Without a doubt, bacterial pneumonia complicates the course of illness for many patients with influenza and accounts for some of its associated mortality [8]. Thus, prudent pandemic preparedness should include stockpiles of antibiotics, as well as vaccines and antiviral agents. But we should not stop there. The findings of Morens et al. [1] notwithstanding, poorly understood host factors surely explain much of what happened in 1918–1919 and what might happen again with the next pandemic [9]. Because most of the world’s people will not have access to pandemic vaccines and antiviral drugs, and many will also have difficulty obtaining antibiotics, other agents that target the host response must be sought [10]. For many, these widely available and inexpensive agents could mitigate the conditions that give rise to bacterial pneumonia.

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References

Reply to Fedson
Dr. Fedson has raised interesting points about fatal influenza during the 1918–1919 pandemic. A high attack rate and a low mortality rate among children have been characteristic of all influenza pandemics for which reliable data have been examined, going as far back as 1847 and 1889 [1, 2]. Similarly, seasonal influenza in partly immune populations is also typically associated with a low mortality rate among children beyond infancy and the early toddler years. This was also true of the 1918–1919 pandemic, which had a unique “W-shaped” age-specific mortality curve distinct from those of earlier and later pandemics, which had “U-shaped” mortality curves. (Pandemic influenza typically produces mortality peaks in infancy and old age, creating what is referred to as a “U-shaped” age-specific mortality curve; from 1918–1920, a third mortality peak for individuals 20–40 years old produced a “W-shaped” curve). Beyond the first few years of life, children thus seem to have a low risk of dying after influenza virus infection. The underlying determinants of this phenomenon are poorly understood. Many possibilities remain unexplored, including the maturational properties of the human airway, maturational differences in the immune response to viral infection, cell receptor patterns, and the possibility that the narrower airway lumina of children prevent larger virus-containing droplets from directly reaching cells in the lower respiratory tract.

Dr. Fedson draws an analogy between fatal 1918 influenza and modern fatal cases of H5N1 influenza, proposing that “cytokine storms” may have been involved in the 1918 fatalities. Even though insufficient data are available from fatal cases of H5N1 influenza, most deaths occur relatively late after onset. Patients with H5N1 influenza also typically receive early antibiotic therapy, as well as heroic emergency care and intensive supportive care [3]. There is also a possibility that unidentified host susceptibility factors may be involved [4]. We thus remain uncertain about the pathogenesis of fatal H5N1 disease. As we have noted [5], the clinical courses and laboratory findings of patients with H5N1 influenza appear to be different from those of typical severe human influenza cases.

Regarding Osler’s use of the term “toxemia” in the decades before 1918, this word was fairly commonly used at that time in descriptions of various infectious diseases and seems to have had multiple and often vague meanings. It could have been a description of “cytokine storms,” bacterial toxemia, sepsis, or the terminal pulmonary edema or massive alveolar damage associated with severe hypoxia and cyanosis. Given the hundreds of 1918–1919 publications we reviewed, we suspect that the latter was the most common correlate of “toxemia” in descriptions of 1918 influenza deaths. Pathologists and other physicians in 1918 generally agreed that the influenza–bacterial pneumonia combination seen during the pandemic differed very little in type, progression, and severity from the measles–bacterial pneumonia combination seen during the 1917 epidemics or from the endemic pneumonia seen each year [5]. This suggests to us that the major cause of increased mortality in 1918 was simply a higher incidence of influenza’s most significant and most fatal complication, bacterial pneumonia.

Although we remain uncertain about the reasons for the age-specific patterns Dr. Fedson identifies and do not believe data on H5N1 influenza are sufficient to evaluate whether findings from 1918 influenza pathogenesis studies are relevant to modern cases of H5N1 influenza, we agree that host factors must be involved in the epidemiology, including the age-specific mortality patterns, of the 1918 pand-
Does Contrast Enhancement Predict Survival in Progressive Multifocal Leukoencephalopathy?

To the Editor—I read with interest the recent article by Engsig et al. [1]. The authors used the lack of contrast enhancement on computed tomography (CT) or magnetic resonance imaging (MRI) scans to identify patients with progressive multifocal leukoencephalopathy (PML). They also reported that the only 2 patients with PML who developed immune reconstitution inflammatory syndrome (IRIS) after the initiation of highly active antiretroviral therapy (HAART) had no signs of contrast enhancement [1]. In patients with PML, MRI can detect more lesions than CT. In 1997, von Giesen et al. [2] included the lack of contrast enhancement on MRI scans as a diagnostic criterion for PML in HIV-positive patients. This feature helped distinguish PML from more common AIDS-defining diseases, such as toxoplasmosis and non-Hodgkin lymphoma. Actually, rare instances of PML with contrast enhancement on either CT or MRI scans have been reported since 1984 for both HIV-negative and HIV-positive patients [3–9]. In some cases these contrast-enhanced areas were shown to have causes other than PML (e.g., leukemic infiltrates [10]); however, in most cases they were areas of JC virus–associated demyelination.

Although some patients with PML who have contrast-enhancing lesions die [4], contrast enhancement may indicate an inflammatory response and, thus, herald immunologic elimination of virus, leading to improved survival [11]. In 1998, Berger et al. [12] showed that contrast enhancement, typically faint and peripheral, was seen on 10% of CT and 15% of MRI scans. In another study, the same group showed that contrast enhancement on radiographic images was observed for 3 (50%) of 6 long-term survivors, compared with 4 (8.9%) of 45 short-term survivors [13]. In 1999, Post et al. [14] showed that, in HIV-positive patients with PML, no MRI abnormalities statistically significantly correlated with patient survival in either univariate or multivariate analysis with the exception of mass effect, which was significantly associated with shorter survival.

Similarly, among 7 patients with PML (5 HIV-negative patients with hematological conditions and 2 HIV-positive patients), Küker et al. [15] encountered contrast enhancement only once after successful treatment, and it heralded clinical remission with elimination of virus from the cerebrospinal fluid. Nelson et al. [16] demonstrated that the pathological parenchymal blush and arteriovenous shunting seen angiographically in some patients with PML reflect small-vessel proliferation and perivascular inflammatory changes. Gray et al. [17] reported that contrast enhancement was seen for all 8 cases of IRIS occurring in patients with AIDS after immune restoration was induced by HAART; interestingly, PML is often exacerbated by IRIS in patients with AIDS.

In light of these data, it would be interesting to learn from Engsig et al. what the prevalence of contrast enhancement was among long-term survivors of PML versus PML progressors in their large cohort.

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