A Review on the unfolded protein response (UPR) and pathological reprogramming of somatic cells, a research article on acute respiratory tract influenza infection and *S. pneumoniae* superinfection, and a research article and related Commentary on the pathology of *Exserohilum* infections associated with steroid injections were selected for the September 2013 AJP CME Program in Pathogenesis. The authors of the referenced articles and the planning committee members and staff have no relevant financial relationships with commercial interests to disclose.

Questions #1-5 are based on: Johno H, Kitamura M: Pathological in situ reprogramming of somatic cells by the unfolded protein response. Am J Pathol 2013, 183:644-654; http://dx.doi.org/10.1016/j.ajpath.2013.05.008


Upon completion of this month’s journal-based CME activity, you will be able to:

- Discuss endoplasmic reticulum (ER) stress.
- Describe the role of the unfolded protein response (UPR) in normal and pathological situations.
- Discuss differentiation of thyroid epithelial cells.
- Understand influenza infection.
- Describe bacterial superinfections.
- Discuss the outbreak of infections associated with epidural and intra-articular steroid injections.
- Describe the pathological features of *Exserohilum* meningitis.

1. **The endoplasmic reticulum (ER) is an intracellular compartment that provides a unique environment for appropriate folding and maturation of newly synthesized proteins. Based on the referenced Review, select the ONE statement that is NOT TRUE:** [See Am J Pathol 2013, 183:644-654.]

   a. Accumulation of unfolded proteins in the ER results in ER stress.
   b. ER stress can be caused by decreased general protein synthesis.
   c. To alleviate ER stress, cells activate evolutionarily conserved signaling cascades, such as the unfolded protein response (UPR).
   d. The UPR involves induction of ER chaperones and upregulation of ER-associated degradation.

2. **The UPR leads to restoration of ER function. Based on the referenced Review, select the ONE statement that is NOT TRUE:** [See Am J Pathol 2013, 183:644-654.]

   a. The UPR is comprised of two major signaling pathways mediated by protein kinase-like ER kinase (PERK) and activating transcription factor 4 (ATF4).
   b. The UPR influences cellular states of activation and differentiation.
   c. The UPR is involved in cell differentiation during embryogenesis.
   d. The UPR may be involved in the dedifferentiation and redifferentiation of local cells during the process of tissue repair and fibrosis.
3. Excessive stress leads chondrocytes to be unable to repair or replace damaged areas of cartilage. Based on the referenced Review, select the ONE statement that is NOT TRUE: [See Am J Pathol 2013, 183:644-654.]
   a. ER stress inducer tunicamycin causes modest suppression of type II collagen and marked inhibition of aggrecan expression in mature chondrocytes.
   b. In patients with osteoarthritis, both the UPR and cellular dedifferentiation are detectable in chondrocytes.
   c. Mouse model studies have shown induction of ER stress in chondrocytes and delayed endochondral bone formation.
   d. Transgenic mutant type X collagen mice exhibit short limbs and a decreased hypertrophic zone.

4. Thyroid epithelial cells (also called follicular cells or principal cells) are responsible for the production and secretion of thyroid hormones. Based on the referenced Review, select the ONE statement that is NOT TRUE: [See Am J Pathol 2013, 183:644-654.]
   a. Differentiation of thyroid epithelial cells is accompanied by synthesis and secretion of thyroglobulin, a thyroid hormone precursor.
   b. ER chaperones are not expressed during thyroid epithelial cell differentiation.
   c. Studies in rat models have shown that selective UPR pathways are induced in differentiating thyroid epithelial cells.
   d. Induction of ER stress by tunicamycin and thapsigargin results in substantial down-regulation of thyroid-specific genes encoding thyroglobulin, thyropheroxidase, and thyroid transcription factors in differentiated PC12 thyroid cells.

5. In the response to injury, terminally differentiated local cells are reprogrammed to undergo differentiation or trans-differentiation to gain active mitogenic and metabolic properties. Based on the referenced Review, select the ONE statement that is NOT TRUE: [See Am J Pathol 2013, 183:644-654.]
   a. In epithelial-mesenchymal transition (EMT), resident epithelial cells gain a phenotype characteristic of fibroblasts.
   b. EMT is required during normal embryonic development and wound healing.
   c. EMT may lead to transformation into malignant cells and fibrogenic myofibroblasts.
   d. The UPR may facilitate EMT in some cell types via deactivation of the transforming growth factor (TGF)-β signaling pathway.

6. Bacterial superinfection and associated lung immunopathology are major contributors to hospitalizations and mortality after influenza. Based on the referenced article, select the ONE statement that is NOT TRUE: [See Am J Pathol 2013, 183:868-880.]
   a. Influenza remains one of the leading causes of deaths from respiratory tract infection.
   b. Influenza predisposes to secondary bacterial superinfection that often occurs during the recovery phase from influenza.
   c. During the Spanish flu pandemic of 1918, an estimated 1 million people died and the secondary bacterial pneumonia was a common cause of death.
   d. Although the influenza virus that causes seasonal flu is less virulent and lethal than the virus associated with the Spanish flu pandemic, most hospitalizations and mortality associated with seasonal flu are due to bacterial superinfections or exacerbations of underlying disease.

7. Seasonal influenza infection alone typically causes a transient illness in otherwise healthy individuals. Based on the referenced article, select the ONE statement that is NOT TRUE: [See Am J Pathol 2013, 183:868-880.]
   a. Viral clearance is achieved by 7 to 10 days after viral infection.
   b. Bacterial superinfections often occur within the first two weeks of influenza infection.
   c. Bacterial superinfections after influenza infection are caused primarily by Streptococcus pneumoniae, Staphylococcus aureus, or Pseudomonas aeruginosa.
   d. S. pneumoniae is the most common bacterial respiratory tract pathogen and is the fifth leading cause of death worldwide.

8. Deleterious lung immunopathology is a prominent feature of influenza-associated bacterial superinfection, characterized by massive neutrophilic infiltration and suppurative bronchopneumonia. Based on the referenced article, select the ONE statement that is NOT TRUE: [See Am J Pathol 2013, 183:868-880.]
   a. Mouse models of influenza and bacterial superinfection have been used to recapitulate the clinical histopathological findings of influenza-associated bacterial superinfection.
   b. Immunopathology in the lung of murine models is conventionally defined as the major histopathological changes resulting from an excessive host immune response, including inflammatory infiltration and consolidation and lung tissue injury that may negatively affect the host’s clinical performance.
   c. During influenza epidemics and pandemics, the use of antibiotics is the mainstay of treatment against bacterial superinfections.
   d. Corticosteroids are the standard of care in cases of influenza-associated bacterial superinfections.
9. Phaeohyphomycosis is a commonly used term that lumps together diseases caused by >100 species of fungi in 60 genera spanning several orders. Based on the referenced article and the related Commentary, select the ONE statement that is NOT TRUE: [See Am J Pathol 2013, 183:881-892 and related Commentary, Am J Pathol 2013, 183:661-664.]

a. Like all black molds, Exserohilum spp. are geographically restricted.
b. E. rostratum is isolated from soil and marine environments.
c. E. rostratum is a phytopathogen for grasses and its use for biocontrol of weeds has been studied.
d. The dark color of the hyphal walls in Exserohilum spp. is due to melanin.

10. Epidural and intra-articular steroid injections are commonly administered for treatment of back, neck, and peripheral joint pain, especially in elderly patients. Based on the referenced article and the related Commentary, select the ONE statement that is NOT TRUE: [See Am J Pathol 2013, 183:881-892 and related Commentary, Am J Pathol 2013, 183:661-664.]

a. Individual cases of infection from spinal injections of steroids are common and develop in an estimated 5% of patients.
b. Introduction of skin flora into the injection site is the most common cause of infection and S. aureus is the most commonly implicated organism.
c. Outbreaks of infections associated with contaminated epidural or intra-articular injections are unusual.
d. Fungal infections associated with spinal injections are exceedingly rare and are most frequently attributed to Aspergillus.

11. September 2012 marked the beginning of the largest reported outbreak of infections associated with epidural and intra-articular injections. Based on the referenced article and the related Commentary, select the ONE statement that is NOT TRUE: [See Am J Pathol 2013, 183:881-892 and related Commentary, Am J Pathol 2013, 183:661-664.]

a. Contamination of methylprednisolone acetate with the black mold, E. rostratum, was the primary cause of the outbreak.
b. More than 17,000 vials from three contaminated lots were distributed to medical centers across the United States.
c. Approximately 800 people were injected with the potentially contaminated drug before discovery of the source of contamination.
d. Through May 6, 2013, 741 cases and 55 deaths in 20 states had been associated with the outbreak, making it the largest recognized cluster of infections associated with epidural and intra-articular steroid injections.

12. The collection of samples from 40 patients with E. rostratum meningitis represents a unique resource to understand the spectrum of disease. Based on the referenced article and the related Commentary, select the ONE statement that is NOT TRUE: [See Am J Pathol 2013, 183:881-892 and related Commentary, Am J Pathol 2013, 183:661-664.]

a. Fatal cases had necrosuppurative to granulomatous meningitis and vasculitis, with thrombi and abundant angioinvasive fungi.
b. Immunohistochemistry was a highly sensitive method for detection of fungus in formalin-fixed, paraffin-embedded (FFPE) tissues.
c. Immunohistochemistry identified hyphal forms and granular fungal antigens.
d. PCR identified Exserohilum in fresh tissues but not in FFPE tissues.