced a mild grippe prior to the occurrence of his present complaints (Baumann and de Leeuw 1933).

The New York physician Sachs noted that in many cases, including the majority of those seen in consultation practice, a distinct episode of influenza had preceded the onset of the lethargic disorder by several weeks, similar to post-diphtheritic palsies which also occurred with a delay of weeks after the initial infection. But he also noted that:

> if this was a post-influenzal infection, it was curious that previous epidemics of influenza had not been followed more frequently by similar disorders. The

> condition was so different from anything that had occurred before that it was impossible that it should not have been noted (Sachs 1919).

Some authors even admitted making influenza diagnoses in EL cases, only to correct them when the characteristic signs of EL later appeared (Micheli 1921; Rossi 1924; Rietti 1935, pp. 41–43).

The skeptics' position was supported by many German medical dissertations. Among the most extensive was that of Baer, who in 1924 analyzed data for 134 EL patients: he found that influenza infection preceded the first EL signs by at least 3 months in seven cases and arrived at about the same time in 41, while in the great majority (86) there was no evidence of influenza in the case history.

The nature of "flu-like symptoms"

In reports where the nature of the "flu-like symptoms" was elaborated, *reference to catarrhal symptoms was remarkably rare*. Economo commented that, if EL and influenza shared a common etiology, "it is difficult to understand how, given the very large number of encephalitis cases, an accompanying respiratory illness was not seen more regularly and frequently" (Economo 1929b). Economo believed that the EL pathogen accessed the body via the airways, but, in contrast to influenza, did not propagate thence into the lower respiratory organs. Guizzetti (1920) similarly noted that autopsied EL cases did not present the tracheo-bronchial redness and swollen lymph nodes which were characteristic of the then prevalent influenza. Baumann and de Leeuw (1933) noted:

> The only conclusion we would like to provisionally derive from the descriptions by Stern and von Economo is that the deeper airways are infested in the initial stage of influenza encephalitis to a greater degree, while the infection of the respiratory tract in encephalitis lethargica is restricted to pharyngitis.

These authors also remarked that EL differed from influenza in that no major organ, apart from the brain and respiratory tract, were significantly affected (Siegmund 1921). There is some evidence, however, that the liver was implicated in EL (example, Rizzo 1924; O'Flynn and Critchley 1925; Graziani 1926; Schargorodsky and Scheimann 1927a,b).

EL patients who presented "flu-like" symptoms suffered more from pharyngitis than classical influenza symptoms. This is particularly interesting as it provides the potential seeds of a link between historical EL and the recently reported cases of EL-like disease associated with chronic streptococcal throat infections (Dale et al. 2004). Such infection of the respiratory tract should be distinguished from the centrally determined respiratory tics which were characteristic of chronic EL (review: Jelliffe 1927).

In any case, the prevalence of influenza (genuine and attributed) in 1918/1919 rendered quite high the possibility of co-incidental infection with both disorders (Millian 1919). As early as 1919, however, there were reports of multiple EL cases where no history of influenza could be established (for instance, Bassoe 1919). "It seems, however, to be definitely established that while some cases of epidemic encephalitis follow closely on the heels of an attack of influenza, others originate independently and have no traceable connection with ordinary clinical influenza" (Jordan 1927b). The problem was further aggravated by the recognition that at least a third of "post-encephalitic" cases did not include even "flu-like symptoms" in their histories: these were the cases of "post-encephalitic disorder without acute phase" (see, for example, Amsel 1931).

Comparison of symptoms in influenza and EL

Franz Högler (1920) discussed three cases he had observed in Vienna. In the first, encephalitis appeared 2½ months after light influenza, but it presented as an autonomous illness, characterized by extreme lethargy, although without impaired consciousness or delirium; the clinical symptoms were all referable to discrete brainstem lesions. His two other cases, in contrast, presented encephalitis as a complication of more serious influenza, and were marked by severe, non-localized cerebral manifestations, including deep somnolence and monoplegia. These two clinical syndromes, argued Högler, were clearly different clinical entities.

Economo recognized in his early cases not a variation of influenza, but rather a neuropathological picture akin to polioencephalitis (Economo 1917a). Similarly, while Cruchet was initially perplexed by the symptomatic variety of his cases, he classified them under the term "epidemic encephalomyelitis," and not as a sequel of the influenza which had affected northern France since at least 1915 (Cruchet et al. 1917). The first cases described in England were not confused with influenza, but with botulism. A close review of the medical literature published during the First World War, including the official military medical reports, also fails to reveal any allusion to influenza in cases which might be classified as EL. In short, the immediate judgment of those who encountered EL firsthand was that it constituted a new disorder, rather than an aberrant form of influenza (Schjerning 1921–1922; Macpherson et al. 1922/23; Bailey et al. 1929; Butler et al. 1943).

"Somnolence" in influenza encephalitis and EL

Somnolence was initially regarded as the primary symptom of EL, but extreme sleepiness could also accompany

influenza. There was evidently some confusion regarding the sleep which characterized acute EL, at least prior to 1924, and the prostration of influenza; Economo curtly remarked that "someone sleeping for a few days after a serious bout of influenza has nothing to do with lethargic encephalitis" (Economo 1920b). Abrahams (London) commented in 1922 on the difference between the "sleep" of EL and that of influenza encephalitis. He recorded that most patients presenting the comatose form of influenza during the 1918/1919 pandemic suffered insomnia, but that some cases slipped into coma for a period of hours to a few days. Further:

> The patient, whilst completely unconscious of his surroundings with total absence of any suffering, would move restlessly from side to side with his head thrown back and mouth partly opened. Such a case presented a particularly ghastly ensemble when to these features were added a sickly yellow pallor of the hollow sunken cheeks, pallid lavender hue of lips and ears, rapid sighing respirations, and incontinence of urine and fæces with a constantly heavy smell of a more or less intolerable character (Abrahams 1922).

This contrasted sharply with typical depictions of EL sleep:

> During the now increasing somnolence it is not unusual to observe patients, as soon as they are left to themselves, fall asleep while sitting or standing, and even while walking or during meals, with indications of tiredness and yawning, with food in their mouths. They have the appearance of being in a light slumber or sometimes even of deep sleep with its typical breathing pattern, even snoring. If aroused by calling or shaking, they wake up quickly and completely, are well oriented and fully conscious, and can respond appropriately to questioning. They are fully aware of the situation, execute all requests promptly, get up when requested, walk about, but, if left to themselves, soon relapse into sleep. This sleep therefore appears deceptively similar to normal sleep (Economo 1929a, p. 41).
>
> Some lethargic patients state that during the whole time that they were supposed to be asleep that they could hear everything that was going on around, but could not rouse themselves. In many apparently asleep, one is surprised on asking a question to find how readily it is answered, without any apparent waking up. In other cases the reply might be delayed an appreciable time, but shows clearly that the question was understood (Hall 1924, p. 73).

Sachs (1919) commented in a similar vein: "the patient lay inert with closed eyes and expressionless face but was apparently aware of what was going on about him and readily responded by nodding to questions that were put to him in a low tone of voice." This lethargy typically lasted from a few days to a few weeks; in exceptional cases it might last for months, but in such cases it tended to progress to a deeper form, sometimes to a comatose state from which recovery was unlikely.

The course of EL as a distinguishing factor

Based on their extensive experience (81 cases at the Johns Hopkins Hospital), Happ and Mason (1921) were assisted in the differentiation of the two diseases by the mode of onset of the disorder (EL rarely announced itself as stormily as influenza encephalitis), the temperature course (the rise in EL was more gradual and less severe) and CSF analysis (during the acute phase: cellular and/or globulin increase).

Ocular symptoms, particularly diplopia and paralyses of accommodation, were often regarded as harbingers of EL. Such symptoms were, however, not pathognomic for EL, and were particularly familiar in diphtheria, as well as in influenza. During the 1890s pandemic, reports of ocular symptoms, as well as *N. facialis* paresis, were particularly common in the German literature. But *N. oculomotorius* (III cranial nerve) paralyses were relatively uncommon in influenza encephalitis, whereas they were characteristic of EL (review: Cords 1921). More typical for influenza, and also reported during the 1918/19 pandemic, was impairment of *N. abducens* (VI) function, leading to paralysis of the lateral rectus muscle, and of the *N. facialis* (VII); further, these paralyses were usually combined with significant cerebral symptoms (Stricker 1892; Böhmig 1919; Pichler 1919; Marcus 1920). Ocular muscle problems in general were less prominent during the 1918/1919 pandemic than in the previous pandemic (Zimmermann 1919; cf. Eversbusch 1890; Galezowski 1890; Uhthoff 1890).

Differences were also noted with respect to *changes in reflexes*. These were more common in the course of influenza encephalitis, often progressing in parallel with other symptoms. Altered reflex responses were less frequently encountered in EL, and often disappeared after only a few days. Diagnostically significant was also the general *absence of pyramidal abnormalities* in EL, whereas in influenza encephalitis they were all too common (Rümke-Bakker and Bouman 1921; Economo 1929a, pp. 47f.; Baumann and de Leeuw 1933).

But as Hall (1924, p. 109) noted: "'By their fruits ye shall know them' is indeed applicable to this disease." EL firmed as an autonomous clinical entity not because of its early years, which may well have been retrospectively consigned to the category of "historical curiosity," as an atypical neurological complication of influenza. It was the

chronic EL symptoms which set the disorder apart not only from influenza, but also from other alternatives: any of a constellation of psychiatric symptoms, oculogyria and parkinsonism, in particular, were regarded as sufficient to secure an EL diagnosis in the 1920s and 1930s, and no disorder has since been identified which reproduces these symptoms in the same manner as EL. Stern noted that the course of influenza encephalitis was generally rapid, and could resolve itself completely, although focal deficits might persist. But:

> Above all, there is neither in the older nor in more recent literature any report that any of these typical cerebral encephalitis cases, whether initiated in an apoplectic manner or acutely during severe pulmonary influenza, has later developed into an incurable chronic-neurasthenic and then myostatic stage (Stern 1928, pp. 352f).

This was perhaps the major reason influenza declined as an explanation for EL toward the end of the 1920s. Whereas recidivist influenza—a return to ill-health following apparent recovery—was a well-known and feared feature of the disorder, the complicated neuropsychiatric aspects of chronic EL were something new, different not in degree but in quality from chronic influenza. These phenomena—the behavioral changes, the neuro-vegetative abnormalities, parkinsonism—could not readily be reconciled with what was known of influenza. But this recognition required time, as physicians became better acquainted with the disease and its victims with the passage of time.

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