**ANSWERS for CME Questions # 1-50**

<table>
<thead>
<tr>
<th>Volume/Issue</th>
<th>Month</th>
<th>Questions #</th>
<th>Answers</th>
</tr>
</thead>
<tbody>
<tr>
<td>172/1</td>
<td>January</td>
<td>1-5</td>
<td>1e, 2c, 3c, 4d, 5b</td>
</tr>
<tr>
<td>172/2</td>
<td>February</td>
<td>6-10</td>
<td>6b, 7b, 8a, 9c, 10e</td>
</tr>
<tr>
<td>172/3</td>
<td>March</td>
<td>11-14</td>
<td>11b, 12e, 13c, 14a</td>
</tr>
<tr>
<td>172/4</td>
<td>April</td>
<td>15-18</td>
<td>15d, 16c, 17d, 18e</td>
</tr>
<tr>
<td>172/5</td>
<td>May</td>
<td>19-23</td>
<td>19a, 20e, 21c, 22b, 23a</td>
</tr>
<tr>
<td>172/6</td>
<td>June</td>
<td>24-27</td>
<td>24c, 25a, 26d, 27e</td>
</tr>
<tr>
<td>173/1</td>
<td>July</td>
<td>28-30</td>
<td>28e, 29d, 30e</td>
</tr>
<tr>
<td>173/2</td>
<td>August</td>
<td>31-34</td>
<td>31a, 32b, 33b, 34c</td>
</tr>
<tr>
<td>173/3</td>
<td>September</td>
<td>35-38</td>
<td>35e, 36e, 37c, 38d</td>
</tr>
<tr>
<td>173/4</td>
<td>October</td>
<td>39-42</td>
<td>39e, 40c, 41a, 42c</td>
</tr>
<tr>
<td>173/5</td>
<td>November</td>
<td>43-46</td>
<td>43c, 44a, 45b, 46e</td>
</tr>
<tr>
<td>173/6</td>
<td>December</td>
<td>47-50</td>
<td>47a, 48b, 49b, 50c</td>
</tr>
</tbody>
</table>

Explanations of answers to questions are divided by the issue in which the questions appeared.
ANSWERS for CME Questions # 1-5

1e, 2c, 3c, 4d, 5b

1. Neutrophils constitute the first line of defense against invading bacteria. Based on the referenced Biological Perspectives article about signaling events during the interaction of neutrophils with the endothelium, select the ONE statement that is NOT true: [See Am J Pathol 2008 172: 1-7; the authors of the referenced article did not disclose any potential conflicts of interest]

   a. Inhibition of neutrophil recruitment can have positive effects on anti-bacterial inflammation, ischemia-reperfusion injury, and autoimmune disease. [This statement is TRUE.]
   b. In leukocyte adhesion deficiency (LAD), a defect in neutrophil recruitment is associated with recurrent bacterial infections that can be lethal. [This statement is TRUE.]
   c. Activated neutrophils manifest a number of functional responses such as spreading, transmigration through the endothelium, phagocytosis, superoxide production, and degranulation. [This statement is TRUE.]
   d. The first contact between neutrophils and the endothelium of postcapillary venules, a process known as capture or tethering, is mediated by selectins and their counter-receptors. [This statement is TRUE: Selectin binding and the presentation of chemokines by endothelial cells induce activation of signaling pathways in neutrophils that cause changes in integrin conformation.]
   e. Binding of E-selectin to P-selectin glycoprotein ligand (PSGL)-1 requires sialylated and fucosylated O-glycans and tyrosine sulfation. [This statement is FALSE: PSGL-1 is a disulfide-bonded homodimer highly expressed on microvilli of leukocytes. Binding of E-selectin to PSGL-1 requires sialylated and fucosylated O-glycans but does not require tyrosine sulfation.]

2. Neutrophil interactions with the endothelium involve signaling events. Based on the referenced Biological Perspectives article, select the ONE statement that is NOT true: [See Am J Pathol 2008 172: 1-7; the authors of the referenced article did not disclose any potential conflicts of interest]

   a. Interaction of PSGL-1 with the cytoskeleton requires a juxtamembrane region of 18 amino acids of the PSGL-1 cytoplasmic tail. [This statement is TRUE: The cytoplasmic tail of PSGL-1 interacts with moesin and ezrin.]
   b. Proteins of the ezrin-radixin-moesin (ERM) family function as linking proteins between the plasma membrane and the actin cytoskeleton. [This statement is TRUE: ERM proteins play an important role in the formation of protrusive plasma membrane structures.]
   c. The carboxy-terminal domain of ezrin and moesin can bind to the cytoplasmic tail of PSGL-1. [This statement is FALSE: The carboxy-terminal domain of the ERM proteins can bind F-actin, whereas the amino-terminal domain binds to the cytoplasmic tail of PSGL-1.]
   d. The amino-terminal region of ERM proteins contains an immunoreceptor tyrosine-based activation motif (ITAM)-like motif that can directly interact with spleen tyrosine kinase (Syk). [This statement is TRUE: PSGL-1 engagement induces tyrosine phosphorylation of Syk.]
   e. Slow rolling on E-selectin is abolished by pharmacological blockade of Syk and is absent in Syk-deficient bone marrow chimeric mice. [This statement is TRUE.]
3. L-selectin is involved in rolling and activation of leukocytes. Based on the referenced Biological Perspectives article, select the ONE statement that is NOT true: [See Am J Pathol 2008 172: 1-7; the authors of the referenced article did not disclose any potential conflicts of interest]

   a. L-selectin is a type I transmembrane glycoprotein with an amino-terminal C-type lectin domain followed by an epidermal growth factor (EGF)-like domain, two short consensus repeats, a transmembrane domain, and a cytoplasmic tail. [This statement is TRUE: L-selectin interacts with sialylated ligands expressed by the endothelium.]

   b. The carboxy-terminus of the cytoplasmic tail of L-selectin is constitutively associated with calmodulin, directly interacts with α-actinin, and forms a complex with vinculin and talin. [This statement is TRUE: The presence of vinculin and talin increases the binding affinity of α-actinin for L-selectin.]

   c. Truncation of the α-actinin binding site at the carboxy-terminal end of the cytoplasmic tail of L-selectin leads to reduced tethering and rolling and an inability to recognize carbohydrates. [This statement is FALSE: The α-actinin binding site consists of 11 residues at the carboxy-terminal end of the cytoplasmic tail of L-selectin. Despite the reduced functionality of the truncated form of L-selectin lacking most of the cytoplasmic domain, the mutant retains the ability to recognize carbohydrates and is still localized to microvillar tips, suggesting that other cytoskeletal proteins are required to anchor L-selectin to microvilli.]

   d. Moesin binds to the cytoplasmic tail of L-selectin after stimulation. [This statement is TRUE: Two residues (Arg-357 and Lys-362) in the ERM-binding domain of human L-selectin contribute to the interaction with the amino-terminal domain of moesin. Mutation of these two amino acids results in a reduction of induced shedding, lower levels of L-selectin in microvilli, and decreased tethering efficiency.]

   e. Ezrin is constitutively associated with the cytoplasmic tail of L-selectin. [This statement is TRUE.]

4. Although multiple sclerosis (MS) is the most common neurological disease of young adults, its pathogenesis remains incompletely understood. Based on the referenced article and related Commentary, select the ONE statement that is NOT true: [See Am J Pathol 2008 172: 8-10 and Am J Pathol 2008 172:146-155; one of the authors is supported by the Lundbeck Foundation, which is listed on the Copenhagen stock exchange and funds grants to support research and scientific activities in Denmark as well as Danish scientists abroad.]

   a. T cells and inflammatory cytokines play an important role in the pathogenesis of MS lesions. [This statement is TRUE: Pathologically distinct areas in the brain can be characterized as acute, chronic active, and inactive lesions, depending on the degree of mononuclear cell infiltrates and the level of destruction of myelin sheaths.]

   b. Previous studies of MS and its corresponding animal model, experimental autoimmune encephalomyelitis (EAE), have suggested that a type I response with CD4 T cells of helper type 1 (TH1 cells) represents a pro-inflammatory, destructive immune reaction whereas a type 2 response with TH2 cells reflects a modulatory, non-pathogenic immune reaction. [This statement is TRUE: The notion has been that a TH2 response can even protect from autoimmune disease caused by TH1-dependent mechanisms.]

   c. Interleukin (IL)-12 knock-out mice are highly susceptible to EAE induction. [This statement is TRUE: IL-12 knock-out mice lack the specific p35 subunit but do not lack the p40 subunit, which is shared by IL-12 and IL-23.]

   d. IL-23 alone can drive TH17 cell differentiation of naïve T cells. [This statement is FALSE: A combination of IL-6 and TGF-β is required for TH17 cell differentiation. Differentiated TH17 cells are maintained and expanded by IL-23, but IL-23 alone is unable to drive TH17 cell differentiation of naïve T cells.]

   e. IL-17 is produced by TH cells that are distinct from the traditional TH1 and TH2 cell subsets. [This statement is TRUE.]
5. IL-17-secreting cells have been detected in MS as well as in rheumatoid arthritis and inflammatory bowel disease. Based on the referenced article and related Commentary, select the ONE statement that is NOT true: [See Am J Pathol 2008 172: 8-10 and Am J Pathol 2008 172:146-155; one of the authors is supported by the Lundbeck Foundation, which is listed on the Copenhagen stock exchange and funds grants to support research and scientific activities in Denmark as well as Danish scientists abroad.]

   a. IL-17 is a pro-inflammatory cytokine. [This statement is TRUE.]
   b. IL-17 immunoreactivity was detected to the same degree in astrocytes of control central nervous system tissue and of active areas of MS lesions. [This statement is FALSE: IL-17 immunoreactivity was detected in astrocytes in active areas of MS plaques but not in control central nervous system tissue or inactive MS lesions.]
   c. CD8⁺ T cells were positively immunostained for IL-17 at frequencies similar to those of CD4⁺ T cells in MS tissues. [This statement is TRUE.]
   d. CD8⁺ T cells are more frequent in chronically inflamed MS plaques compared with CD4⁺ T cells. [This statement is TRUE.]
   e. Axonal damage in MS lesions correlates with the number of CD8⁺ T cells. [This statement is TRUE.]
6. The role of autophagy as a mediator of cell death is not completely understood. Based on the referenced article and related Commentary about autophagy and neuronal cell death, select the ONE statement that is NOT true: [See Am J Pathol 2008 172:284-287; the authors of the referenced article did not disclose any potential conflicts of interest; and Am J Pathol 2008 172:454-469; one of the authors is affiliated with Vertex Pharmaceuticals.]

a. The incidence of cerebral palsy from perinatal hypoxia/ischemia is >2 per 1,000 births. [This statement is TRUE: Furthermore, the incidence of arterial ischemic stroke is approximately 1 per 4,000 term infants.]

b. Patterns of neuronal cell death after hypoxic/ischemic injury are significantly different in rodent models compared to human cases of encephalopathy. [This statement is FALSE: The patterns of neuronal death after hypoxic/ischemic injury in rodent models appear similar to those involved in human cases of hypoxic/ischemic encephalopathy. Mouse knockout studies have thus provided essential mechanistic clues about human cases of hypoxic/ischemic injury.]

c. Phosphoinositide 3-kinase inhibitors and rapamycin have diverse cellular effects that extend beyond autophagy regulation. [This statement is TRUE: These classes of drugs also modulate survival/death kinases by 3-methyladenine as well as regulation of protein synthesis and differentiation through mammalian target of rapamycin (mTOR).]

d. Although pediatric neurodegeneration is also seen with lysosomal storage disorders, the primary deficit here is not induction of autophagy. [This statement is TRUE: The primary defect in lysosomal storage disorders is inadequate lysosomal clearance of sequestered material.]

e. The proportion of the cellular mitochondrial complement that undergoes depolarization has been proposed to determine whether a stressed cell undergoes autophagy, apoptosis, or necrosis. [This statement is TRUE.]
7. The identification of autophagy (Atg) genes whose products are involved in specific ubiquitin-like conjugation reactions that are essential for extension of autophagic membranes has revolutionized the study of autophagy. Based on the referenced article and related Commentary, select the ONE statement that is NOT true: [See Am J Pathol 2008 172:284-287; the authors of the referenced article did not disclose any potential conflict of interest; and Am J Pathol 2008 172:454-469; one of the authors is affiliated with Vertex Pharmaceuticals.]

a. Atg7 acts as an E1-activating enzyme to produce high-energy thioester bonds involving LC3/Atg8 and Atg12. [This statement is TRUE: LC3/Atg8 and Atg12 are ubiquitin-fold proteins that are transferred to their E2 enzymes Atg3 and Atg10, respectively.]

b. Atg3 and Atg12 are E2-conjugating enzymes that require E3 participation to transfer LC3/Atg8 and Atg12 to phosphatidylethanolamine and Atg5, respectively. [This statement is FALSE: Atg3 and Atg12 do not require E3 participation to transfer LC3/Atg8 and Atg12 to their respective targets at the growing autophagic membrane.]

c. Neurons require at least basal levels of autophagy for maintenance of health and function in vivo. [This statement is TRUE: Knockout mouse studies targeting Atg5 and Atg7 have demonstrated that both initiation and successful completion of autophagic degradation are essential for basal neuronal health.]

d. Autophagic cell death can be executed independently of intact apoptotic machinery. [This statement is TRUE: It has been proposed that autophagic cell death is important mainly in apoptosis-deficient cells.]

e. Apoptotic neuronal cell death after hypoxic/ischemic injury is accompanied by the activation of caspases whereas autophagy is caspase independent. [This statement is TRUE.]

8. Advanced renal fibrosis with kidney failure is a major healthcare burden worldwide, and only limited therapeutic options are currently available. Based on the referenced article concerning the role of macrophages in renal fibrosis, select the ONE statement that is NOT true: [See Am J Pathol 2008 172:288-298; the authors of the referenced article did not disclose any potential conflicts of interest]

a. Galectin-3 is a β-galactoside-binding lectin of approximately 30 kDa that is up-regulated when macrophages differentiate into dendritic cells. [This statement is FALSE: Galectin-3 is highly expressed and secreted by macrophages. It is up-regulated when monocytes differentiate into macrophages. Galectin-3 is down-regulated when macrophages differentiate into dendritic cells.]

b. Experimental hydronephrosis induced by unilateral ureteric obstruction (UUO) is a clinically relevant animal model of progressive renal fibrosis. [This statement is TRUE: UUO mimics congenital obstructive nephropathy, with progression through the different stages of obstructive nephropathy leading to tubulointerstitial fibrosis.]

c. Galectin-3 expression was markedly increased in the renal interstitium and tubular epithelium in UUO-treated mice compared with a sham-operated control group. [This statement is TRUE.]

d. Galectin-3-/- mice are protected from renal fibrosis following UUO. [This statement is TRUE.]

e. Cross-over experiments using wild-type and galectin-3-/- macrophage supernatants and renal fibroblasts confirmed that secretion of galectin-3 by macrophages is critical in the activation of renal myofibroblasts to a pro-fibrotic phenotype. [This statement is TRUE.]

9. *Streptococcus pneumoniae* is the most common cause of community-acquired pneumonia. Based on the referenced article concerning the role of galectin-3 in the pathophysiology of pneumococcal infection, select the ONE statement that is NOT true: [See Am J Pathol 2008 172:395-405; the authors of the referenced article did not disclose any potential conflicts of interest]

a. In the lung, resident alveolar macrophages are the first line of cellular defense against invading pathogens. [This statement is TRUE: Resident alveolar macrophages play a phagocytic role during the early stages of infection.]

b. Galectin-3 has antimicrobial activity towards *Candida albicans*. [This statement is TRUE.]

c. Galectin-3, which is abundantly expressed in mouse neutrophils, contains a glycine-rich carboxy-terminal domain through which it crosslinks carbohydrate ligands. [This statement is FALSE: Galectin-3 is not expressed in mouse neutrophils. Galectin-3 contains a single carboxy-terminal domain and a glycine-rich amino-terminal domain through which it forms oligomers and functions to cross-link both carbohydrate and non-carbohydrate ligands.]

d. Galectin-3-/- mice develop more severe pneumonia following infection with *S. pneumoniae* compared to wild-type mice. [This statement is TRUE.]

e. Treatment with recombinant galectin-3 protects galectin-3-deficient mice from developing severe pneumonia. [This statement is TRUE.]
10. Several members of the galectin family of proteins are emerging as targets for cancer therapy. Based on the referenced article, select the ONE statement that is NOT true: [See Am J Pathol 2008 172:545-553; the authors of the referenced article did not disclose any potential conflicts of interest]

a. The increased expression of galectin-1 in activated endothelial cells is accompanied by a translocation of the protein to the outer cell membrane. [This statement is TRUE: It is likely that extracellular galectin-1 is required for the attachment and migration of activated endothelial cells over the extracellular matrix.]

b. Faint expression of galectin-2, -4, and -12 was detected in quiescent human endothelial cells. [This statement is TRUE.]

c. Galectin-3 expression was not affected by activation of endothelial cells. [This statement is TRUE.]

d. Galectin-8 is a tandem-repeat galectin that can modulate cellular adhesion and intracellular signaling through interactions with integrins. [This statement is TRUE.]

e. An analysis of galectin mRNA expression levels in endothelial cells provided evidence for splice variants of galectin-3, -8 and -9. [This statement is FALSE: There was evidence of alternative splicing of galectin-8 and -9 mRNAs. There was only one polymerase chain reaction product of galectin-3 cDNA. The presence of multiple bands upon galectin-3 staining of Western blots is related to varied phosphorylation of the protein and/or proteolytic modifications.]
11. Pathogenic pathways leading to fatal neurodegenerative conditions in humans and animals known as prion diseases or transmissible spongiform encephalopathies (TSEs) are poorly understood. Based on the referenced Biological Perspectives article, select the ONE statement that is NOT true: [See Am J Pathol 2008 172: 555-565; the authors of the referenced article did not disclose any potential conflicts of interest]

a. Conformational change of the normal cellular form of prion protein (PrPc) to a pathological, disease-associated form (PrP^TSE) is considered central to pathogenesis and formation of the infectious agent or prion. [This statement is TRUE: PrPc is alpha helix dominant, whereas PrP^TSE features a predominantly beta-pleated structure. PrP^TSE is resistant to protease treatment.]

b. PrPc is a 253-amino acid long polypeptide that is encoded by a gene (PRNP) on the long arm of chromosome 18. [This statement is FALSE: PRNP is on the short arm of chromosome 20.]

c. At least 15 PRNP polymorphisms are known. [This statement is TRUE: Although there are several polymorphisms, only the methionine/valine at codon 129 is clearly influential in all disease forms.]

d. The PrP^TSE polypeptide is synthesized in the endoplasmic reticulum in three topological forms, designated SecPrP, NtmPrP, and CtmPrP. [This statement is TRUE: Secretory (SecPrP) molecules are attached to the outer leaflet of the lipid bilayer exclusively by a C-terminal glycosyl-phosphatidylinositol anchor. NtmPrP and CtmPrP molecules span the lipid bilayer with either the N or C terminus.]

e. Generation of PrP^TSE from PrPc occurs after the arrival of PrPc at the cell surface. [This statement is TRUE.]

12. Neuropathogenesis of prion diseases evolves in complex ways on several frontlines. Based on the referenced Biological Perspectives article, select the ONE statement that is NOT true: [See Am J Pathol 2008 172: 555-565; the authors of the referenced article did not disclose any potential conflicts of interest]

a. The most frequent prion disease form in humans is sporadic Creutzfeldt-Jakob disease (sCJD). [This statement is TRUE.]

b. The routes of infection in naturally acquired prion diseases comprise uptake of prions via the alimentary tract or through scarification of gums, skin, and conjunctiva. [This statement is TRUE: The spread of prions depends on their site of entry, strain, dose, and species as well as the PrP genotype of the host.]

c. Demonstration of morphological features of apoptosis, DNA fragmentation, and activation of caspase-3 supports apoptosis as a relevant cell death pathway in prion disease. [This statement is TRUE: However, the variability of results suggests that apoptosis is not the exclusive pathway.]

d. It has been speculated that autophagic vacuoles may precede spongiform change and thus contribute to the overall pathology of prion diseases. [This statement is TRUE: Autophagy is a degradative mechanism involved in the recycling and turnover of cytoplasmic components. Autophagic vacuoles have been described in prion diseases and may result from intraneuronal accumulation of PrP^TSE that overloads the catabolic machinery, followed by eventual bulk removal of damaged neurons.]

e. Prominent spongiform change is a histopathological hallmark in all forms of prion diseases. [This statement is FALSE: Spongiform change is characterized by small (<10 μm) round or oval vacuolization of the neuropil. Some disease forms, like Gerstmann-Straussler-Scheinker (GSS) disease or fatal familial insomnia (FFI) in humans do not feature prominent spongiform change. In CJD the presence of vacuoles in cell bodies is uncommon.]
13. Intimal hyperplasia of autologous vein grafts is a critical problem affecting the long-term patency of many types of vascular reconstruction. Based on the referenced article and related Commentary, select the ONE statement that is NOT true: [See Am J Pathol 2008 172:566-570 and Am J Pathol 2008 172: 839-848; the authors of the referenced articles did not disclose any potential conflicts of interest]

   a. In 2005, over 450,000 coronary artery bypass procedures were performed in the United States. [This statement is TRUE: Besides coronary artery bypass surgery, vein grafting is used in the treatment of mesenteric ischemia and peripheral artery occlusive disease as well as in the creation of arterio-venous fistulas for hemodialysis.]

   b. Hemodialysis access dysfunction costs more than 1 billion dollars per year, and access-related admissions account for 25% of all hospitalizations in the US. [This statement is TRUE.]

   c. The use of vein grafts is preferred above arterial grafts in coronary artery bypass procedures because veins show higher patency rates. [This statement is FALSE: Arterial grafts show higher patency rates and are preferred above vein grafts. Examples of arterial grafts include left/right internal mammary artery, radial artery, and gastro-epiploic artery. Since appropriate autologous arteries are not always available, the use of vein grafts is still prominent in the treatment of ischemic heart disease.]

   d. Endothelial cell damage/loss is considered to be the inciting event for the development of intimal hyperplasia. [This statement is TRUE: Activated endothelial cells, platelets, and macrophages release growth factors and cytokines that cause vascular smooth muscle cell proliferation and migration into the subendothelial space of the intima.]

   e. Patients suffering from atherosclerosis and undergoing vein grafting are treated with anticoagulants, statins, and angiotensin-converting enzyme (ACE)-inhibitors to prevent thrombosis, lower cholesterol levels, and control blood pressure, respectively. [This statement is TRUE: This treatment regimen is primarily directed at reducing the atherosclerotic risk and is not efficacious in reducing intimal hyperplasia.]

14. The predominant cellular component within the intimal hyperplasia lesion is smooth muscle cells, and smooth muscle cell proliferation is believed to play a key role in pathogenesis. Based on the referenced article and related Commentary, select the ONE statement that is NOT true: [See Am J Pathol 2008 172:566-570 and Am J Pathol 2008 172: 839-848; the authors of the referenced articles did not disclose any potential conflicts of interest]

   a. In an experimental mouse model using wild-type mice that had been transplanted with bone marrow from a green fluorescent protein (GFP) transgenic mouse, smooth muscle cells of bone marrow origin that express GFP can be detected by immunohistochemistry at 2, 4, 8, and 16 weeks after grafting. [This statement is FALSE: GFP expression was detected at 2 and 8 weeks but not at 16 weeks after grafting. The loss of GFP expression is possibly due to lack of robust GFP expression at later time points due to changes in transcription profiles of maturing cells rather than loss of bone marrow-derived smooth muscle cells. DNA of bone marrow-derived cells was detected at 16 weeks.]

   b. Theoretical sources of smooth muscle cells within the venous intimal hyperplasia lesion include bone marrow-derived cells, the vein graft, the adjacent artery, and the adventitia. [This statement is TRUE.]

   c. The failure rate of vein grafts is known to be increased in patients with renal failure. [This statement is TRUE: It has been reported that there is an imbalance between progenitor endothelial cells and smooth muscle cells in patients with end-stage renal disease.]

   d. The majority of neointimal endothelial cells and vascular smooth muscle cells in the intimal hyperplasia lesions were derived from a non-bone marrow source. [This statement is TRUE.]

   e. In the PREVENT (Project of Ex Vivo Vein Graft Engineering via Transfection) trial, edifoligide was no more effective than placebo in preventing vein graft failure 12 to 18 months after surgery. [This statement is TRUE: Edifoligide is a transcription factor decoy that interacts with the binding site of the transcription factor E2F, which is involved in controlling the expression of multiple genes responsible for cell cycle progression.]
15. In addition to acting in the nervous system, nerve growth factor (NGF) exerts an array of biological actions on inflammation, the immune system, and cell proliferation. Based on the referenced article and related Commentary about the role of NGF and its receptor system in the pathogenesis of psoriasis, select the ONE statement that is NOT true: [See Am J Pathol 2008 172: 865-867 and Am J Pathol 2008 172: 961-971; the authors of the referenced articles did not disclose any potential conflicts of interest]

   a. NGF is a 118-amino acid hormone involved in the development and maintenance of sensory and sympathetic nerve fibers. [This statement is TRUE.]
   b. NGF has a regulatory role on axonal regeneration and collateral re-innervation in denervated skin after injury to cutaneous nerves. [This statement is TRUE: Topical administration of NGF significantly accelerates regeneration of nerve fibers.]
   c. NGF has two receptors: the death receptor p75NTR and the tyrosine kinase receptor TrkA. [This statement is TRUE: TrkA is a high affinity receptor, and p75NTR is a low affinity receptor.]
   d. NGF-reactive sensory nerve fibers are easily revealed since they are usually myelinated and have relatively thick diameters about half the size of a keratinocyte. [This statement is FALSE: NGF-reactive sensory nerve fibers are usually unmyelinated. They are difficult to reveal as they have very thin diameters, typically about one-tenth of the size of a keratinocyte.]
   e. NGF produced by keratinocytes is functionally active and can induce neuritogenesis. [This statement is TRUE.]

16. The deregulation of cell growth and differentiation in various pathologies provides a rationale for exploring the potential value of NGF and its receptors as both biomarkers and therapeutic targets. Based on the referenced article and related Commentary, select the ONE statement that is NOT true: [See Am J Pathol 2008 172: 865-867 and Am J Pathol 2008 172: 961-971; the authors of the referenced articles did not disclose any potential conflicts of interest]

   a. Psoriasis is characterized by a thickening of the epidermis due to increased proliferation and altered differentiation of keratinocytes, resulting in characteristic plaques over the skin. [This statement is TRUE: Major histological features include a pro-inflammatory reaction with infiltrating leukocytes and dilated blood vessels in the dermis.]
   b. The Koebner phenomenon refers to the appearance of psoriatic lesions in the uninvolved skin of psoriasis patients at the site of cutaneous trauma. [This statement is TRUE.]
   c. A clear down regulation of NGF in Koebner lesions was observed starting as early as 24 hours after trauma, with a peak effect in the third week. [This statement is FALSE: An upregulation of NGF in Koebner lesions was observed as early as 24 hours after trauma, with a peak in the second week.]
   d. Cultured keratinocytes from the non-lesional skin of psoriatic patients produced ten times more NGF than keratinocytes from healthy individuals. [This statement is TRUE.]
   e. NGF has been shown to activate T lymphocytes, to induce the release of inflammatory mediators, and to trigger angiogenesis through endothelial cell multiplication. [This statement is TRUE.]
17. Accurate estimates of somatic mutation rates of oncogenes and tumor suppressor genes are a vital but missing link in the quantitative understanding of tumorigenesis. Based on the referenced article concerning the in vivo rate of somatic APC mutations, select the ONE statement that is NOT true: [See Am J Pathol 2008 172: 1061-1068; the authors of the referenced article did not disclose any potential conflict of interest]

a. Familial adenomatous polyposis (FAP) is a hereditary cancer syndrome caused by germline APC mutation. [This statement is TRUE.]

b. The authors assumed that sporadic bowel cancer emerges via the same genetic pathway as FAP, but with an extra initiating APC “hit.” [This statement is TRUE.]

c. The calculations suggest that alleles of the APC tumor suppressor gene mutate to yield a selected protein change at a rate approximately 30 times faster than previous estimates. [This statement is TRUE: Alleles of the APC gene mutate to produce a selected protein change about $6 \times 10^{-5}$ times a year.]

d. 75% of APC mutations found in bowel cancers are nonsense or frameshift mutations. [This statement is FALSE: More than 95% of APC mutations found in bowel cancers are nonsense or frameshift mutations. They take the form of small deletions or insertions, or point mutations, resulting in truncation of the protein.]

e. Among the factors that confound estimates of mutation rates taken from incidence data include the assumed number of cell lineages at risk and calendar year effects. [This statement is TRUE.]

18. The importance of adult stem cells in the development of neoplastic diseases is gaining better appreciation. Based on the referenced article concerning the role of stem cells in sarcomagenesis, select the ONE statement that is NOT true: [See Am J Pathol 2008 172: 1069-1080; the authors of the referenced article did not disclose any potential conflict of interest]

a. The four major histological subtypes of liposarcoma exhibit a wide spectrum of adipogenesis. [This statement is TRUE.]

b. The results suggest that dedifferentiated liposarcomas, pleomorphic liposarcomas, myxoid/round cell liposarcomas, and well-differentiated liposarcomas correspond to transformation of a mesenchymal stem cell at increasingly mature steps in adipogenesis. [This statement is TRUE.]

c. In an analysis of the pathways represented by genes expressed in dedifferentiated liposarcomas versus normal fat cells, cell cycle genes and purine metabolism account for the most up-regulated pathways in dedifferentiated liposarcomas. [This statement is TRUE: Even after excluding the effects of differentiation and the potential contribution of the immature differentiating cell’s cycle in comparison to the normal mature cell, cell cycle genes and purine metabolism still accounted for the most up-regulated pathways in these cancer cells.]

d. A set of 2,026 unique genes was identified as overexpressed in dedifferentiated liposarcoma versus normal fat cells. [This statement is TRUE: Similarly, 799 unique genes were identified as overexpressed in human mesenchymal stem cells differentiating along the adipocytic lineage at day 7 versus terminally differentiated adipocytes at day 21.]

e. Liposarcomas are exquisitely sensitive to etoposide. [This statement is FALSE: Etoposide is a clinically utilized topoisomerase II inhibitor. Gene expression analysis suggests that topoisomerase II alpha (TOPIIa) expression is not related to tumorigenesis but rather to adipogenesis. Alternatively, the overexpression of TOPIIa may make liposarcoma cells less sensitive to etoposide compared to tumor cells that lack such overexpression.]
19. Recently, there have been reports of human-to-human transmission of H5N1 influenza, causing increased fear of a human pandemic. Based on the referenced Review article, select the ONE statement concerning H5N1 influenza that is NOT true. [See Am J Pathol 2008 172: 1155-1170; the authors of the referenced article did not disclose any potential conflicts of interest.]

a. According to World Health Organization (WHO) data, the fatality rate of laboratory-confirmed cases of human H5N1 infection is greater than 85%.  [This statement is FALSE: The WHO has reported 348 laboratory-confirmed cases, of which 216 were fatal, resulting in a fatality rate of approximately 60%.] 

b. The first known case of the avian influenza A virus subtype H5N1 crossing the avian-human species barrier occurred in 1997.  [This statement is TRUE: In 1997, 18 individuals were infected, 6 of whom died. In early 2003, avian influenza re-emerged among humans in Hong Kong, and since 2004, numerous infections have occurred in other Asian and non-Asian countries.] 

c. Human infections mainly result from poultry-to-human transmission.  [This statement is TRUE.] 

d. In both humans and animal models, the H5N1 virus appears to be capable of spreading beyond the lungs.  [This statement is TRUE: Virus has been isolated and viral antigens have been detected in various extra-pulmonary organs.] 

e. In human cases, lymphopenia has been associated with disease severity.  [This statement is TRUE: Furthermore, in animal experiments, infection with highly pathogenic H5N1 isolates has been associated with severe lymphopenia. H5N1 virus causes progressive depletion of lymphocytes, whereas infection with low pathogenic virus did not affect total white blood cell counts in mice.] 

20. H5N1 influenza is still a relatively novel disease with poorly understood pathology and pathogenesis. Based on the referenced Review article, select the ONE statement that is NOT true: [See Am J Pathol 2008 172: 1155-1170; the authors of the referenced article did not disclose any potential conflicts of interest.] 

a. There are several limitations of pathological findings from human H5N1 autopsies, including the fact that most patients had received various interventional therapies aimed at limiting tissue injury and viral replication, as well as the paucity of cases that succumbed during the early phase of the infection.  [This statement is TRUE: Animal studies have provided important supplementary information with respect to the natural course of H5N1 influenza.] 

b. The finding that the H5N1 virus is transmissible from mother to fetus might reflect enhanced pathogenicity of the virus.  [This statement is TRUE: Care should be taken when handling delivery or abortion from H5N1-infected mothers.] 

c. Serum cytokine and chemokine levels have been found to correlate with viral load in pharyngeal specimens, suggesting that viral loads may induce hypercytokinemia and hyperchemokinemia.  [This statement is TRUE.] 

d. Up-regulation of functional tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) in H5N1-infected macrophages may be another important factor in the pathogenesis of H5N1 influenza virus infection.  [This statement is TRUE: TRAIL is a death receptor ligand that triggers apoptosis of cells by binding to death receptor ligands expressed on target cells.] 

e. The lungs of infected patients typically show diffuse alveolar damage (DAD) and viral inclusions, and cytopathic changes in type II pneumocytes have been demonstrated in most autopsy cases.  [This statement is FALSE: The lungs typically show DAD. Hyperplasia of type II pneumocytes has
been demonstrated in most autopsy cases but viral inclusions or other cytopathic changes have not been observed in pneumocytes.]

21. Timely suppression of viral replication is the mainstay of therapy in H5N1 infection. Based on the referenced Review article, select the ONE statement that is NOT true: [See Am J Pathol 2008 172: 1155-1170; the authors of the referenced article did not disclose any potential conflicts of interest.]

   a. Oseltamivir is the principal antiviral agent of choice. [This statement is TRUE: Oseltamivir is a neuraminidase inhibitor.]
   b. Many H5N1 isolates are resistant to amantadines. [This statement is TRUE.]
   c. Data on treatment with corticosteroids and other immunomodulating agents demonstrate significant clinical benefit in treatment of human H5N1 infection. [This statement is FALSE: Corticosteroids have failed to show any clear benefits in the treatment of H5N1 infection or other viral respiratory infections, including SARS.]
   d. The level of cleavability of hemagglutinin (HA) determines the virulence of avian influenza viruses in poultry. [This statement is TRUE: Avirulent viruses usually possess HAs with a single arginine residue at the cleavage site that can only be cleaved by extracellular trypsin-like proteases present in the upper respiratory and gastrointestinal tracts, thus limiting infections to these sites. In contrast, virulent viruses have HAs with multiple residues at the cleavage site that can be activated by ubiquitous proteases and may therefore cause systemic infections.]
   e. Resistance to oseltamivir has been reported in three human H5N1 cases in which there is a tyrosine substitution at position 274 of the neuraminidase protein. [This statement is TRUE: Neuraminidase is a sialidase that cleaves the HA of progeny virions from the sialic acid-containing receptors on the surface of the host cells, thus separating the particles from the infected cells in which they were generated.]

22. The molecular and cellular mechanisms that are responsible for the development of chronic obstructive pulmonary disease (COPD) are not well understood. Based on the referenced article concerning the role of cigarette smoke in COPD, select the ONE statement that is NOT true: [See Am J Pathol 2008 172: 1222-1237; the authors of the referenced article did not disclose any potential conflict of interest.]

   a. Per puff, cigarette smoke contains an estimated 10^{15} - 10^{17} oxidants/free radicals and ~4,700 different chemical compounds, including reactive aldehydes, quinones, and semiquinones. [This statement is TRUE: Cigarette smoke is a potent inflammatory stimulus that induces pro-inflammatory mediators and recruits macrophages and neutrophils to the lung tissue.]
   b. In phagocytes, NADPH oxidase is a highly regulated membrane-bound enzyme that is composed of eight subunits, half of which are membrane associated and together constitute the flavocytochrome b^{558}. [This statement is FALSE: In phagocytes, NADPH oxidase is composed of six subunits. Of these p22^phox and gp91^phox are membrane associated and together constitute the flavocytochrome b^{558}. The other components are located in the cytoplasm of resting cells. Upon activation, the cytoplasmic components translocate to the cell membrane where they bind to flavocytochrome b^{558}, thus forming active NADPH oxidase.]
   c. NADPH oxidase is the main cellular source of reactive oxygen species (ROS) in mononuclear and granulocytic leukocytes. [This statement is TRUE: Active NADPH oxidase catalyzes the transfer of electrons from NADPH to molecular oxygen producing the superoxide anion (O_2^-), hydroxyl radical, and hydrogen peroxide.]
   d. The authors hypothesized that inhibition of cellular ROS release by targeted ablation of components of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase would protect the lungs against detrimental effects of cigarette smoke; however, the inflammatory response was significantly increased and was accompanied by development of distal airspace enlargement and alveolar destruction. [This statement is TRUE.]
   e. Treatment of peritoneal macrophages with the nuclear factor kappa B (NF-kB) inhibitor BAY117082 reversed the cigarette smoke-induced release of pro-inflammatory mediators. [This statement is TRUE: The expression of pro-inflammatory mediators is regulated by the transcription factor NF-kB. NF-kB activity is mainly controlled by its association with the inhibitory IkB proteins that prevent NF-kB from entering the nucleus.]
23. The recently adopted term “diabesity” reflects the escalating rates of both obesity and diabetes during the past two decades. Based on the referenced article concerning the role of Shp2 in the development of diabesity, select the ONE statement that is NOT true: [See Am J Pathol 2008 172: 1312-1324; the authors of the referenced article did not disclose any potential conflict of interest.]

a. According to WHO, ~15% of adults worldwide have a body mass index (BMI) of >30 kg/m^2. [This statement is FALSE: Approximately 8% of adults worldwide (~300 million adults) are extremely obese, defined by a BMI >30 kg/m^2. Obesity decreases life expectancy between 3 and 13 years, and it constitutes one of the main causes of morbidity and mortality worldwide.]

b. Obesity is the most common cause of insulin resistance in humans. [This statement is TRUE: Insulin resistance leads to the failure of insulin to stimulate glucose uptake and suppress hepatic gluconeogenesis, constituting a major risk factor for the metabolic syndrome, type 2 diabetes, and cardiovascular disease.]

c. Shp2 is a Src homology (SH) 2 domain-containing nontransmembrane protein tyrosine phosphatase and is ubiquitously expressed. [This statement is TRUE: Mice homozygous for a Shp2 N-terminal deletion mutation die at mid-gestation.]

d. Obesity and diabetes are predisposing factors for non-alcoholic fatty liver. [This statement is TRUE: Non-alcoholic fatty liver is a precursor of steatohepatitis, in which the liver is programmed for lipogenesis rather than glycogenesis.]

e. In the current study, neuron-specific Shp2 deletion in CRE3-Shp2^lox/lox mice led to obesity and diabetes with associated pathophysiological complications resembling human pathology. [This statement is TRUE.]
24. Mitochondria are complex organelles that are absolutely required for the development, function, and longevity of eukaryotic cells and organisms. Based on the referenced Award Lecture, select the ONE statement that is NOT true. [See Am J Pathol 2008 172: 1445-1456; the author of the referenced article did not disclose any potential conflicts of interest.]

a. Oxidative phosphorylation (OXPHOS) disorders can be maternally inherited via mutations in mtDNA. [This statement is TRUE: In humans, the oxidative phosphorylation (OXPHOS) complexes I-V in the inner mitochondrial membrane comprise ~80 protein subunits, 13 of which are encoded by maternally inherited mtDNA.]

b. In humans, mtDNA is a double-stranded circle of 16,569 base pairs that encodes 13 mRNAs, 2 rRNAs, and 22 tRNAs. [This statement is TRUE: The mRNAs encode essential integral membrane components of the OXPHOS complexes, the rRNAs are subunits of mitochondrial ribosomes, and the tRNAs mediate translation of the 13 mRNAs by these dedicated mitochondrial ribosomes.]

c. In mammals, mature mRNAs that are encoded by mtDNA have long 5'-untranslated sequences. [This statement is FALSE: Mammalian mature mRNAs that are transcribed from mtDNA are devoid of significant 5'-untranslated sequences, and thus the mechanism of ribosome binding and mitochondrial translation initiation remains obscure.]

d. Transcripts derived from HSP2 and LSF promoters on the heavy (H) and light (L) strands, respectively, are near genome-length polycistronic products. [This statement is TRUE: Transcripts from the HSP1 promoter on the H strand are terminated at a specific site in the tRNALeu gene, downstream of the 16S rRNA, and produce mainly two rRNAs (12S and 16S).]

e. tRNA processing is believed to be the major mechanism that liberates the majority of the 37 mature RNA molecules from the polycistronic primary transcripts. [This statement is TRUE: The rRNAs and most mRNAs are immediately flanked by tRNAs in mtDNA.]

25. There are several hallmark features of mammalian mtDNA. Based on the referenced Award Lecture, select the ONE statement that is NOT true: [See Am J Pathol 2008 172: 1445-1456; the author of the referenced article did not disclose any potential conflicts of interest.]

a. In each mammalian cell, there is a single mtDNA molecule packaged into a nucleoprotein complex called a nucleoid. [This statement is FALSE: In mammalian cells, mtDNA is maintained at a high copy number. Within the mitochondrial matrix, complexes of 2-10 mtDNA molecules are packaged into nucleoprotein complexes (nucleoids) that are largely inner membrane associated.]

b. The D-loop regulatory region of mammalian mtDNA contains four sequence elements (including CSB I, CSB II, CSB III, and OI, which is the origin of H-strand synthesis) that are postulated to be important for initiation of transcription-primed, leading-strand DNA synthesis according to the asymmetric model of mtDNA replication. [This statement is TRUE: The D-loop is a stable three-stranded DNA structure that begins at OI.]
c. Except for the mtDNA-encoded rRNAs and tRNAs, all of the factors required for transcription, RNA processing, translation, replication, and repair of mtDNA are encoded by nuclear genes, translated by cytoplasmic ribosomes, and imported into mitochondria to their sites of action. [This statement is TRUE: Approximately 1,500 nucleus-encoded proteins in the mitochondrion are devoted to mitochondrial gene expression and mtDNA maintenance. Even the RNA polymerase that transcribes mtDNA (POLRMT) is encoded by nuclear DNA.]

d. Transcription of human mtDNA is directed by a dedicated mitochondrial RNA polymerase (POLRMT) that is a member of the bacteriophage T3/T7 family of single-subunit RNA polymerases. [This statement is TRUE: Unlike the bacteriophage RNA polymerases, however, POLRMT has a large amino terminal extension that contains two pentatricopeptide repeat domains, which are conserved only in vertebrate mtRNA polymerases.]

e. Most, if not all, mitochondrial RNA polymerases require associated transcription factors for function. [This statement is TRUE: The functional requirement of transcription factors is an additional difference between bacteriophage RNA polymerases and POLRMT.]

26. Mutations in mtDNA contribute to human disease. Based on the referenced Award Lecture, select the ONE statement that is NOT true: [See Am J Pathol 2008 172: 1445-1456; the author of the referenced article did not disclose any potential conflicts of interest.]

a. The A1555G mutation in the 12S rRNA gene is associated primarily with non-syndromic and/or aminoglycoside antibiotic-induced deafness. [This statement is TRUE: Associated deafness and mitochondrial phenotypes are influenced strongly by the nuclear genetic background.]

b. A polymorphism near the h-mtTFB1 gene provides a protective effect in individuals with deafness-associated A1555G mutation. [This statement is TRUE: h-mtTF1 acts as a transcription factor and also methylates a conserved stem-loop in mitochondrial 12S rRNA. While the mechanisms through which h-mtTFB1 modifies the A1555G deafness phenotype remains unknown, it is likely that it is through its impact on mitochondrial translation either indirectly, via its transcription factor function, or directly, via its methylation of the 12S rRNA. An altered and malfunctioning ribosome conformation imposed by the A1555G mutation could, in principle, be restored by lack or alteration of methylation of the nearby stem-loop.]

c. A vicious cycle of mitochondria-driven oxidative stress is often postulated as a key feature of aging and age-related pathology. [This statement is TRUE: According the so-called “Free Radical Theory of Aging,” mitochondrial reactive oxygen species (ROS) damage components and ultimately lead to loss of normal cell and tissue function that underlie the aging process.]

d. Like nuclear DNA replication, mtDNA replication occurs exclusively in S phase. [This statement is FALSE: mtDNA replication occurs in all stages of the cell cycle and persists even in non-dividing cells.]

e. Mutations in genes encoding mitochondrial and cytoplasmic deoxynucleotide salvage enzymes cause a subset of inherited human mtDNA depletion syndromes. [This statement is TRUE: For example, a recent report found linkage of mutations in the p53R2 subunit of ribonucleotide reductase (RNR) in mitochondrial disease patients with severe mtDNA depletion in muscle.]

27. Epidemiological studies have demonstrated that the use of methamphetamine (meth) is common among patients infected with human immunodeficiency virus (HIV); however, there has been a lack of direct evidence that meth promotes HIV infection of target cells. Based on the referenced Commentary and related article, select the ONE statement that is NOT true: [See Am J Pathol 2008 172: 1467-1470; the authors of the referenced articles did not disclose any potential conflicts of interest.]

a. Approximately 4.9% of Americans have tried meth at least once in their life. [This statement is TRUE: In the United States, approximately 1.5 million individuals regularly use/abuse meth.]

b. Meth treatment of human blood monocyte-derived macrophages resulted in a significant and dose-dependent increase of HIV reverse transcriptase activity. [This statement is TRUE: However, the conclusive evidence of meth’s effects on increasing HIV-1 replication in human subjects remains difficult to prove since factors such as multi-drug use and antiretroviral therapy significantly affect HIV-1 progression in this population.]

c. SCH23390 and SKF83566, which are dopamine D1 receptor (D1R) antagonists, blocked the meth-mediated increase in the HIV infectivity of macrophages. [This statement is TRUE.]

d. CCR5, the chemokine receptor used by HIV-1 as a co-receptor for macrophage infection, is upregulated in meth-treated macrophages. [This statement is TRUE.]

e. Meth has the ability to stimulate endogenous interferon α (IFN-α) expression in macrophages, suggesting that upregulation of D1R is a mechanism responsible for the action of meth on HIV. [This statement is FALSE: Meth has the ability to suppress endogenous IFN-α in macrophages. This meth action is mediated by D1R.]
28. Reactive oxygen and nitrogen species, including the reactive oxidant peroxynitrite, are generated in parenchymal, endothelial, and infiltrating inflammatory cells during cardiovascular, inflammatory, neurodegenerative, and other disorders. Based on the referenced Biological Perspectives article on the role of the peroxynitrite-poly(ADP-ribose) polymerase (PARP) pathway in human disease, select the ONE statement that is NOT true. [See Am J Pathol 2008 173:2-13; one of the authors of the referenced article is a founder, owns stock in, and is a prior Chief Scientific Officer of Inotek Inc., the developer of PARP inhibitors.]

a. Peroxynitrite is a reactive nitrogen species formed from the diffusion-limited reaction of nitric oxide and superoxide anion. [This statement is TRUE: Peroxynitrite has been identified as a pathophysiologically relevant trigger of PARP activation and can also induce pathophysiological alterations independently from PARP.]

b. The most abundant isoform of the PARP enzyme family is the 116-kDa nuclear enzyme poly(ADP-ribose) polymerase 1 (PARP-1). [This statement is TRUE: PARP-1 functions as a DNA damage sensor and signaling molecule, binding to both single- and double-stranded DNA breaks. Upon binding to damaged DNA, PARP-1 forms homodimers and catalyzes the cleavage of NAD⁺ into nicotinamide and ADP-ribose to form long branches of ADP-ribose polymers on target proteins such as histones and PARP-1 itself.]

c. Numerous transcription factors, DNA replication factors, and signaling molecules become poly(ADP-ribosylated) by PARP-1. [This statement is TRUE: PARP-mediated activation of nuclear factor κB (NF-κB) appears to be of critical importance.]

d. PARP activation contributes to the development of disease by driving the cell into a state of dysfunction and energy deficit and by catalyzing the activation of pro-inflammatory pathways. [This statement is TRUE.]

e. Like hydroxyl radical, peroxynitrite can cross cell membranes, enter the nucleus, and trigger breaks in the strands of DNA. [This statement is FALSE: Hydroxyl radical cannot travel significant distances. Peroxynitrite is the only known species with the capacity of having both a long enough half-life to travel within and between cells and the ability to break DNA.]

29. Peroxynitrite formation has been implicated in pathogenesis of stroke and degenerative diseases of the central and peripheral nervous system. Based on the referenced Biological Perspectives article, select the ONE statement that is NOT true. [See Am J Pathol 2008 173:2-13; one of the authors of the referenced article is a founder, owns stock in, and is a prior Chief Scientific Officer of Inotek Inc., the developer of PARP inhibitors.]

a. Elevated free nitrotyrosine, nitrite, and nitrate levels are detected in the cerebrospinal fluid of patients with stroke, Alzheimer’s disease, Parkinson’s disease, amyotrophic lateral sclerosis, and multiple sclerosis. [This statement is TRUE: Once generated in the diseased brain, peroxynitrite may exert its toxic effects via multiple mechanisms, including protein nitration and oxidation, lipid peroxidation, mitochondrial damage, depletion of antioxidant reserves, activation or inhibition of various signaling pathways, and DNA damage followed by the activation of PARP-1.]
b. Nitrotyrosine rapidly accumulates in the brain following transient or permanent ischemia. [This statement is TRUE: The nitrotyrosine accumulation is markedly prevented by strategies blocking nitric oxide or superoxide generation, as well as by treatments aimed at directly scavenging peroxynitrite.]

c. In the early stages of stroke (up to 24 hours), the activation of PARP is present primarily in neuronal elements, followed by a second wave of PARP activation (at 3-4 days after stroke) in infiltrating immune/inflammatory cells. [This statement is TRUE.]

d. The activation of PARP in Alzheimer’s disease mainly localizes to Lewy bodies. [This statement is FALSE: Lewy bodies are a characteristic feature of Parkinson’s disease. The activation of PARP in Alzheimer’s disease mainly localizes to small pyramidal neurons.]

e. Inflammatory plaques in multiple sclerosis patients are characterized by increased immunoreactivity for iNOS and nitrotyrosine. [This statement is TRUE.]

30. MicroRNAs (miRNAs) play an important role in human disease. Based on the referenced article concerning Hodgkin/Reed-Sternberg (HRS) cells of Hodgkin lymphoma, select the ONE statement that is NOT true: [See Am J Pathol 2008 173:242-252; the authors of the referenced article did not disclose any potential conflicts of interest.]

a. PRDM1, also known as Blimp-1, is expressed as two isoforms, α and β, as a result of alternative promoter usage. [This statement is TRUE: The β form lacks the amino-terminal acidic domain and part of the PR domain and is functionally impaired.]

b. The PRDM1 gene has been shown to be inactivated by a classic mechanism for tumor suppressor genes in diffuse large B-cell lymphoma. [This statement is TRUE.]

c. HRS cells resemble post-germinal center cells both immunophenotypically and genetically. [This statement is TRUE: HRS cells lack BCL-6 and consistently express interferon regulatory factor-4 (IRF4). They harbor somatic mutations in their immunoglobulin genes but show no evidence of ongoing somatic hypermutation.]

d. High levels of miR-9 and let-7a in Hodgkin lymphoma cell lines correlated with low levels of PRDM1. [This statement is TRUE.]

e. The most distal of the three complementary binding sites for miR-9 in the 3’ untranslated region of PRDM1 appears to be the major effector of translational repression. [This statement is FALSE: Although all three putative miR-9 binding sites predicted in the PRDM1 3’ untranslated region show conserved pairing with the miR-9 sequence, the most proximal target site appears to the major effector.]
31. Abnormalities in the nucleolar morphology of cancer cells have attracted the attention of tumor pathologists for over a century. Based on the referenced Review on the relationship between the nucleolus and cancer, select the ONE statement that is NOT true. [See Am J Pathol 2008 173:301-310; the authors of the referenced article did not disclose any potential conflicts of interest.]

   a. In hematoxylin and eosin-stained histological sections from routinely processed tissue samples, the nucleoli are intensely stained by hematoxylin. [This statement is FALSE: Nucleoli are intensely stained by eosin due to their very high protein content.]
   
   b. Transcriptionally active ribosomal genes are located in the fibrillar centers and the dense fibrillar component of nucleoli. [This statement is TRUE: At the electron microscope level, fibrillar centers appear as roundish structures of varying size, with a very low electron opacity. The dense fibrillar component frequently constitutes a rim intimately associated with the fibrillar centers and is composed of densely packed fibrils.]
   
   c. rRNA molecules, which are produced in the fibrillar centers and the dense fibrillar component, migrate to the granular component of the nucleolus where they undergo maturation for ribosome subunit constitution. [This statement is TRUE.]
   
   d. Nucleolin, nucleophosmin, upstream binding factor (UBF), and the largest RNA polymerase I subunit are selectively stained by the same silver-staining methods used to visualize the nucleolar organizer regions (NORs) on metaphase chromosomes. [This statement is TRUE: These proteins are called AgNOR proteins, and the silver-stained fibrillar components are called interphase AgNORs. Morphometric analysis can precisely quantify the interphase NORs, which are visualized at the light microscope level as well-defined black dots within the nucleolar body.]
   
   e. The number and the area occupied by interphase AgNORs within the nucleolus are directly related to both the whole nucleolar size and its transcriptional activity. [This statement is TRUE: The evaluation of the distribution of the interphase AgNORs appears to be a very simple method for quantifying nucleolar changes and also for obtaining precise information on the ribosome biogenesis activity of the cell at the light microscope level.]

32. Nucleolar changes related to tumorigenesis can be evaluated in human tumors. Based on the referenced Review on the relationship between the nucleolus and cancer, select the ONE statement that is NOT true. [See Am J Pathol 2008 173:301-310; the authors of the referenced article did not disclose any potential conflicts of interest.]

   a. The nucleolar changes of practically all human cancers have been evaluated and shown to be highly variable and independent of the histogenesis of the tumors as well as within the same tumor sample. [This statement is TRUE.]
   
   b. Nucleolar hypertrophy and functional upregulation of the nucleolus are always characteristics of cancer cells. [This statement is FALSE: Although nucleolar hypertrophy and functional upregulation of the nucleolus are generally considered to be characteristics of cancer cells, some studies demonstrate that nucleolar size and functional activity are sometimes lower than those of the corresponding normal cells. The nucleolar changes in tumors are closely related to the number of proliferating cells within the cancer tissue and the rapidity of proliferation of the cycling cells, which are highly variable parameters in human tumors and are sometimes at lower levels than in the corresponding proliferating normal tissues.]
c. The upregulation of the nucleolar function occurring in proliferating cells is due to the products of the same proto-oncogene and tumor suppressor genes that control cell proliferation. [This statement is TRUE: Changes of proto-oncogenes and tumor suppressor genes occur very frequently in a variety of human cancers that are responsible not only for the loss of the normal control mechanisms of cell proliferation and cell cycle progression but also for an enhanced ribosome biogenesis.]

d. c-Myc, which is over-expressed in a variety of human hematological malignances and solid tumors, directly enhances RNA polymerase I transcription activity by binding to specific consensus elements of rDNA and recruiting selectivity factor I (SL1) to the rDNA promoter. [This statement is TRUE: SL1 is necessary for rDNA transcription by recruiting RNA polymerase I, in a complex with UBF, to the rRNA gene promoter.]

e. Cyclins D and E control normal cell cycle progression and may be over-expressed or altered in a number of human tumors. [This statement is TRUE: Cyclins D and E also induce the phosphorylation of UBF by cyclin-dependent kinase 4 (Cdk4)-cyclin D1- and Cdk2-cycline E mechanisms, thus enhancing the transcription of ribosome genes.]

33. Genetic changes involving the retinoblastoma tumor suppressor protein (pRB) and p53 pathways are very relevant to neoplastic transformation and have important effects on ribosome biogenesis. Based on the referenced Review on the relationship between the nucleolus and cancer, select the ONE statement that is NOT true. [See Am J Pathol 2008 173:301-310; the authors of the referenced article did not disclose any potential conflicts of interest.]

   a. E2Fs are a family of transcription regulators that regulate the expression of genes whose products are necessary for S phase progression. [This statement is TRUE: During the cell cycle, pRB controls passage through the G1/S phase restriction point by interacting with E2Fs.]
   
   b. In its active hyperphosphorylated form, pRB is bound to E2Fs and prevents them from activating E2F target genes. [This statement is FALSE: pRB undergoes a progressive phosphorylation through the cell cycle phases. In its active hypophosphorylated form, pRB is bound to E2Fs and prevents them from activating E2F target genes. In its hyperphosphorylated form, pRB no longer binds to E2Fs, which are released to activate the target genes.]
   
   c. In cycling cells the progressive phosphorylation of pRB from early G1 phase to G2 phase induces a progressive increase of the rRNA transcription rate, along with a progressive enlargement of the nucleolar size, from the G1 to the G2 phase. [This statement is TRUE: Active non-phosphorylated pRB inhibits rRNA synthesis by binding to UBF.]
   
   d. The presence of very enlarged nucleoli in cancer tissues is frequently associated with a poor clinical outcome. [This statement is TRUE: Nucleolar hypertrophy is a valuable prognostic parameter in tumor pathology.]
   
   e. In addition to p53’s role in a variety of cellular stress responses that lead to apoptosis or induction of the Cdk2 inhibitor p21Cip1, inhibition of cyclin E/Cdk2, and pRB-dependent cell cycle arrest, p53 directly influences ribosome biogenesis. [This statement is TRUE: Accumulation of wild-type p53 inhibits RNA Pol I transcription by binding to SL1, thus hindering the formation of the UBF-SL1 complex necessary for RNA polymerase I recruitment to the rRNA gene promoter.]

34. The effect of sustained hyperglycemia on pancreatic pathophysiology is not well understood. Based on the referenced article, select the ONE statement that is NOT true. [See Am J Pathol 2008 173:442-450; the authors of the referenced article did not disclose any potential conflicts of interest.]

   a. Early apoptosis was detected in human pancreatic islet microvascular endothelial cells (MECs) following 24-28 hours in high glucose. [This statement is TRUE: DNA fragmentation and activation of the caspase family represent early steps of apoptosis in eukaryotic cells.]
   
   b. Under conditions of sustained hyperglycemia, islet MECs showed progressively reduced phosphorylation of Akt. [This statement is TRUE: Akt activation is crucial for the ability of factors such as insulin, insulin growth factor (IGF)-I, and vascular endothelial growth factor (VEGF) to inhibit apoptosis in cultured endothelium.]
   
   c. Hyperglycemia upregulated the tyrosine phosphorylated form of the transmembrane protein nephrin. [This statement is FALSE: Hyperglycemia downregulated the tyrosine phosphorylated form of the transmembrane protein nephrin, without affecting its cellular expression or distribution. Phosphorylated nephrin associates with PI3K and activates the multifunctional Akt-dependent pathways.]
   
   d. Pravastatin treatment inhibited apoptosis and increased Akt phosphorylation. [This statement is TRUE: Akt is a major effector of the PI3K survival signaling pathway.]
   
   e. Increased production of the pro-inflammatory cytokine interleukin (IL)-1β by islet MECs was detected under hyperglycemic conditions. [This statement is TRUE: IL-1β has been shown to impair insulin release in human islets and to induce Fas expression enabling Fas-mediated apoptosis, thus implicating an inflammatory process in the pathogenesis of glucotoxicity in the diabetic condition.]
35. Autoimmune diseases (AIDs) affect approximately 5% to 8% of the population of the United States. Based on the referenced Review, select the ONE statement that is NOT true. [See Am J Pathol 2008 173:600-609; the authors of the referenced article did not disclose any potential conflicts of interest.]

   a. AIDs are more common in women than in men. [This statement is TRUE: Conservative estimates indicate that around 78% of the people affected with AIDs are women.]
   b. The basic immune response differs between men and women. [This statement is TRUE: Women respond to infection, vaccination, and trauma with increased antibody production, resulting in protection against infection, whereas inflammation is usually more severe in men resulting in an increased mortality in men.]
   c. The number of different autoantibodies present in an individual is a good predictor of the risk of developing AID. [This statement is TRUE: For example, the likelihood of a child developing type 1 diabetes within five years is 10% in the presence of one autoantibody, 30% for two autoantibodies, and greater than 60% if three autoantibodies are present.]
   d. The number of autoantibodies increases with age, regardless of sex. [This statement is TRUE: Therefore, even though an increased antibody response protects women from infections, it also increases the risk of developing an AID.]
   e. Idiopathic pulmonary fibrosis (IPF), a typical example of an AID that is more prevalent in males, manifests clinically early in life. [This statement is FALSE: AIDs that are more prevalent in males, such as myocarditis and ankylosing spondylitis, usually manifest clinically early in life. IPF is an exception of an AID that exhibits a higher incidence in males and manifests later in life. In IPF, the early acute phase of disease does not manifest clinically. Signs and symptoms of disease do not appear until lung fibrosis is established.]

36. AIDs progress from an acute pathology associated with an inflammatory immune response to a chronic pathology associated with fibrosis. Based on the referenced Review, select the ONE statement that is NOT true. [See Am J Pathol 2008 173:600-609; the authors of the referenced article did not disclose any potential conflicts of interest.]

   a. Acute inflammation can involve a predominantly Th1 (macrophages/neutrophils) and/or Th17 (neutrophils) response, as occurs after viral or bacterial infections or injury, or a predominantly Th2 response (eosinophils), as occurs for asthma and allergy. [This statement is TRUE: Most acute inflammatory responses do not manifest clinically as AIDs and resolve once the infection has been cleared or the damaged tissue has healed.]
   b. The immune system recognizes the presence of infectious organisms and damage to tissues using pattern recognition receptors (PRRs) such as Toll-like receptors (TLRs). [This statement is TRUE: TLR expression on antigen-presenting cells is upregulated in response to infection with bacteria or viruses, or inoculation with adjuvants like complete Freund's adjuvant and/or pertussis toxin.]
c. TLR signaling usually induces Th1-directed immunity in response to infection and also provides a potent negative signal preventing the development of Th2 cells. [This statement is TRUE: One exception is TLR2 signaling, which increases Th2 responses and interleukin (IL)-10, thereby inhibiting Th1 immune responses.]
d. Estrogens and androgens directly influence the immune response by interacting with hormone receptors on immune cells. [This statement is TRUE.]
e. Estrogen receptors in the heart are found only on infiltrating immune cells, whereas androgen receptors are found on infiltrating immune cells as well as on/in cardiac muscle, smooth muscle, and endothelial cells. [This statement is FALSE: Both estrogen and androgen receptors in the heart are found on infiltrating immune cells and on/in cardiac muscle, smooth muscle, and endothelial cells.]

37. Genetically-determined mutations in individual intermediate filament protein-encoding genes account for, or are associated with, more than 70 distinct human disorders. Based on the referenced article, select the ONE statement that is NOT true. [See Am J Pathol 2008 173:752-761; the authors of the referenced article did not disclose any potential conflicts of interest.]

a. K6a and K6b belong to a subset of keratin genes with constitutive expression in epithelial appendages and inducible expression in additional epithelia when subjected to environmental challenges or disease. [This statement is TRUE: Mutations in K6a or K6b cause a broad spectrum of epithelial lesions that differentially affect nail, hair, and glands in humans.]
b. Mutations altering the coding sequence of the keratins K6a, K6b, K16 or K17 cause pachyonychia congenital, which often features marked anomalies in sebaceous glands. [This statement is TRUE.]
c. Steatocystoma multiplex and two palmoplantar keratoderma variants are associated with the affected target protein K16. [This statement is FALSE: Steatocystoma multiplex is associated with K17. The palmoplantar keratoderma variants are associated with K16.]
d. Hedgehog signaling is essential for the morphogenesis and post-natal cycling of hair follicles. [This statement is TRUE.]
e. K6a expression coincides with Hedgehog signaling in ductal tissue. [This statement is TRUE.]

38. The morphogenesis of sebaceous glands is not well understood. Based on the referenced article, select the ONE statement that is NOT true: [See Am J Pathol 2008 173:752-761; the authors of the referenced article did not disclose any potential conflicts of interest.]

a. Sebocytes arise from a pool of mitotically active, transit-amplifying basal cells located in the outermost aspect of the gland. [This statement is TRUE: Sebocytes undergo holocrine secretion in the hair canal.]
b. The ultimate source for the sebocyte lineage in adult mouse skin is a small pool of committed progenitor cells tucked within the outer root sheath at or near the point of sebaceous gland branching from hair follicles. [This statement is TRUE.]
c. Blimp-1 is a transcriptional repressor that helps maintain sebocytes in a relatively quiescent state. [This statement is TRUE.]
d. Sebaceous glands cannot form in the absence of K6a and K6b. [This statement is FALSE: Sebaceous glands can form in the absence of K6a and K6b, but the significance of this observation is unclear as K5 and possibly K75 may compensate for the loss of K6.]
e. Activation of Hedgehog signaling and c-Myc stimulates sebaceous gland morphogenesis. [This statement is TRUE: In mouse skin, activation of Hedgehog signaling and c-Myc stimulates sebaceous gland morphogenesis and eventually causes sebaceous gland tumors.]
39. Gestational trophoblastic disease (GTD) is a unique group of diseases that are derived from the conceptus rather than from the patient. Based on the referenced article and related Commentary, select the ONE statement that is NOT true. [See Am J Pathol 2008 173:1165-1172 and Am J Pathol 2008 173:911-914; the authors of the referenced articles did not disclose any potential conflicts of interest.]

a. Hydatidiform moles are aberrant placental derivatives that are prone to malignant transformation. [This statement is TRUE: Most hydatidiform moles spontaneously regress after suction evacuation. However, up to 30% will develop persistent gestational trophoblastic neoplasia with metastatic potential.]

b. Choriocarcinoma is the most common type of gestational trophoblastic neoplasia (GTN) and is the most primitive trophoblastic tumor. [This statement is TRUE: Placental site trophoblastic tumor and epithelioid trophoblastic tumor are other examples of GTN that develop from hydatidiform moles.]

c. Cytotrophoblasts differentiate into either syncytiotrophoblasts or extravillous trophoblastic cells. [This statement is TRUE.]

d. The neoplastic cytotrophoblastic cells in placental site trophoblastic tumors differentiate mainly into cells resembling implantation site extravillous trophoblastic cells. [This statement is TRUE: In contrast, the neoplastic trophoblastic cells in epithelioid trophoblastic tumors differentiate into extravillous trophoblastic cells similar to those in the chorion laeve.]

e. The clinical outcome in most patients with GTN is very poor, even after combined chemotherapy and adjuvant surgical procedures. [This statement is FALSE: The clinical outcome in most patients with GTN is excellent after combined therapy. Choriocarcinoma is one of only a few human cancers in which metastatic disease is potentially curable.]

40. Embryonic stem cells and cancer cells share some similarities. Based on the referenced article and its related Commentary, select the ONE statement that is NOT true. [See Am J Pathol 2008 173:1165-1172 and Am J Pathol 2008 173:911-914; the authors of the referenced articles did not disclose any potential conflicts of interest.]

a. Nanog is a transcription factor found in pluripotent embryonic stem cells. [This statement is TRUE: The name Nanog is derived from Irish mythology, Tir na nOg, which means the land of eternal youth.]

b. Nanog expression is high in undifferentiated embryonic stem cells and is downregulated during differentiation. [This statement is TRUE: Nanog is a member of the homeobox family of DNA-binding transcription factors.]

c. Nanog immunoreactivity in early normal placentas was higher in syncytiotrophoblasts and extravillous trophoblastic cells than in cytotrophoblasts. [This statement is FALSE: Nanog immunoreactivity in early normal placentas was mainly observed in cytotrophoblast and was only focal and weak in other trophoblastic subpopulations including syncytiotrophoblasts and extravillous trophoblastic cells.]

d. Hydatidiform moles expressed higher levels of Nanog as compared to first trimester placentas. [This statement is TRUE.]

e. Higher mRNA and protein expression levels of Nanog in hydatidiform moles were associated with increased risk of developing persistent GTD. [This statement is TRUE.]
41. The molecular etiology of GTN remains unclear. Based on the referenced article and its related Commentary, select the ONE statement that is NOT true. [See Am J Pathol 2008 173:1165-1172 and Am J Pathol 2008 173:911-914; the authors of the referenced articles did not disclose any potential conflicts of interest.]

   a. Nanog knockdown resulted in decreased cellular proliferation, mobility, and invasion of choriocarcinoma cells. [This statement is FALSE: Knockdown of Nanog decreased mobility and invasion of choriocarcinoma cells but had no apparent effect on cellular proliferation. This suggests that Nanog is essential for cell survival but may not be sufficient to stimulate cellular proliferation.]
   
   b. The Nanog gene is located on chromosome 12p. [This statement is TRUE: It is of interest to note that many germ cell tumors of the testis harbor a unique structural abnormality, isochromosome 12p.]
   
   c. Ectopic expression of NECC1 in choriocarcinoma cells suppressed tumorigenicity and induced terminal differentiation, suggesting that NECC1 is a potential tumor suppressor gene in choriocarcinomas. [This statement is TRUE: NECC1 is a newly identified homeobox gene.]
   
   d. Downregulation of E-cadherin, HIC-1, p16, and TIMP3 resulting from promoter hypermethylation was frequently found in choriocarcinomas. [This statement is TRUE: The data suggest that reduced expression of E-cadherin, HIC-1, p16, and TIMP3 may participate in choriocarcinoma development.]
   
   e. Histologic grading and expression of cellular proliferation markers such as proliferating cell nuclear antigen (PCNA) and Ki-67 in GTN do not correlate with clinical outcome. [This statement is TRUE.]

42. Angiogenesis is an integral component of many physiological and pathological conditions such as wound healing, inflammation, and tumor growth. Based on the referenced article, select the ONE statement that is NOT true: [See Am J Pathol 2008 173:1220-1228; the authors of the referenced article did not disclose any potential conflicts of interest.]

   a. Thrombospondin-1 (TSP-1) inhibits growth factor-induced endothelial cell proliferation and migration in vitro and suppresses neovascularization in vivo. [This statement is TRUE: TSP-1 is a matricellular protein.]
   
   b. Systemic application of a TSP-1-derived peptide inhibits tumor growth in a dose-dependent manner. [This statement is TRUE: Clinical trials are underway.]
   
   c. Shear stress withdrawal leads to increased CD36 expression in cultured human umbilical vein endothelial cells (HUVECs). [This statement is FALSE: Shear stress withdrawal leads to reduced CD36 expression.]
   
   d. Endothelial cells that had been pre-conditioned to a CD36low phenotype with vascular endothelial growth factor (VEGF) became insensitive to anti-proliferative TSP-1 signaling. [This statement is TRUE.]
   
   e. The data are consistent with the hypothesis that CD36 downregulation in capillary sprout endothelial cells facilitates angiogenesis in the presence of TSP-1. [This statement is TRUE: VEGF and withdrawal of shear stress downregulate endothelial CD36 expression.]
43. An estimated 80 million American adults suffer from cardiovascular disease. Based on the referenced Review, select the ONE statement that is NOT true. [See Am J Pathol 2008 173:1253-1264; the authors of the referenced article did not disclose any potential conflicts of interest.]

a. The use of leukocyte count, C-reactive protein (CRP), interleukin (IL)-18, IL-6, and soluble CD40 ligand as inflammatory markers has become a useful tool for clinicians. [This statement is TRUE: Evidence supports a role of inflammation in propagating the transition from early atherogenesis to thrombotic events such as myocardial infarction or stroke.]

b. As proinflammatory cytokines are recruited to the vessel wall to promote the attachment, rolling, and infiltration of leukocytes into the intimal layers, the formation of oxidized low-density lipoprotein (LDL) is believed to play a pivotal role in amplifying the inflammatory response. [This statement is TRUE: While the initial events following endothelial injury resemble an innate immune response to modified LDL, characteristics of the adaptive immune response also resonate in a chronic setting.]

c. Numerous studies have consistently demonstrated the benefit of antibiotic treatment in prevention of coronary events. [This statement is FALSE: Infectious agents damage the endothelial lining and promote a pro-adhesive and pro-coagulant surface that is critical in the initiation of atherosclerotic disease. However, clinical inconsistencies remain, such as the lack of apparent benefits from antibiotic treatment in the secondary prevention of coronary events.]

d. Tumor necrosis factor (TNF)-α is a systemic mediator of inflammation linked to proliferation, apoptosis, and differentiation. [This statement is TRUE: TNF-α binds TNF receptor-1 and -2 to activate components of the mitogen-activated protein (MAP) kinase pathways and increase the levels of pro-inflammatory transcription factors such as nuclear factor (NF)-κB.]

e. In response to growth factors, smooth muscle cells derived from the vessel wall migrate and proliferate throughout the intima and secrete collagen, vascular endothelial growth factor (VEGF), TNF-α, IL-1, and other pro-inflammatory molecules. [This statement is TRUE: As lesions progress to intermediate and eventually mature fibrous plaques, associated fundamental processes remain largely driven by inflammation.]

44. Recent work has described a genetic rift between modern-day humans and our ancestors as a result of widespread changes in diet, physical activity, and other factors. Based on the referenced Review, select the ONE statement that is NOT true. [See Am J Pathol 2008 173:1253-1264; the authors of the referenced article did not disclose any potential conflicts of interest.]

a. An increase in polyunsaturated fatty acid intake in modern diets has resulted in an ω-6/ω-3 ratio that is estimated to have decreased several-fold over pre-agricultural levels. [This statement is FALSE: Modern dietary patterns are characterized by a five-fold increase in the ω-6/ω-3 ratio. The ratio, rather than the absolute levels of these fatty acids, is critical as a predictor of atherogenic risk. Polyunsaturated fatty acids can be subdivided by the position of their double bond into ω-6 and ω-3 fatty acids. Lean game, wild fruits, flaxseed, nuts, and fish are a rich source of ω-3 fatty acids such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).]
b. Grains are rich sources of ω-6 fatty acids and are low in ω-3 fatty acids. [This statement is TRUE: The mechanisms attributed to the ability of ω-3 fatty acids to suppress inflammation include the replacement of corresponding ω-6 pools in membrane phospholipids, as well as a reduction in proinflammatory transcription factors, cytokines, adhesion molecules, chemokines, and reactive oxygen species (ROS).]

c. Fish oil is a prominent source of ω-3 fatty acids and has been demonstrated to exert a suppressive effect on the production of inflammatory molecules linked to atherogenesis. [This statement is TRUE: For example, fish oil enhances endothelial-derived relaxing factor (nitric oxide) release from endothelial cells, harnessing the potent anti-inflammatory actions of this molecule. EPA and DHA function to reduce platelet-derived growth factor (PDGF), thereby suppressing proliferation and migration of sub-intimal cell types.]

d. When compared to diets relying more heavily on wild plants, those with high grain intake are associated with reduced levels of ascorbate, carotene, thiamine, folate, riboflavin, and vitamins A and E. [This statement is TRUE: These molecules serve as essential cofactors and antioxidants. Deficiencies may further contribute to injury under conditions of inflammatory-driven oxidative stress in the vascular wall.]

e. A clear link between vitamin intake and the reversal of atherosclerosis is lacking in clinical trials. [This statement is TRUE: It has been suggested that optimal protection with vitamins occurs through targeting of the earliest inflammatory changes in atherosclerosis; thus, their effectiveness in the reversal of advanced disease would not be surprising.]

45. Lyme disease is a tick-borne infection caused by the spirochete *Borrelia burgdorferi*. Based on the referenced article, select the ONE statement that is NOT true. [See Am J Pathol 2008 173:1415-1427; the authors of the referenced article did not disclose any potential conflicts of interest.]

a. The organ pleiotropism of *B. burgdorferi* results in diverse disease manifestations such as chronic arthritis, myocarditis, and neuroborreliosis. [This statement is TRUE: Lyme neuroborreliosis affects up to 25% of patients with erythema migrans, the red skin rash that signals the point of entry of the spirochete.]

b. Although they are found in the encephalomyelitis manifestation of neuroborreliosis, intrathecal anti-*B. burgdorferi* antibodies are not detectable in the meningitis manifestation. [This statement is FALSE: Lymphocytic pleocytosis in the cerebrospinal fluid and intrathecal anti-*B. burgdorferi* antibodies are present in both meningitis and encephalomyelitis associated with neuroborreliosis.]

c. Neuroborreliosis involves both the peripheral and central nervous systems. [This statement is TRUE.]

d. Brain lesions from Lyme neuroborreliosis show vasculitis and subarachnoid hemorrhage as well as multifocal encephalitis with large areas of demyelination in perivascular white matter. [This statement is TRUE: Patients with encephalomyelopathy complain of specific memory and/or intellectual impairment, often associated with incapacitating fatigue.]

e. Neurologic disturbance limited to the spinal cord can manifest clinically as acute transverse myelitis and leptomeningitis. [This statement is TRUE.]

46. Inflammation plays an important role in the pathogenesis of neuroborreliosis. Based on the referenced article, select the ONE statement that is NOT true: [See Am J Pathol 2008 173:1415-1427; the authors of the referenced article did not disclose any potential conflicts of interest.]

a. Astrocytes are among the cells that are a source of the interleukin (IL)-6 produced in the central nervous system in response to a *B. burgdorferi* infection. [This statement is TRUE.]

b. Transcripts of genes that regulate inflammation as well as apoptosis of oligodendrocytes and neurons were significantly perturbed after live *B. burgdorferi* penetrated slices of rhesus macaque brain cortex in an *ex vivo* model, as assessed by microarray analysis. [This statement is TRUE.]

b. Interleukin (IL)-1β was produced by microglia in spirochete-stimulated brain tissue. [This statement is TRUE: IL-1β is a cytokine that plays a role in mediating inflammation in the central nervous system.]

c. Spirochetes elicited both the upregulation of IL-8 transcript in brain tissues and production of the chemokine by astrocytes and microglia. [This statement is TRUE.]

d. Tumor necrosis factor (TNF)-α was detected by immunofluorescence staining in brain sections stimulated with live spirochetes. [This statement is FALSE: Although TNF-α transcripts were found by microarray analysis to be significantly increased in spirochete-stimulated tissues, TNF-α was not detected by immunofluorescence staining. Rhesus TNF-α is readily detectable with the anti-human TNF-α antibodies used in the study. Possibly, there was a lag in the kinetics of translation of TNF-α transcripts, or translation of the transcripts was inhibited.]
47. The renin-angiotensin system (RAS) is a hormonal cascade that influences blood pressure and cellular function, including proliferation, angiogenesis, inflammation, and the stimulus of growth factor pathways. Based on the referenced article and related Commentary, select the ONE statement that is NOT true: [See Am J Pathol 2008 173:1591-1594 and Am J Pathol 2008 173:1911-1918; the authors of the referenced articles did not disclose any potential conflicts of interest.]

   a. Angiotensin converting enzyme (ACE) initiates the RAS pathway by cleaving angiotensinogen to generate angiotensin I.  
      [This statement is FALSE: The RAS pathway is initiated by prorenin, the inactive precursor of rennin, an enzyme that cleaves angiotensinogen to generate angiotensin I. Subsequent conversion of angiotensin I by ACE results in angiotensin II.]

   b. Renin is an aspartyl protease that consists of two homologous lobes. [This statement is TRUE: The cleft between the lobes contains the active site with two catalytic aspartic residues.]

   c. Angiotensin type I and type II receptors (AT1-R and AT2-R) are the most well characterized binding partners of angiotensin II. [This statement is TRUE: Angiotensin II binding to AT1-R results in vasoconstriction, cardiac hypertrophy, and decreased renal blood flow. Angiotensin type III and IV receptors are poorly characterized.]

   d. Blockade of the RAS with ACE or AT1-R inhibitors reduces the deleterious effects of angiotensin II. [This statement is TRUE: ACE and/or AT1-R inhibitors are commonly used for treating renal and cardiovascular disease.]

   e. (Pro)renin receptor interacts with prorenin to exert renin activity. [This statement is TRUE: (Pro)renin receptor activates prorenin by inducing a conformational change in the prorenin molecule rather than cleaving the prosegment through conventional proteolysis.]

48. Prorenin and the (pro)renin receptor have a pathological role in ocular disease. Based on the referenced article and the associated Commentary, select the ONE statement that is NOT true: [See Am J Pathol 2008 173:1591-1594 and Am J Pathol 2008 173:1911-1918; the authors of the referenced articles did not disclose any potential conflicts of interest.]

   a. The eye has a local RAS, with elements expressed in the retina and choroid. [This statement is TRUE: Although prorenin and renin synthesis have been identified in the retina, the main source is likely to be the glomerular juxtaglomerular cells of the kidney.]

   b. Prorenin binding to its receptor promotes choroidal neovascularization (CNV) solely by activating tissue RAS. [This statement is FALSE: Prorenin binding to its receptor activates not only tissue RAS, but also the RAS-independent extracellular signal-regulated kinase (ERK) pathway, both of which contribute to choroidal neovascularization (CNV).]

   c. A synthetic handle region peptide (HRP), which blocks prorenin binding to its receptor, reduces ocular disease. [This statement is TRUE: HRP has successfully been used to treat ocular disease in models of endotoxin-induced uveitis, retinopathy of prematurity, and laser-induced CNV.]

   d. The HRP was more beneficial than the AT1-R blocker losartan in suppressing CNV. [This statement is TRUE: Addition of HRP to mice in which RAS was deactivated by either the pharmacological blockage of AT1-R or the genetic ablation of AT1-R or angiotensinogen resulted in further suppression of CNV and macrophage infiltration.]

   e. In diabetic retinopathy, plasma and vitreal prorenin levels are elevated approximately 100-fold. [This statement is TRUE: A similar situation may occur in retinopathy of prematurity, where elevated prorenin levels have been reported in the retina.]
49. Melatonin is a neuromodulator that may provide neuroprotection in different systems. Based on the referenced article, select the ONE statement that is NOT true: [See Am J Pathol 2008 173:1702-1713; the authors of the referenced article did not disclose any potential conflicts of interest.]

a. Melatonin may act as a protective agent in ocular conditions such as photokeratitis, cataract, glaucoma, retinopathy of prematurity, and ischemia/reperfusion injury. [This statement is TRUE: Melatonin expression is protective in experimental free radical-related ocular diseases.]

b. Hamster retinal melatonin levels significantly decrease after pinealectomy, suggesting that the majority of melatonin in the retina is not produced locally. [This statement is FALSE: Hamster melatonin levels increase after pinealectomy, suggesting that retinal melatonin is generated within the tissue itself, as in other species.]

c. Melatonin possesses free radical scavenging and antioxidant activities. [This statement is TRUE: Melatonin possesses widespread free radical scavenging and antioxidant activities. Some of its scavenging actions are likely due to its metabolites, cyclic 3-hydroxymelatonin, N1-acetyl-N2-formyl-5-methoxykynuramine, and N-acetyl-5-methoxykynuramine.]

d. The neuroprotective role of melatonin may be through its interaction with calmodulin or microtubulin components. [This statement is TRUE: Melatonin may also block increases in intracellular Ca²⁺ levels, inhibit the nitridergic pathway, decrease vascular endothelial growth factor levels, or decrease retinal glutamate synaptic concentrations.]

e. Melatonin contributes to preserve blood-ocular barrier integrity. [This statement is TRUE: Melatonin significantly decreases the effect of lipopolysaccharide (LPS) on protein concentration and cell number in hamster aqueous humor. Melatonin also attenuates the post-ischemic increase in blood-brain barrier permeability following ischemic stroke in mice.]

50. Melatonin prevents the induction of experimental uveitis, an acute, recurrent, or persistent ocular inflammation with disruption of the blood-ocular barrier. Based on the referenced article, select the ONE statement that is NOT true: [See Am J Pathol 2008 173:1702-1713; the authors of the referenced article did not disclose any potential conflicts of interest.]

a. In the presence of melatonin, reduced cell infiltration was observed in the iris, ciliary body, limbus, retina, and vitreous. [This statement is TRUE: Melatonin prevents the clinical signs of experimental uveitis, including cell infiltration, dilation of the iris and conjunctival vessels, and anterior segment inflammation.]

b. Melatonin prevents lipopolysaccharide (LPS)-induced ultrastructural changes in photoreceptor organization. [This statement is TRUE: In retinas from eyes treated with LPS, altered shapes of photoreceptor outer segment's discs were observed. In retinas from eyes injected with LPS in the presence of melatonin, outer segments were similar in structure to those observed in retinas from vehicle-injected eyes.]

c. Visual function was not improved by melatonin treatment. [This statement is FALSE: The presence of melatonin prevented electroretinographic changes induced by LPS injection and successfully rescued the retina from inflammatory damage.]

d. Melatonin prevents the LPS-induced upregulation of the inflammatory mediator nuclear factor (NF)κB. [This statement is TRUE: LPS increases expression of both the p65 and p50 subunits of NFκB. This induction does not occur in the presence of melatonin.]

e. Melatonin preserves the blood-retinal barrier in experimental uveitis. [This statement is TRUE: In LPS-injected eyes, lanthanum fills almost the entire length of the intercellular junctions of endothelial cells. LPS-induced lanthanum deposits on the albuminal side of retinal epithelial cells are prevented by melatonin treatment.]