

from classic systemic lupus erythematosus autoantigens can stimulate TLR7 and TLR8 (other plasmacytoid-dendritic-cell-specific TLRs) to secrete interferon- α .⁴ Although circulating plasmacytoid dendritic cells are reduced in number in systemic lupus erythematosus, these cells can infiltrate inflamed skin in this disorder.⁵

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THE AUTHORS REPLY: In response to the comments of Pappas and colleagues: we acknowledge that on occasion anti-double-stranded DNA antibodies occur in patients with diseases other than

lupus. Indeed, the earliest reports of the occurrence of these antibodies in autoimmune liver disease go back more than 30 years.¹ However, as we have recently reviewed in detail,² in conjunction with other contributory factors, there is strong evidence that implicates anti-double-stranded DNA antibodies in the development of lupus. But the mere presence of these antibodies is not necessarily pathogenic. For example, patients with myeloma proteins that happen to be anti-double-stranded DNA antibodies (even in concentrations that exceed 10 g per liter) do not have the clinical features of lupus.³

We concur with the interesting comments of Mohty. The role of TLRs in the development of autoimmunity is clearly of interest. Space restrictions limited our ability to expand on this, as well as some other areas of interest, in our review.

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Acute Lower Respiratory Tract Infection

TO THE EDITOR: In his review of inflammatory responses in infected lungs, Mizgerd (Feb. 14 issue)¹ notes that animal models of influenza A virus pneumonia indicate that neither neutrophil leukocytes nor cytokine signaling seems to be important in the case of the highly pathogenic influenza virus infections that cause global pandemics. However, this influenza virus directly inhibits pulmonary epithelial sodium transport, which removes water from the alveolar space by osmosis: Viral hemagglutinin binds to receptors on respiratory epithelial cells, inhibiting epithelial sodium-channel-mediated clearance of pulmonary fluid through a pathway involving phospholipase and protein kinase C.^{2,3} Reduced epithelial sodium transport also occurs in pulmonary edema

associated with septicemia⁴ and is a potential target for treatment of lung injury by beta-agonists.⁵

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THE AUTHOR REPLIES: The pathophysiology of highly pathogenic influenza virus infections is at present poorly understood. The lack of lifesaving effects from depleting neutrophils or individually interrupting any of several different cytokines in studies of H5N1 avian influenza infections in mice, as described and further expanded by Salomon et al.,¹ does not rule out the possibility that cytokines or neutrophils exacerbate the pathogenesis of H5N1 or other severe influenza infections, because of the necessarily limited scope of these early experiments. Studies cited by Eisenhut demonstrate that an influenza virus is capable of impairing epithelial fluid transport, but whether such impairment is necessary for edema accumulation during infection is unknown. Notably, those epithelial-transport studies did not examine highly pathogenic viruses. Finally, the significance of

alveolar edema as compared with that of other pulmonary and extrapulmonary pathological features²⁻⁴ has not been determined and may well vary among different influenza virus infections. Thus, it is premature to rule out roles for cytokines and neutrophils or to rule in roles for impaired epithelial fluid transport. The interesting point raised by Eisenhut is one of many important avenues for further investigation.

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Cortical Arousal in Children with Severe Enuresis

TO THE EDITOR: Children with nocturnal enuresis are generally believed to be deep sleepers with impaired arousability.¹ However, there are conflicting data with regard to sleep patterns in children with enuresis.^{2,3} Nocturnal enuresis often occurs with unstable bladder contractions in conjunction with polysomnographic changes from deep sleep to lighter sleep but without full awakening,⁴ suggesting that a relationship may exist between bladder overactivity and deranged arousability. We therefore investigated sleep patterns and cortical arousal in relation to bladder activity in children with severe enuresis.

Children with primary nocturnal enuresis that was severe and refractory (≥ 5 wet nights per week) and normal age-matched children without enuresis were prospectively recruited. Simultaneous nighttime polysomnography and continuous cystometry were conducted in the presence of a bedside observer. Unstable bladder contractions, episodes of nocturnal enuresis, and voided volume were assessed in all patients. Sleep stages and cortical arousals were analyzed by means of polysomnography.

Thirty-five patients (28 boys and 7 girls) with

severe refractory nocturnal enuresis and 21 normal controls were evaluated. Among the patients with nocturnal enuresis, the mean age was 9.6 years (range, 6 to 14), and the mean number of wet nights per week was 6.1. All patients had markedly reduced nocturnal bladder capacity (mean, 44% of age-expected bladder capacity⁵) and unstable bladder contractions. Light non-rapid-eye-movement sleep occurred significantly more frequently, and deep non-rapid-eye-movement sleep and rapid-eye-movement sleep occurred significantly less frequently in patients with enuresis than in controls. Cortical arousals occurred more frequently (i.e., there was a higher arousal index) in patients with enuresis (Table 1). (The cortical arousal index ranges from 1.12 to 12.48, with a higher score indicating frequent cortical arousals.) Cortical arousals and the arousal index were significantly and positively correlated with unstable bladder contractions ($P < 0.01$).

With the use of a temperature probe (display accuracy, $\pm 0.1^\circ\text{C}$) that was placed inside the urine-collection bag or diaper to detect episodes of enuresis,⁴ we could precisely record episodes of nocturnal enuresis and bladder activity without