The American Academy of Clinical Toxicology Question of the Day.

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Published In/Presented At

Surmaitis R, Khalid M, McKeever R, Vearrier D, Greenberg M. The American Academy of Clinical Toxicology Question of the Day. Dis Mon. 2017 Aug;63(8):182-234. doi: 10.1016/j.disamonth.2017.03.005. Epub 2017 Jun 2.

Disease-a-Month 63 (2017) 182–234

Contents lists available at ScienceDirect

Disease-a-Month

journal homepage: www.elsevier.com/locate/disamonth

The American Academy of Clinical Toxicology Question of the Day

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Question 1: What is the OSHA “action level” for lead? What is the OSHA requirement for the temporary removal of employees from lead exposure?

Answer: The OSHA action level means “employee exposure, without regard to the use of respirators, to an airborne concentration of lead of 30 micrograms per cubic meter of air (30 μg/m3) averaged over an 8-hour period.” OSHA requires the removal of covered employees from lead exposure as follows: “The employer shall remove an employee from work having an exposure to lead at or above the action level on each occasion that a periodic and a follow-up blood sampling test conducted pursuant to this section indicate that the employee's blood lead level is at or above 60 micrograms/100 g of whole blood; and, The employer shall remove an employee from work having an exposure to lead at or above the action level on each occasion that the average of the last three blood sampling tests conducted pursuant to this section (or the average of all blood sampling tests conducted over the previous six (6) months, whichever is longer) indicates that the employee's blood lead level is at or above 50 micrograms/100 g of whole blood; provided, however, that an employee need not be removed if the last blood sampling test indicates a blood lead level below 40 micrograms/100 g of whole blood.” (http://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=standards&p_id=10030).

Commentary: Adults with occupational lead exposures are at risk for developing lead toxicity. Occupational Safety and Health Administration (OSHA) is responsible for establishing workplace safety regulations regarding chemical exposures. Physicians need to be aware of OSHA’s regulations when providing recommendations for adults with occupational lead exposure and to know when OSHA notification is required. RS.

Question 2: What is the mechanism of action for strychnine and what are the clinical findings that are classically described for strychnine poisoning?

Answer: The cited reference notes “Strychnine competitively blocks the neuroinhibitory transmitter glycine at postsynaptic sites, especially in the spinal cord. This results in hyperexcitability and convulsions. These convulsions typically involve flexor spasm of the upper limbs, extensor spasm of the lower limbs, opisthotonos, and spasms of the jaw muscles (risus sardonicus).” Patients typically do not lose consciousness but rather tend to be “hyper-alert” with even minimal stimulation triggering spasms. (Meatherall R et al. Toxicokinetics of acute strychnine poisoning. (1997 J Tox Clin Tox 35(6): 617 and O'Callaghan WG, et al. Unusual strychnine poisoning and its treatment: Report of eight cases. 1982 Br Med J Clin Res Ed 285:478).

Commentary: Strychine is an uncommon but potentially lethal poison. The severity of muscle spasms may lead to life-threatening acidosis and respiratory failure. Treatment for strychnine poisoning includes benzodiazepines, non-depolarizing neuromuscular blockade, and intubation. RS.

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http://dx.doi.org/10.1016/j.disamonth.2017.03.005

Question 3: What are the nine isotopes considered to be potential toxicants that may be used in RDDs (radiological dispersion devices)?

Answer: Americium-241; Californium-252; Cesium-137; Cobalt-60; Iridium-192; Plutonium-238; Polonium-210; Radium-226 and Strontium-90 are the isotopes considered to be potential toxicants in RDDs. (http://www.remm.nlm.gov/rdd.htm#isotopes).

Commentary: RDDs are devices that purposefully cause dissemination of radiation without a nuclear detonation. "Dirty bombs" are the most publicly known type of RDD. Death may result from the explosion itself rather than radiation. The public fear of radiation caused by the device may be greater than the actual health risks associated with radiation (http://www.nrc.gov/reading-rm/doc-collections/fact-sheets/fs-dirty-bombs.html). RS.

Question 4: What are metal halide and mercury vapor bulbs? What hazards have been recently associated with halide and mercury vapor light bulbs?

Answer: The FDA notes "Metal halide and mercury vapor bulbs are bright, long-lasting sources of light,

most often used to light streets, gyms, sports arenas, banks, and stores. The bulbs have an inner quartz tube, containing the mercury vapor discharge, enclosed by an outer glass bulb that filters out harmful short-wavelength UV radiation. If the outer bulb breaks and the inner tube continues to operate unshielded, intense UV radiation is emitted. UV exposure at this level can cause eye and skin burns, as well as blurred or double vision, headaches, and nausea." (http://www.fda.gov/Radiation-EmittingProducts/RadiationSafety/AlertsandNotices/ucm116540).

Commentary: Ultraviolet radiation exposure due to broken metal halide and mercury vapor bulbs may cause intense skin and eye burns. Precautionary measures to avoid such an exposure are discussed in the article. Immediate actions that should be carried out in such an event are discussed. Injuries occurring from these exposures should be reported to the bulb manufacturer, the nearest FDA district office, and the state health department. MK.

Question 5: What are DDVP pest strips?

Answer: The cited reference points out that Dichlorvos-impregnated resin strips (DDVP pest strips) are among the few organophosphate products still available for indoor residential use. These strips act by inhibiting acetylcholinesterase activity in the brain and nerves of insect pests and are designed to gradually release DDVP vapor for up to 4 months. Acute illnesses in humans associated with nonlethal acute exposures usually resolve completely, but recovery is not always rapid. (MMWR. Notes from the Field: Acute Illness Associated with Use of Pest Strips — Seven U.S. States and Canada, 2000–2013. January 17, 2014 / 63(02); 42-43).

Commentary: The article reports cases of organophosphate toxicity associated with the domestic use of DDVP pest strips in the US and Canada. Many such cases are due to failure to follow the manufacturer's instructions. Females (77 %) of age group 20-64 years were most frequently affected with most of them having neurologic symptoms (68%). MK.

Question 6: What is the chemical chloropicrin (military designation: PS) used for?

Answer: Chloropicrin (PS) is an irritant with characteristics of a tear gas. It has also found use in agriculture as a soil fumigant. It has also been used as a chemical warfare agent and a riot control agent. It was used in large quantities during World War I and was stockpiled during World War II. However, it is no longer authorized for military use. Chloropicrin has an intensely irritating odor and inhalation of as little as 1 ppm may cause eye irritation and may provide warning of the potential for exposure. (http://www.cdc.gov/NIOSH/ershdb/EmergencyResponseCard_29750034.html).

Commentary: Chloropiricin is a commonly used soil fumigant and potential source of occupational poisoning among agricultural workers. Symptomatic inhalational exposure may cause coughing, choking, difficulty breathing or shortness of breath. RS.

Question 7: What is kajal?

Answer: Kajal is a lead-containing traditional eye cosmetic that originates from Afghanistan and is often applied to the eyelids of Afghan children. It has been brought to the U.S. by the Afghan immigrant community and thus has been identified as a potential lead hazard for children. Laboratory analysis of this material has been reported to be as high as 70% lead content for this substance. The cited reference notes "Despite the FDA import ban on kohl, surma, and kajal, these products still appear in households, transported in personal luggage and distributed illegally by retailers. The risk for high BLLs caused by repeated exposure to multiple lead-contaminated consumer products and accumulation is a concern." (Childhood Lead Exposure Associated with the Use of Kajal, an Eye Cosmetic from Afghanistan — Albuquerque, New Mexico, 2013. MMWR November 22, 2013 / 62(46); 917-919).

Commentary: The cited article explains the importance of a foreign toxic substance that is used by Afghan immigrants and is a potential source of lead toxicity. Many physicians may not be aware of this seemingly innocuous cosmetic substance that is a potential lead hazard in immigrants and refugees from Asia, Middle East, and Africa. MK.

Question 8: Recently a large number of cases of exposure to a substance named "black mamba" was reported in the state of Colorado. What is "black mamba"?

Answer: "Black mamba" is a novel synthetic cannabinoid known as ADB-PINACA ((N-[1-amino-3,3-dimethy-1-oxobutan-2-yl]-1-pentyl-1H-indazole-3-carboxamide). This substance has been reported to be associated with both neurotoxicity and cardiotoxicity. (Monte A, Bronstein A, Heard K and Iwanicki J. An outbreak of exposure to a novel synthetic cannabinoid. 2013 NEJM 37:389-390).

Commentary: The use of new synthetic cannabinoids, including ADB-PINACA, is increasing. These products are more potent than other commonly abused synthetic cannabinoids. Efforts are made by law enforcement officials, medical toxicologists, and public health officials in limiting the distribution and use of ADB-PINACA. MK.

Question 9: What was Zyklon B?

Answer: Zyklon B was used as a killing agent by the Nazis operating death camps during World War II. Zyklon B consisted of liquid HCN adsorbed onto a carrier – "wood fiber disks, dia gravel, or small blue cubes". The cited reference notes "A "typical" can of Zyklon contained 200 grams of HCN adsorbed onto the carrier, and was stored in metal tins marked with a death's head and warning that read: "Giftgas!" (Deathly poisonous gas!)". (Harmon B. TECHNICAL ASPECTS OF THE HOLOCAUST: Cyanide, Zyklon-B, and Mass Murder. Available at http://nizkor.org/ftp.cgi/camps/auschwitz/cyanide/cyanide.001).

Commentary: Zyklon B was an important toxin used during the Holocaust. It was the most reportedly used toxic gas in concentration camps and responsible for the most deaths and serves as a reminder to the high lethality associated with cyanide exposure. RS.

Question 10: What is Feer Syndrome?

Answer: Feer syndrome is also known as acrodynia or pink disease. The cited reference notes these syndromes are all related to elemental mercury and, less commonly, inorganic mercury salt intoxication primarily in children. (Mercer JJ, et al. Acrodynia and hypertension in a young girl secondary to elemental mercury toxicity acquired in the home. 2012 Pediatric Dermatology Vol. 29 No. 2 199–201).

Commentary: It is also called "raw-beef hands" or erythroderma polyneuropathy. It presents as a triad of hypertension, acral desquamation, and neuropsychiatric abnormalities. There was suggested, but unproven, association between acrodynia and Kawasaki disease, since it was found in cases of Kawasaki disease. However, it should be considered in the differential diagnosis of presumed Kawasaki diseases especially those with atypical presentations. MK.

Question 11: There have been only a very limited number of cases of cobalt toxicity reported to be due to hip arthroplasty. What clinical situation has been reported to be the most common associated with cobalt toxicity in this setting?

Answer: According to the cited reference, "There have been 13 documented cases of cobalt toxicity from hip arthroplasties in the literature: 7 were due to wear of metal-on-metal hip arthroplasties, while the others followed the revision of a fractured ceramic hip." (Tower S. Arthroprosthetic cobaltism: neurological and cardiac manifestations in two patients with metal-on-metal arthroplasty. 2010 J Bone Joint Surg Am 92:2847-51 as cited in Gilbert CJ et al.

Hip pain and heart failure: The missing link. 2013 Canadian J Cardiology 29:638-639. Systemic cobalt toxicity from total hip arthroplasties: review of a rare condition Part 2. measurement, risk factors, and step-wise approach to treatment. Bone Joint J. 2016 Jan;98-B(1):14-20).

Commentary: There have now been 18 documented cases of systemic cobalt toxicity by January 2016. Above cited article discusses the reported cases of cobalt toxicity due to the use of cobalt-chromium alloys in hip arthroplasty. Clinical features of toxicity and step wise treatment approach is outlined in detail (Systemic cobalt toxicity from total hip arthroplasties: review of a rare condition Part 2. measurement, risk factors, and step-wise approach to treatment. Bone Joint J. 2016 Jan;98-B(1):14-20). MK.

Question 12: What is Haff disease and what toxin is associated with this disorder?

Answer: Haff disease involves the development of rhabdomyolysis and muscle weakness after consumption of fresh water fish. According to the cited reference, cases have "rarely been reported in the United States but have been frequently reported from the Baltic region". The authors point out "While the etiology is unknown, it is felt to be a toxin. Palytoxin, found in marine fish, has been associated with rhabdomyolysis, and may serve as a model for further study of the suspected toxin responsible for rhabdomyolysis after consumption of fresh water fish." (Langley RL and Bobbitt WH. Haff disease after eating salmon. 2007 Southern Med Journal 100(11): 1147-1150).

Commentary: Haff disease was first recognized in Europe in 1924, and is rarely reported in the US. Rhabdomyolysis and muscle weakness after freshwater fish consumption should raise suspicion for Haff disease. Suspected cases should be reported to the CDC. MK.

Question 13: How quickly does non-cardiogenic pulmonary edema related to heroin overdose develop?

Answer: Non-cardiogenic pulmonary edema related to heroin overdose is an uncommon complication of heroin overdose. Most authorities report that this phenomenon occurs within 4 hours of the overdose with many cases occurring immediately following the overdose. Clinicians should be aware of the potential for delayed onset of this problem (Sporer KA and Dorn E. Heroin-related non-cardiogenic pulmonary edema: a case series. 2001 Chest 120(5):1628-1632).

Commentary: Non-cardiogenic pulmonary edema is a rare clinical finding of a common drug exposure. Its delayed presentation should be considered when determining how long to monitor patients following heroin overdose in the emergency department. RS.

Question 14: Following death, to what degree does the decomposition of the human body generate detectable blood ethanol levels?

Answer: According to the cited reference, "the data are consistent with previous studies and suggest that decomposition is rarely an important factor in causing blood ethanol concentrations above 70 mg%, but further study needs to be

undertaken." (Hanzlick R. Ethanol concentration in decomposing bodies: Another look, less concern. Letter to the Editor, 2009 Am J For Med and Path, 30(1): 88).

Commentary: Interpretation of autopsy reports, including review of the laboratory studies, is an important skill for physicians. This study concludes that a post-mortem ethanol concentration above 70%mg is suggestive of ante mortem ethanol ingestion. This may have legal ramifications and provide insight into the role of ethanol's involvement in the manner of death. RS.

Question 15: What is the toxic component of the venom of the Black Widow spider (Latrodectus mactans)? What is the mechanism of action of this toxin?

Answer: The toxic component of Black Widow spider venom is alpha latrotoxin. Alpha latrotoxin binds to pre-synaptic receptors (neurexin I-alpha and latrophilin). This binding triggers neurotransmitter release from presynaptic sites and results in excessive motor end plate stimulation causing muscular spasm, local sweating, piloerection, and elevated blood pressure. (Baba A and Cooper JR. The action of black widow spider venom on cholinergic mechanisms in synaptosomes. 1980 J Neurochem 34(6):1369-1379 as quoted in Murphy C, et al Anaphylaxis with Latrodectus antivenin resulting in cardiac arrest. 2011 J Med Tox 7(4):317-321).

Commentary: Black widow spider bites are common in the US. Treatment with anti-venin is available but is reserved for life-threatening envenomation. Envenomation may mimic serious medical conditions such as acute coronary syndrome and appendicitis. MK.

Question 16: Which medications are associated with false positive phencyclidine urine screens?

Answer: The authors of the cited reference concluded: "False-positive urine screens for PCP are associated with tramadol and dextromethorphan and may also occur with diphenhydramine. Positive PCP screens associated with alprazolam, clonazepam, and carvedilol were also associated with polysubstance abuse." (Rengarajan A and Mullins ME. How often do false-positive phencyclidine urine screens occur with use of common medications? 2013 Clin Tox 51:493-496).

Commentary: National institute on Drug Abuse recommends drug testing for phencyclidine for federal employees. A confirmatory test such as gas chromatography-mass spectrometry (GC/MS) is performed as various OTC and prescription medications may give false positive urine PCP immunoassay. MK.

Question 17: What characterizes the syndrome of cannabinoid hyperemesis (CHS)?

Answer: According to the cited reference: "Presentation of cannabinoid hyperemesis syndrome occurs with cycles of symptom free intervals. This syndrome has been broken down to 3 phases: pre-emetic or prodromal, hyperemetic, and recovery. The prodromal phase can last for months to even years, with patients enduring morning sickness, anxiety, and abdominal pain. In this stage, patients usually can maintain normal eating habits and will continue their marijuana usage because they believe it is helping alleviate their nausea. The hyperemetic phase can last as few as 48 hours if treated with appropriate therapy. It is characterized by paroxysms of intense and persistent cyclic vomiting, upward of 5 times an hour, sometimes without warning. Patients also can have weight loss, abdominal pain, and dehydration. It is within this phase that patients typically begin to take compulsory hot water showers or baths. Patients find this to be the only alleviating measure to control symptoms and this readily becomes a learned behavior. The recovery phase can extend from days to months and is associated with general patient wellness, weight gain, regular frequency of bathing, and return of normal eating patterns." (Beech RA et al. Cannabinoid hyperemesis syndrome: A case report and literature review. 2015 J Oral Maxillofac Surg 73:1907-1910).

Commentary: CHS is an often under recognized disease leading patients to suffer for long periods of time and unnecessary hospital visits and diagnostic testing. Early recognition and recommendation of marijuana abstinence is the key to helping these patients. RS.

Question 18: What is the occupational disorder known as "tulip fingers"?

Answer: "Tulip fingers", is an allergic contact dermatitis that may develop in workers in the horticultural industry and trade who handle tulip flowers and stalks. This manifests as digits that appear to be hyperkeratotic with multiple small painful fissures. This results from exposure to tuliposide A, a glycoside compound that hydrolyzes to form alpha-methylene butyrolactone. This hydrolysis product is the likely specific culprit allergen that causes "tulip fingers". (Bruze M. et al. Occupational dermatoses in nursery workers. 1996 Am J Contact Derm 7(2): 100-103).

Commentary: Tulip finger is a painful hyperkeratotic occupational condition. It is usually seen in flower bulb industry in seasons when bulbs are peeled and stored. The resulting allergic and irritant effects may range from localized fissure formation to finger erosion or extensive eczema that may involve the entire hand. MK.

Question 19: It has been reported that 70% of illicit cocaine may be adulterated with the drug levamisole. What are the specific clinical syndromes likely related to levamisole-adulterated cocaine?

Answer: According to the cited reference, "Three distinct clinical syndromes seem to exist: CIMDL (cocaine-induced midline destructive lesions), levamisole-associated agranulocytosis and levamisole associated cutaneous vasculopathy." (Specks U. The growing complexity of the pathology associated with cocaine use. 2011 J Clin Rheumatol 17:167-168 as cited in Larocque A and Hoffman RS. Levamisole in cocaine: Unexpected news from an old acquaintance. 2012 Clin Tox 50(4): 231-241).

Commentary: Levamisole is an anthelminthic used in animals. It was previously used as a chemotherapeutic and antirheumatic in humans. According to the DEA, 69% of cocaine seized on the US borders contains levamisole. In addition to agranulocytosis and vasculitis, levamisole may cause cutaneous necrosis with predilection for the ears. MK.

Question 20: Recombinant granulocyte-colony stimulating factor (G-CSF) is widely used for neutrophil recovery after chemotherapy, bone marrow/peripheral stem cell transplantation and in the management of neutropenia due to other causes including AIDS and certain hematologic problems involving deficient granulocyte production. What are the most common adverse effects associated with the use of G-CSF and what are the potentially life-threatening complications of this therapy?

Answer: According to the cited reference, "The most common adverse events are bone pain (84%), headache (80%) and fatigue. Life-threatening complications such as stroke, myocardial infarction and splenic rupture, resulting from short-term or long-term use of these agents, however rare, can occur." (Akyol G et al. A rare but severe complication of filgrastim in a healthy donor: Splenic rupture. 2014 Transfusion Apheresis Sci 50:53-55).

Commentary: Adverse drug effects associated with G-CSF can be potentially life-threatening. The subset of patients receiving G-CSF typically have significant morbidities, making any adverse drug effect potentially more serious. The referenced article describes splenic rupture as a potential complication and recommends "monitoring of G-CSF recipients must include; close monitoring vital signs, abdominal physical examination, daily complete blood count, as needed computed tomography and abdominal ultrasonography." RS.

Question 21: What is the clinical scenario known as LAST? What factors influence the development of LAST as well as its severity?

Answer: "LAST" stands for "local anesthetic systemic toxicity". The cited reference notes "Factors known to influence the likelihood and severity of local anesthetic systemic toxicity (LAST) include individual patient risk factors, concurrent medications, location and technique of block, specific LA compound, total LA dose, timing of detection and adequacy of treatment." (Sagir A and Goyal R. An assessment of the awareness of local anesthetic systemic toxicity among multi-specialty postgraduate residents. 2014 J Anesth. DOI 10.1007/s00540-014-1904-9).

Commentary: Local anesthetic systemic toxicity mainly involves the cardiovascular and central nervous systems. Lidocaine, benzocaine or prilocaine may cause methemoglobinemia. In addition to the supportive treatment, lipid emulsion therapy may provide benefit in lipophilic local anesthetic toxicity. MK.

Question 22: What are the clinical indicators for yellow phosphorus ingestion?

Answer: The diagnosis is often presumptively and primarily based on history. The cited reference notes there are no specific tests to facilitate the diagnosis of yellow phosphorus ingestion or poisoning. Phosphorus blood levels are specifically not helpful. The authors point out: "if the history is unclear, a garlicky odor and luminescence of vomitus or stool may be helpful. Faint fumes emanating from the stool are called smoking stool syndrome". (Ates M et al. Living donor liver transplantation for acute liver failure in pediatric patients caused by the ingestion of fireworks containing yellow phosphorus. 2011 Liver Transplantation 17:1286-1291).

Commentary: Yellow phosphorus is found in some fireworks. Toxicity and death can result following pediatric ingestion. Clinical features highlighted in this question such as "smoking stools/vomitus" and "garlicky odor" may facilitate an earlier diagnosis. RS.

Question 23: Which form of mercury is found in the vaccine preservative thimerosol? Which vaccines, used in the US, still contain thimerosol?

Answer: Ethyl mercury has been used as a preservative in some vaccines. Thimerosol is still found in the influenza vaccines but has essentially been removed from all other vaccines routinely used in the US.(Cao Y., et al. Efficacy of succimer chelation of mercury at background exposures in toddlers. 2011 J Pediatr 158:480-485).

Commentary: Pregnant patients are often concerned if vaccines contain mercury and their potential harm to the developing fetus. Healthcare providers should be knowledgeable about ingredients of recommended vaccines. The CDC and American College of Obstetrics and Gynecology (ACOG) recommend pregnant patients receive the inactivated influenza vaccine (which may contain thimersol) as soon as it is offered regardless of gestation. (http://www.acog.org/Resources-And-Publications/Committee-Opinions/Committee-on-Obstetric-Practice/Influenza-Vaccination-During-Pregnancy). RS.

Question 24: What is phototoxic dermatitis?

Answer: According to the cited reference, phototoxic dermatitis is "an inflammatory, photochemically evoked skin reaction caused by concomitant exposure to sun and photosensitizing substances (furocoumarins are one such group) which increase the reactivity of skin to ultraviolet radiation." (Zink A and Ring J. Phototoxic dermatitis. 2014 NEJM 371:6).

Commentary: Phototoxic dermatitis affects the sun exposed areas of the body and is caused by exposure to UV light and photosensitizing substances that may be found in facial massage creams. Physicians should consider phototoxic dermatitis in differential diagnosis of rash in sun-exposed areas. MK.

Question 25: What is the so-called "DRESS syndrome" and which culprit drug (or drugs) is/are most commonly associated with this clinical problem? What is the recommended treatment for the DRESS Syndrome?

Answer: The Drug Reaction with Eosinophilia and Systemic Symptom Syndrome (DRESS Syndrome) is a severe systemic adverse drug-induced reaction usually involving fever, hyper-eosinophilia, hepatic involvement, and lymphadenopathy. Most cases are associated with carbamazepine or allopurinol however DRESS has been associated with at least 50 different drugs. Cessation of the suspected culprit drug as well as treatment with systemic corticosteroids is the generally recommended treatment for DRESS Syndrome. (Cacoub P, et al. The DRESS Syndrome: A literature review. 2011 Amer J Med, 124(7):588-597).

Commentary: DRESS Syndrome may be fatal so it is crucial that healthcare professionals be able to recognize the diagnosis. As clinical features can be non-specific; diagnosis relies on suspicion of the syndrome. The regiSCAR score can

facilitate in classifying the likelihood that the patient has DRESS syndrome. Early recognition will help ensure the offending agent is withheld, which is the most important first step in treatment. RS.

Question 26: What is cassava, what potentially harmful chemical is contained in cassava, and what disorder may result from the ingestion of improperly processed cassava?

Answer: Cassava is a plant root harvested from August through October and is the main staple in a variety of rural African locales. So-called "bitter cassava", is high in cyanogenic glucoside. Flour is produced from cassava roots which are then cooked and eaten as a porridge. Studies have shown "average total cyanogenic potential of 40–46 mg HCN equivalents/kg flour (fresh weight) in some samples of cassava". The ingestion of cassava, in some cases, has been associated with a disorder known as konzo. The cited reference notes "Konzo is characterized by the sudden onset of irreversible spastic paraparesis, associated with prolonged high dietary cyanogenic glucoside consumption and a diet deficient in sulphur amino acids". (Cliff J, et al. Konzo and continuing cyanide intoxication from cassava in Mozambique. 2011 Food Chem Tox 49:631-635).

Commentary: Cassava ingestion may result in acute or chronic cyanide poisoning when improperly prepared. The above cited reference states impoverished areas, poor preparation, and climate change as contributors to intermittent Konzo epidemics throughout Mozambique. RS.

Question 27: What is the association between the development of atrial fibrillation and the administration of bisphosphonates?

Answer: A recently published meta-analysis concluded "Evidence from randomized controlled trials and observational studies suggests a significantly increased risk of atrial fibrillation requiring hospitalization, but no increase in risk of stroke or cardiovascular mortality, with the use of bisphosphonate". (Sharma A et al. Risk of serious atrial fibrillation and stroke with use of bisphosphonates: Evidence from a meta-analysis. 2013 Chest 144(4): 1311-1322).

Commentary: Use of bisphosphonates are associated with significantly increased risk of atrial fibrillation that may require hospitalization. However, no increased risk of cardiovascular mortality and stroke were reported after reviewing several RCTs and observational studies. MK.

Question 28: What effect is associated with Coprinus atramentarius ingestion?

Answer: Disulfram effect. The Coprinus atramentarius mushroom contains the toxin coprine. Coprine and its major metabolite both inhibit aldehyde dehydrogenase. If the Coprinus atramentarius mushroom is ingested with ethanol, the accumulation of acetaldehyde will cause flushing, nausea, and vomiting. (Carlsson A, et al. On the disulfram-like effect of coprine, the pharmacologically active principle of Coprinus atramentarius. Acta Pharmacol Toxicol (Copenh). 1978 Apr;42(4):292-7).

Commentary: The Coprinus genus of mushrooms, sometimes referred to as the inky cap mushroom, may be ingested after being foraged. The mushroom does not result in adverse health effects unless ethanol is co-ingested. MK.

Question 29: What laboratory finding is suggestive for the diagnosis of bromism?

Answer: Negative anion gap with hyperchloremia. Bromides produce a falsely elevated chloride level, which leads to a negative anion gap calculation. A chloride level greater than 115 meq/L is suggestive of bromide ingestion. (Horowitz BZ. Bromism from excessive cola consumption. Journal of Toxicology: Clinical Toxicology. 1997;35(3):315-20).

Commentary: Bromism was historically an iatrogenic result of treatment with bromide for epilepsy and today sporadically results from sodium or potassium bromide ingestion. An epidemic of bromide poisoning occurred in Angola in 2007 from the use of sodium bromide for table salt. The features of bromism include ataxia, confusion, fatigue, and other neuropsychiatric symptoms. Bromism may be treated with hemodialysis. MK.

Question 30: Some workers in the semiconductor industry and in some aspects of ore refining industries may be at risk for exposure to arsine. What are the physical characteristics of arsine and what are the clinical characteristics, including the most common complications, associated with clinically significant exposure to arsine.

Answer: Arsine is a gas that is colorless and non-irritating. It is approximately 2 ½ times more dense than air. It is soluble in water and usually manifests a "fishy" or "garlicky" odor at concentrations in excess of 0.5 ppm. Following acute exposure patients may manifest dizziness, malaise, nausea, abdominal pain and difficulty breathing. These symptoms are usually slightly delayed following exposure but usually appear within a few hours of exposure. The most serious complications of arsine gas exposure include massive hemolysis with consequent hypoxia and renal failure. (Pullen-James and Woods SEW. Occupational arsine gas exposure. 2006 J National Med Assoc. 98(12): 1998-2001).

Commentary: Arsine exposure is uncommon because it is preventable with personal protective equipment. The initial clinical presentation may be non-specific so a thorough occupational history may led to the diagnosis. The authors specify that arsine exposure should be included in the differential diagnosis for all patients presenting with red/bronze skin and hemoglobinuria. RS.

Question 31: What is the toxin responsible for ciguatera poisoning and from where is this toxin derived?

Answer: The toxin is ciguatoxin and it is derived from dinoflagellates of the genus Gambierdiscus. These grow mainly in association with macroalgae in coral reefs in tropical and subtropical climates. The toxin is transferred through the food web as the algae is consumed by herbivorous fish, which are consumed by carnivorous fish, which are then consumed by humans. (Friedman MA, et al Ciguatera fish poisoning: Treatment, prevention and management. 2008 Marine Drugs; 6:456-479).

Commentary: Ciguatoxin, which is responsible for ciguatera poisoning, bioaccumulates in marine food chains. Ciguatera poisoning is the most commonly reported seafood toxicity in the world. MK.

Question 32: When threatened, certain species of cobra are able to spit their venom towards the face of the human or animal that is providing the perceived threat. How far can a spitting cobra eject venom and do cobras spit their venom in defensive situations in fixed or random patterns?

Answer: If threatened, spitting cobras can eject their venom up to approximately 3 meters. The cited reference describes a study where the results indicated that the spray pattern of spitting cobras is not fixed and that the snake matches the pattern of venom distribution to the size of the target in a fashion that appears to be independent of target distance. (Berthe RA et al. Spitting cobras adjust their venom distribution to target distance. 2009 J Comp Physiol A 195:753-757).

Commentary: Most associate poisoning via snake strictly through envenomation, however this uncommon mechanism of venom exposure should not be overlooked. Intense painful conjunctivitis is the most common symptom of ocular exposure to venom. (Chu ER et al. Venom ophthalmia caused by venoms of spitting elapid and other snakes: Report of ten cases with review of epidemiology, clinical features, pathophysiology and management. 2010 Toxicon 56:259-272). RS.

Question 33: What is the antidote for ricin poisoning and what is the role for hemodialysis in the treatment of ricin casualties?

Answer: No antidote against ricin toxicity is currently available. Ricin in not amenable to removal by hemodialysis. Treatment for ricing related toxicity essentially involves supportive care. (Audi J et al. Ricin poisoning- A comprehensive review. 2005 JAMA 294(18):2342-2351).

Commentary: Ricin is toxic when ingested, inhaled, or injected. Supportive care is the mainstay of treatment as no antidote is available against the ricin toxin. Georgi Markov was assassinated in 1978 by subcutaneous injection of an engineered pellet containing ricin fired into his leg via an umbrella. Weaponized ricin has the potential to be utilized as a weapon of mass destruction. MK.

Question 34: What are the clinical characteristics of the so-called “iron pill aspiration” (IPA) syndrome?

Answer: Ferrous sulfate is the most common iron preparation related to the “iron pill aspiration” (IPA) syndrome which is characterized by the triad: history of aspiration of iron containing pill, intense airway inflammation, and iron particles in bronchial biopsy specimens. (Lee P et al. Syndrome of iron pill aspiration. 2002 Chest 121(4): 1355-1357 as cited in Kupeli E et al. “Pills” and the air passages. 2013 Chest 144(2):651-660).

Commentary: Most physicians recognize potential acute respiratory hazards of an inhaled foreign body, but it is also prudent to be aware of unique dangers if the foreign body is a medication. Specifically, iron may cause severe bronchial stenosis. The author from the above reference recommends iron pills be avoided in patients with swallowing disorders. RS.

Question 35: Rivastigmine is a cholinesterase inhibitor sometimes used in the treatment of dementia. This drug is often used as a transdermal patch however the delivery of this drug transdermally can be associated with significant cutaneous reactions. How can one differentiate irritant reactions to rivastigmine transdermal from true allergic reactions to the drug?

Answer: Most reactions to rivastigmine-containing transdermal patches are of an irritant type. The cited reference notes that these reactions are “diagnosed clinically by the presence of a pruritic, erythematous, eczematous plaque strictly confined to the borders of the patch”. According to the cited source, an allergic reaction due to a transdermal patch “can be differentiated by the presence of vesicles and/or edema and erythema beyond the boundaries of the transdermal patch and lack of improvement of the lesion 48 hours after removal of the offending treatment”. (Greenspoon J et al. Transdermal rivastigmine- Management of cutaneous adverse events and review of the literature. 2011 CNS Drugs 25(7):575-583).

Commentary: Differentiation of an irritant reaction secondary to transdermal rivastigmine from true allergic reaction is important. Confinement of the reaction within the borders of the patch and improvement on removal of the offending agent are consistent with an irritant effect rather than a true allergic reaction to the drug. MK.

Question 36: Succinylcholine is the drug of choice for inducing paralysis in many instances where emergency endotracheal intubation is required. A number of acquired pathological conditions are known to have the potential to cause acute and lethal hyperkalemia with the administration of succinylcholine. What are these conditions?

Answer: The acquired pathological conditions that may cause acute and potentially lethal hyperkalemia with the administration of succinylcholine include upper or lower motor neuron defects; prolonged chemical denervation as may occur in association with some muscle relaxants, magnesium and clostrial toxins; direct muscle trauma, tumor or inflammation; thermal injury; disuse atrophy; and severe infection. (Martyn J, et al. Succinylcholine-induced hyperkalemia in acquired pathologic states. 2006 Anesthesiology 104:158-169).

Commentary: Emergency medicine physicians must perform rapid sequence intubation (RSI) in emergent, time-dependent situations. Clinicians must be aware of the contraindications for succinylcholine use as it necessary to ensure appropriate patient care. RS.

Question 37: What is the recommended dosing for octreotide when used for the treatment of sulfonylurea poisoning?

Answer: The review cited below made the following recommendations based on published clinical and pharmacokinetic data: for children, give octreotide 1-1.5 micrograms/Kg IV or SC followed by 2-3 more doses 6 hours apart; for adults, give octreotide 50 micrograms IV or SC followed by three 50 microgram doses every 6 hours. (Glatstein M et al. Octreotide for the treatment of sulfonylurea poisoning. 2012 Clin Tox 50(9):795-804).

Commentary: The cited article is a review of the published data for sulfonylurea overdose and the treatment with octreotide. Sulfonylurea toxicity may occur in patients with renal insufficiency. In mild cases, treatment with glucose may be sufficient,

whereas in severe cases glucose administration is thought to cause recurrent hypoglycemia due to the pancreatic release of endogenous insulin. While using the recommended dosage of octreotide, IV dextrose infusion should be gradually tapered off. MK.

Question 38: Hydrofluoric acid is a weak organic acid that is used for a variety of applications including glass etching, oil refining, and rust removal, among other uses. What is the typical concentration of HF in household products? In industrial products?

Answer: The concentration of HF in household products is typically less than 10% while the concentration in industrial products may be as high as 70%. (Vohra R, et al. Recurrent life threatening ventricular dysrhythmias associated with acute hydrofluoric acid ingestion: Observations in one case and implications for mechanism of toxicity. 2008. Clin Tox 46:79-84.

Commentary: Occupational and residential hydrofluoric acid exposures are common. Knowledge of standard HF concentrations found in each setting may provide guidance on diagnosis and treatment. RS.

Question 39: Exposure to what chemical has been posited by some to be responsible for a bronchiolitis obliterans syndrome known as "popcorn workers lung"?

Answer: It has been theorized that some workers who may have been exposed to the chemical diacetyl may have developed a bronchiolitis obliterans syndrome that has come to be known as "popcorn workers lung". (Van Rooy F, et al. Bronchiolitis obliterans syndrome in chemical workers producing diacetyl for food flavorings. 2007 Am J Resp Crit Care Med 176:498-504).

Commentary: Bronchiolitis obliterans, also known as cryptogenic organizing pneumonia, is a rare and irreversible fixed obstructive lung disease that has been reported in workers exposed to flavoring chemicals, including those in the microwave popcorn and flavor-manufacturing industries. MK.

Question 40: What are so-called "drug dreams"?

Answer: Drug dreams are also known as "using dreams". These are dreams centered around the act of using specific drugs. The cited reference reports on a study that notes up to 74% of users of illicit drugs report having at least one drug dream over the course of a 36 week observational period. These authors also describe the successful use of the alpha-1 receptor antagonist, prazosin in treating drug dreams. (Gopalakrishna G et al. Two case reports on the use of prazosin for drug dreams. 2016 J Addict Med 10(2): 131-133 and Yee T et al Drug dreams in outpatients with bipolar disorder and cocaine dependence. 2004 J Nerv Ment Dis 192(3): 238-242).

Commentary: According to National Institute on Drug Abuse (NIDA), the consequences of drug dependence and abuse cost $700 billion annually in the US. In recovering drug addicts, drug dreams are one of the important factors for relapse. The cited article reports successful treatment of drug dream by Prazocin, an antihypertensive alpha blocker, however more research and validation is needed in this regard. MK.

Question 41: Complications of toluene abuse (sniffing) include muscular weakness, nausea, vomiting, abdominal pain, hematemesis, altered metal status, cerebellar abnormalities, and peripheral neuropathy. What renal effects have been reported to be associated with toluene abuse?

Answer: A number of cases of renal tubular acidosis have been reported in association with toluene abuse by inhalation. (Streicher HZ et al Syndrome of toluene sniffing in adults. 1981 Ann Int Med 94:758-762 as cited in Kao-Chin K, et al. Hypokalemic muscular paralysis causing acute respiratory failure due to rhabdomyolysis with renal tubular acidosis in a chronic glue sniffer. 2000 Clin Tox 38(6):679-6810).

Commentary: Hypokalemia should be considered in the setting of toluene abuse. In the cited case, hypokalemia subsequently led to muscle paralysis, respiratory failure, rhabdomyolysis, and renal failure. RS.

Question 42: What is the role of the compound 4-dimethylaminophenol (4-DMAP) in the treatment of cyanide poisoning related to fire smoke inhalation?

Answer: 4-DMAP is a nitrate based cyanide antidote that works by oxidizing hemoglobin to methemoglobin. This cyanide antidote is commonly used in Germany but is not generally found in the US. However, with the advent of the use of hydroxycobalamin, methemoglobin-forming agents are no longer as commonly used in the treatment of smoke inhalation related presumptive cyanide poisoning as in the past. In addition, according to the cited reference, "4-DMAP administration may, however, be dangerous as it can cause tissue necrosis or phlebitis at the site of injection and nephrotoxicity…." (Mintegi S et al. Pediatric cyanide poisoning by fore smoke inhalation- A European expert consensus. 2013 Pediatr Emer Care 29:1234-1240).

Commentary: 4-DMAP is frequently used as a cyanide antidote in Germany. In comparison to nitrites, 4-DMAP is a more rapid inducer of methemoglobinemia and may be given intramuscularly. In addition to tissue necrosis and phlebitis, administration of 4-DMAP may cause hypotension. MK.

Question 43: The abuse of marijuana concentrates (e.g. "wax", "butane honey oil" etc.) is increasing in the US. How are these concentrates abused and how does the levels of THC in leaf marijuana compare with levels of THC in marijuana concentrates? What has been the primary hazard noted in the manufacture and production of illicit marijuana concentrates?

Answer: According to the DEA's 2014 National Drug Threat Assessment Summary "These concentrates can be abused using e-cigarettes or consumed in edibles, and have significantly higher tetrahydrocannabinol (THC) levels than leaf marijuana. In 2013, the THC content of leaf marijuana averaged 12.55 percent, while the THC content of marijuana concentrates averaged 52 percent, with some samples testing over 80 percent." The cited monograph goes on to note "Highly flammable butane gas is used to extract the THC from the marijuana leaf, and has resulted in explosions, injuries, and deaths." (http://www.dea.gov/resource-center/dir-ndta-unclass.pdf, accessed March 2015).

Commentary: There are significant differences in potency between marijuana concentrates and leaf marijuana. As marijuana use becomes more prevalent in the US (secondary to legalization and decriminalization) there may be an increase in marijuana concentrate use. RS.

Question 44: What is the phenomenon known as “radiation recall”?

Answer: The cited reference notes: "Radiation recall is an acute inflammatory reaction confined to previously irradiated areas that can be triggered when chemotherapy agents are administered after radiotherapy. It remains a poorly understood phenomenon, but increased awareness may aid early diagnosis and appropriate management. A diverse range of drugs used in the treatment of cancer has been associated with radiation recall.” (Burris HA and Hurtig J. Radiation recall with anticancer agents. 2010 The Oncologist, 15:1227–1237).

Commentary: Radiation and chemotherapy are therapeutic modalities used, sometimes in tandem, for the treatment of a variety of cancers. Increased awareness may aid early diagnosis and appropriate management. RS.

Question 45: What are the manifestations of the so-called reversible cerebral vasoconstriction syndrome (RCVS) and which drugs have been associated with this syndrome?

Answer: The cited reference notes that the clinical manifestations of RCVS include “recurrent sudden-onset and severe (thunderclap) headaches over 1-3 weeks, often accompanied by nausea, vomiting, photophobia, confusion and blurred vision.” The authors go on to point out that “ The major complications are localized convexity non-aneurysmal subarachnoid hemorrhage (22%) and ischemic stroke or intracerebral hemorrhage (7%) which may leave permanent residual neurological deficits.” This syndrome, also known as “drug-induced cerebral arteritis” has been associated cocaine and other drugs that might exert sympathomimetic effects. (Sattar A et al. Systematic review of reversible cerebral vasoconstriction syndrome. 2010 Expert Rev Cardiovasc Ther 8(10): 1417-1421).

Commentary: RCVS affects women two to four times more than men. The mean age of onset is 42 years. Cerebrospinal findings are normal in majority (85%) of the patients. RCVS is typically reversible however long-term symptoms may include chronic migraine and depression. MK.

Question 46: What is polymethylmethacrylate (PMMA) and what is its use in surgical practice?

Answer: Bone cement, polymethylmethacrylate (PMMA), is the synthetic polymer of methyl methacrylate (MMA). It has been commercially used since the 1930s and its use in arthroplasty was popularized in the 1960s. Concerns have been raised regarding inhalational exposure to health care professionals for MMA during operative orthopedic procedures. However significant serum levels of MMA following inhalational exposure to humans have never been documented. (Homlar KC et al. Serum levels of methyl methacrylate following inhalational exposure to polymethylmethacrylate bone cement. 2013 J Arthroplasty 28:406-409).

Commentary: Some occupational exposures may cause teratogenic effects. The cited reference states one of the impetuses for the study was concern regarding MMA exposure to females in the operating suite and possible teratogenic effects. They concluded that given insignificant serum MMA levels after exposure, the probability of any teratogenic effects on the developing fetus is unlikely. RS.

Question 47: What are so-called “AWOL” devices?

Answer: “AWOL” devices are “alcohol without liquid devices”; basically nebulizers that aerosolize alcohol into an inhalable mist to allow for alcohol (ethanol) use via inhaling rather than drinking it. According to the cited reference, “It is advertised that users can feel the effects of alcohol with fewer calories and no hangovers. However these claims have not been substantiated. Although alcohol inhalation may not raise the blood alcohol level to the intoxication threshold, there is a rapid increase in blood alcohol levels. Adverse effects are unknown and require further investigation. (LeFoll B and Loheswaran G. Alcohol inhalation. 2014 CMAJ 186 (10): E399-E399).

Commentary: Inhaled alcohol can reach the brain more quickly which may lead to a higher potential for addiction than ingested alcohol. Inhalation is a novel route of administration for ethanol with a paucity of current research. RS.

Question 48: What is the HAART-associated lipodystrophy syndrome (HALS)?

Answer: The cited reference describes: “The commonly observed adverse effects of HAART vary among treatment regimens and include gastrointestinal symptoms, hepatotoxicity, rash, and metabolic abnormalities associated with lipodystrophy. These abnormalities include significant increases in circulating low-density lipoprotein (LDL) and total cholesterol, triglycerides, and glucose levels, as well as decreased high-density lipoprotein (HDL) cholesterol levels. The combination of lipodystrophy and metabolic syndrome, or more specifically and more commonly dyslipidemia and impaired glucose tolerance in these patients, is defined as HIV/ HAART-associated lipodystrophy syndrome (HALS).” (Paruthi J et al. Adipokines in the HIV/HAART-associated lipodystrophy syndrome. 2013 Metabolism Clin Exp 62:1199-1205).

Commentary: HALS disproportionately affects whites, women, and the elderly. While the underlying mechanism of HALS is not known, nucleoside reversed transcriptase inhibitors (NRTIS) and protease inhibitors (PI) are believed to be the main causes. MK.

Question 49: What is “surgical smoke” and what are the primary risks of exposure to this material for workers who might be exposed to surgical smoke?

Answer: The cited reference notes that surgical smoke is “the gaseous by-product produced when tissue is dissected or cauterized by heat generating devices such as lasers, electrosurgical units, ultrasonic devices and high speed burrs, drills and

saws." The author states "The main risks to the health of perioperative personnel from surgical smoke are acute and chronic respiratory irritation and inflammation, irritation of the eyes and skin, transmission of infection, and genotoxicity by its mutagenic properties". However, the author concludes "Due to the nature of this topic there is no definite proven link between surgical smoke and the effect it has on human health, but neither is there any firm evidence that shows it is safe to be exposed to surgical smoke. Therefore it would seem that until such time as evidence shows that surgical smoke poses no risks to health, a preventative approach would be the sensible option." (Sanderson C. Surgical smoke. 2012 J Perioperative Prac 22(4): 122-128.

Commentary: The cited reference recommends prevention, as the association between surgical smoke and health effects has not been clearly established. Surgical masks are not effective at preventing inhalation of smoke and smoke evacuation systems are recommended. RS.

Question 50: The agent known as British anti-lewisite (BAL) has been recommended as a potential antidote against the arsenical agent lewisite (dichloro[2-chlorovinyl]arsine). What substance is this drug suspended in?

Answer: BAL is suspended in peanut oil and thus it has been suggested BAL not be used in individuals with known peanut allergy. (Kosnett MJ. The role of chelation in the treatment of arsenic and mercury poisoning. 2013 J Med Toxicol 9:347-354).

Commentary: BAL should be administered after screening for G6PD as it may cause hemolysis in G6PD deficient patients. It is used as an antidote in lead, mercury, gold and arsenic poisoning. BAL should be used with caution in patients with renal and hepatic dysfunction and should be discontinued if renal failure occurs. Intramuscular BAL should be given with Ca-disodium-edetate when treating lead encephalopathy. MK.

Question 51: Hypercalcemia is a rare, but reported, complication of chronic vitamin A toxicity. What are the more common manifestations of chronic vitamin A toxicity?

Answer: The most common clinical manifestations of chronic vitamin A toxicity include skeletal pain, hair loss, anorexia, pseudotumor cerebri, liver disease, and psychiatric complaints. (Lippe B et al. Chronic vitamin A intoxication. 1981 Am J Dis Child, 135:634-636) as cited in (Bhalla K, et al. Hypercalcemia caused by iatrogenic hypervitaminosis A. 2005 J Am Diet Assoc, 105:119-121).

Commentary: Chronic vitamin A toxicity may present with nonspecific symptoms as it affects multiple organ systems. Specifically regarding hypercalcemia the cited article states "all patients described in published literature have had resolution of their hypercalcemia after withdrawal of vitamin A." RS.

Question 52: What is the clinical course of acute methyl bromide toxicity?

Answer: The cited reference defined three phases in the clinical course of acute methyl bromide toxicity as follows: "a premonitory phase up to 48 h after exposure, with dimness of vision, diplopia, staggering gait, headache, vertigo, vomiting, euphoria or delirium, or syncope. The phase of cerebral irritation produces seizures, myoclonus, twitching, diaphoresis, and respiratory failure. If the patient survives, the recovery phase ensues." (Wyers H. Methyl bromide intoxication. Br J Ind Med 1945; 2(1): 24–29 as cited in de Souza A, et al. The neurological effects of methyl bromide intoxication. 2013 J Neurol Sci 335:36-41).

Commentary: Methyl bromide toxicity may occur secondary to fumigant exposure. Development of seizure and coma secondary to methyl bromide toxicity may be fatal. Patients may also develop skin bullae or vesicles that occur predominantly in moist skin areas. Patients surviving severe methyl bromide toxicity may have residual neuropsychiatric sequalae. MK.

Question 53: How does heparin induced thrombocytopenia (HIT) differ from all other drug-induced thrombocytopenias?

Answer: HIT is unique with regard to drug-induced thrombocytopenias because it requires platelet activation, rather than coagulation system activation to create the predisposing condition for thrombosis. (Bilen O and Teruya J. Complications of anticoagulation. 2012 Disease-a-Month 58(8):440-447).

Commentary: Barring contraindications, heparin is an anticoagulant routinely administered to hospitalized patients for deep vein thrombosis prophylaxis. HIT is a common adverse drug reaction associated with heparin and it is important to be aware of the underlying pathophysiology. RS.

Question 54: During the first Gulf War some troops were treated with what compound as a prophylaxis against nerve agent toxicity?

Answer: Some troops received the carbamate anticholinesterase compound pyridostigmine. (Abu-Qare AW and Abou-Donia MB. Sarin: health effects, metabolism and methods of analyisis. 2002 Food and Cje, Tox 40:1327-1333).

Commentary: Sarin is a highly volatile, colorless, and odorless liquid. On August 21st 2013, civilians in Syria were attacked by sarin gas that claimed several lives. The acute cholinergic syndrome occurs when 75-80 % of ACHE is inhibited by sarin. MK.

Question 55: What is considered to be the most venomous fish in the world? What types of toxins are contained in the venom of this fish? What are the clinical characteristics consistent with envenomation from this fish?

Answer: The most venomous fish in the world is widely considered to be the stonefish (genus Synanceia). The venom includes four bio-active factors; 1- a hyaluronidase, 2-a capillary permeability factor, 3-a "lethal factor"- stonustoxin SNTX, a potent hypotensive agent with myotoxic and neurotoxic effects and 4- a pain producing factor. According to the cited reference: "Envenomation results in excruciating localized pain and gross edema which may involve the entire extremity and regional lymph nodes, peaking around 60 to 90 minutes and lasting up to 12 hours if untreated. The severity of pain

may lead to unconsciousness and possible drowning. Systemic effects may include pallor, diaphoresis, nausea, muscle weakness, dyspnea, headache, and delirium: convulsions, hypotension and syncope have been reported…." (Lee JYL et al. Stonefish envenomations of the hand- A local marine hazard: A series of 8 cases and review of the literature. 2004 Ann Acad Med Singapore 33:515-520).

Commentary: Stonefish are primarily found along the coasts of the Indian and Pacific oceans, and are a potentially life-threatening envenomation. There is an antivenom available for the treatment of stonefish envenomation. RS.

Question 56: What is the most serious potential adverse neurologic effect associated with acute inhalational exposure to high concentrations of the chemical ethylbenzene in the occupational setting?

Answer: The most serious potential adverse neurologic effect associated with acute inhalational exposure to high concentrations of the chemical ethylbenzene in the occupational setting is hearing loss. The authors of the cited reference note "This hearing loss is characterized by deterioration in auditory thresholds and alterations in cochlear morphology." (Zhang M et al. Ethylbenzene-induced hearing loss, neurobehavioral function and neurotransmitter alterations in petrochemical workers. 2013 JOEM 55(9): 1001-1006).

Commentary: Ethylbenzene is primarily used by petrochemical workers as a precursor to styrene. Occupational exposures causing ototoxicity need to be recognized to increase prevention. RS.

Question 57: What are the bleeding risks associated with the use of SSRIs?

Answer: The cited reference notes "Because they inhibit platelet aggregation, these agents (SSRIs) increase the risk of gastrointestinal bleeding; however, studies conflict on their association with brain hemorrhage." In the cited study, these authors report on study results showing "Intracranial hemorrhage was related to SSRI exposure in both unadjusted (rate ratio [RR] 1.48, 95% confidence interval [CI] 1.22–1.78) and adjusted analyses (RR 1.51, 95% CI 1.26–1.81). Intracerebral hemorrhage was also associated with SSRI exposure in both unadjusted (RR 1.68 95% CI 1.46–1.91) and adjusted (RR 1.42, 95% CI 1.23–1.65) analyses." (Hackam DG and Mrkobrada M. Selective serotonin reuptake inhibitors and brain hemorrhage-a meta-analysis. 2012 Neurology 79:1862-1865).

Commentary: There may be an increased risk of intracranial and intracerebral hemorrhage with SSRI use. However, absolute risk is likely to be very low since the event is rare. The cited article further reports an increased risk of hemorrhage when anticoagulants were used concomitantly with SSRIs compared to when SSRIs were used alone. MK.

Question 58: When does the FDA recommend the use of a "boxed warning" to be included in prescribing information for any given drug?

Answer: A boxed warning is ordinarily used to highlight for prescribers one of the following situations: 1-There is an adverse reaction so serious in proportion to the potential benefit from the drug (e.g., a fatal, life-threatening or permanently disabling adverse reaction) that it is essential that it be considered in assessing the risks and benefits of using the drug ?OR 2-There is a serious adverse reaction that can be prevented or reduced in frequency or severity by appropriate use of the drug (e.g., patient selection, careful monitoring, avoiding certain concomitant therapy, addition of another drug or managing patients in a specific manner, avoiding use in a specific clinical situation) ?OR 3-FDA approved the drug with restrictions to ensure safe use because FDA concluded that the drug can be safely used only if distribution or use is restricted (Guidance for Industry Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products — Content and Format. U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER) October 2011. Accessed at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075096.pdf).

Commentary: Adverse drug effects are a legitimate public health concern. Healthcare providers must be aware of all FDA "boxed warnings" of drugs they use. Failure to take "boxed warnings" into consideration when prescribing medications could be potentially harmful to patients and may have medicolegal consequences. RS.

Question 59: Poisoning with which substance must be considered if severe gastrointestinal symptoms and pancytopenia co-exit after ingestion of wild plants that may be used in salads, or to flavor drinks or sauces?

Answer: According to the cited reference: "Colchicine poisoning should be considered in unexplained gastrointestinal symptoms and pancytopenia after ingestion of wild plants used to flavor sauces, drinks or salads." (Galland-Decker C et al. Progressive organ failure after ingestion of wild garlic juice. 2016 J Emerg Med 50(1): 55-60).

Commentary: Colchicine toxicity may occur after ingesting wild plants that contain colchicine. Gastrointestinal (G.I) symptoms typically occur in 2-12 hours, followed by bone marrow suppression. Severe toxicity may warrant an intensive care unit admission as patients may develop rhabdomyolysis and multiorgan failure. MK.

Question 60: What are the absorption, distribution, and elimination characteristics of the drug colchicine?

Answer: Colchicine is rapidly absorbed with serum levels peaking at 0.5-3.0 hours post ingestion and is rapidly distributed to all tissues. Its protein binding is 10-50% in therapeutic doses and the volume of distribution ranges from 2 and 12 L/Kg but may be as high as 21 L/Kg in overdose. It undergoes extensive hepatic first pass metabolism and elimination is primarily via hepatic metabolism by cytochrome P450 (CYP 3A4) mediating deacetylation and demethylation followed by biliary excretion. The mean elimination half-time of oral colchicine is 4.4-16 hours in therapeutic doses but may be as high as 11-32 hours in the overdose setting. (Finkelstein Y et al. Colchicine poisoning: the dark side of an ancient drug. 2010 Clin Tox 48(5): 407-414).

Commentary: Colchicine is potentially fatal drug in the setting of overdose. It is important to know its toxicokinetics to further guide treatment. There is no antidote for colchicine toxicity however GI decontamination may be life-saving if initiated promptly. Colchicine's large volume of distribution renders it unamendable to removal through dialysis. RS.

Question 61: What percentage of individuals who receive dimercaprol (BAL) for the treatment of lead poisoning will experience side effects?

Answer: According to the Centers for Disease Control and Prevention, "between 30% and 50% of patients who receive BAL will experience side effects. Mild febrile reactions and transient elevations of hepatic transaminases may be observed. Other minor adverse effects include, in order of frequency, nausea and occasional vomiting, headache, mild conjunctivitis, lacrimation, rhinorrhea, and salivation. Most side effects are transient and rapidly subside as the drug is metabolized and excreted. Intravenous hydration coupled with restricting oral intake can circumvent, in large part, gastrointestinal distress. BAL should not be used for children (or adults) who are allergic to peanuts or peanut products as this drug is formulated as a suspension in peanut oil. (http://www.cdc.gov/nceh/lead/publications/books/plpyc/appendix2.htm#BAL).

Commentary: BAL is a common chelating agent used for the treatment of moderate to severe lead toxicity. It is important to be aware and anticipate potential side effects of the drug prior to its administration. BAL may induce hemolysis in patients with glucose-6-phosphate deficiency. RS.

Question 62: What is the incidence of acute renal failure in patients receiving high dose methotrexate for the treatment of hematologic cancer?

Answer: The cited reference notes that acute renal failure will develop in "approximately 2% of patients who receive high dose methotrexate for the treatment of hematologic cancer." These authors further point out that "acute renal failure can occur even in the absence of toxic methotrexate levels in plasma 24 to 48 hours after infusion". (Garneay AP et al. Acute methotrexate-induced crystal nephropathy. 2015 NEJM 373(27): 2691-2693.

Commentary: Methotrexate is a folate antagonist that inhibits DNA synthesis and repair by inhibiting dihydrofolate (DHF) reductase enzyme. Toxicity usually occurs in patients who take weekly methotrexate dose daily for several days. Leucovorin rescue should be promptly initiated without waiting for MTX levels. Multi-organ failure and sepsis are the leading cause of death in severe toxicity. MK.

Question 63: What is the difference, based on gender, in morning driving risk after taking the zolpidem containing products (e.g. Ambien, Ambien-CR, Edluar, and Zolpimist) for sleep?

Answer: Females clear the drug zolpidem more slowly than males. Thus, at the same nighttime dose of this drug, females will be expected to demonstrate higher blood levels the next morning and presumably greater decrements in driving function and ability. (Farkas RH et al. Zolpidem and driving impairment-Identifying persons at risk. 2013 NEJM 369(8):689-691). (https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/019908s027lbl.pdf).

Commentary: It is important for prescribing healthcare providers to be aware of and disclose the risk of impaired driving the day following zolpidem ingestion to patients. While this reference highlights a key gender difference in the effects of zolpidem, the package insert recommends the same dosage for both men and women. (https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/019908s027lbl.pdf) RS.

Question 64: Trinitrotoluene (TNT) is widely used in the munitions industry. What is the primary health problem of concern for workers in this industry and what is the mechanism for this effect? Which exposure route is of special concern for TNT production workers?

Answer: Considered an "Occupational Sentinel Health Event", the development of anemia in the primary health problem in workers who work with and around TNT. The authors of the cited study indicate "there is evidence that TNT suppresses delta-aminolevulinic acid synthase, caused hemolytic anemia when methemoglobin is produced and causes oxidative damage to red blood cells." Dermal absorption is of special concern with regard to TNT. (Mallon TM et al. Investigation of an outbreak of anemia cases at an Army trinitrotoluene munitions production plant from 2004 to 2005 and subsequent surveillance 2005-2013. 2014 Mil Med 179(11):1374-1383).

Commentary: Workers exposed to TNT are at risk for dermal absorption. Wearing a respirator may dramatically decrease the incidence of hemolytic anemia in these patients. MK.

Question 65: What is the typical neuropathological finding demonstrable on neuroimaging that is associated with methanol poisoning?

Answer: Necrosis of the putamen is the typical neuropathological finding demonstrable on neuroimaging that is associated with methanol poisoning. (Anderson C et al MRI enhancing brain lesions in methanol intoxication. 1997 J Comp Assist Tomog 21(5): 834-836 as cited in Salzman M Methanol Neurotoxicity 2006 Clin Tox 44(1): 89-90).

Commentary: Methanol toxicity may cause permanent neurological dysfunction. In cases of suspected methanol toxicity it is imperative to initiate timely treatment with fomepizole and/or hemodialysis. RS.

Question 66: While most patients suffering from acetaminophen (APAP) toxicity are managed using antidotal therapy with N-acetylcysteine, hemodialysis (HD) may be added to treat some seriously ill patents following massive APAP overdose. What effect does the application of HD to treat these patients have on the efficacy of co-administered N-acetylcysteine?

Answer: The cited reference reports on a study of three (3) seriously ill patients suffering massive APAP overdose. These investigators found “hemodialysis more than doubles the clearance of both acetaminophen and acetylcysteine”. They report “Extraction ratios of acetylcysteine across the dialysis circuit ranged from 73% to 87%”. As a consequence, these authors “recommend doubling the dose [of acetylcysteine] during hemodialysis, with an additional half-load when dialysis exceeds 6 hours.” (Silvotti M. et al. Antidote removal during haemodialysis for massive acetaminophen overdose. 2013 Clin Tox 51 (9): 855-863).

Commentary: N-acetylcysteine (NAC) is the antidote for acetaminophen (APAP) toxicity, and is most effective when initiated within 8 hours. Hemodialysis may be recommended in severe cases of APAP toxicity. MK.

Question 67: Malaria continues to be a serious concern with regard to global health and malaria in pregnancy is responsible for approximately 15% of all maternal deaths in malaria endemic areas. What is the safety of the anti-malarial drug mefloquine in pregnancy?

Answer: The use of the anti-malarial drug, mefloquine, has been controversial in pregnancy. However a recent systematic review reports looking at eighteen articles and found “no indications that mefloquine use during pregnancy carries an increased risk for the developing fetus”. (Gonzalez R et al. Mefloquine safety and tolerability in pregnancy: a systematic literature review. 2014 Malaria Journal 13:75-85).

Commentary: According to WHO, there were 214 million cases of malaria worldwide in 2015. While the cited article concludes no increased risk of mefloquine to the fetus in pregnant patients, it should not be used as a chemoprophylaxis in patients with psychiatric disease. MK.

Question 68: What are the EPA-designated "criteria [air] pollutants" and by what authority does EPA so designate these substances?

Answer: The Clean Air Act requires EPA to set National Ambient Air Quality Standards for six common air pollutants. These commonly found air pollutants (also known as "criteria pollutants") are found all over the United States. They are particle pollution (often referred to as particulate matter), ground-level ozone, carbon monoxide, sulfur oxides, nitrogen oxides, and lead. These pollutants can harm your health and the environment, and cause property damage. Of the six pollutants, particle pollution and ground-level ozone are the most widespread health threats. EPA calls these pollutants "criteria" air pollutants because it regulates them by developing human health-based and/or environmentally-based criteria (science-based guidelines) for setting permissible levels. The set of limits based on human health is called primary standards. Another set of limits intended to prevent environmental and property damage is called secondary standards. (http://www.epa.gov/airquality/urbanair/).

Commentary: The Clean Air Act is an important piece of legislation in the field of environmental toxicology and gives the EPA the authority to regulate pollutant emissions from numerous sources. RS.

Question 69: During which months are brown recluse spider envenomations most prevalent?

Answer: According to the cited reference, "A significant seasonal correlation was recently shown for brown recluse spider activity. For patients with suspected brown recluse spider bites (BRSB), we have observed seasonality. Among 45 cases with features consistent with a BRSB, 43 (95.6%) occurred during April–October. (Rader RK et al. Seasonality of brown recluse populations is reflected by numbers of brown recluse envenomations. 2012 Toxicon 60(1):1-3).

Commentary: Brown recluse spider bites are painless and mostly manifest as a mild local reaction. Severe bites may evolve into hemorrhagic bullae. Systemic manifestations are rare in adults but may occur in children. In 2014, AAPCC reported 1330 brown recluse spider bites with no deaths. MK.

Question 70: A massive outbreak of waterborne illness occurred in the greater Milwaukee area during late March and early April of 1993. What was the infectious agent involved in this outbreak and how many people were estimated to have been affected?

Answer: The outbreak in question involved waterborne cryptosporidium infection and it has been estimated that more than 400,000 people were affected. (MacKenzie WR, et al. A massive outbreak in Milwaukee of cryptosporidium infection transmitted through the public water supply. 1994 NEJM 331(3):161-167).

Commentary: The CDC estimates the outbreak cost $31.7 million in healthcare costs. Sixty-nine patients died as a result, the majority of which had AIDS. (Corso P, et al. Costs of Illness in the 1993 Waterborne Cryptosporidium Outbreak, Milwaukee, Wisconsin . 2003 CDC EID 9:4). RS.

Question 71: The illicit use of ketamine has been reported to cause a certain genitourinary problem characterized by severe dysuria, frequency, urgency and gross hematuria. What is this problem and what is the purported cause?

Answer: This is the so-called ketamine associated ulcerative cystitis. Studies have shown that high concentrations of ketamine and metabolites norketamine and hydroxynorketamine concentrate in the urine following ketamine use. It has been posited that these chemicals may, in some cases, induce bladder irritation as well as some cases of bladder ulceration. (Shahani R et al. Ketamine associated ulcerative cystitis: A new clinical entity. 2007 Urology 69(5): 810-812).

Commentary: Ketamine is structurally similar to PCP. It became available in clinical practice in 1970 and was also used as a drug of abuse. It is commonly used as an anesthetic and in procedural sedation. Ketamine is metabolized in the liver and is actively excreted in the urine. While the primary compound may be detectable in the urine for 5-11 days, nor-ketamine may be detectable up to 14 days. MK.

Question 72: What is welder's siderosis?

Answer: Welder's siderosis refers to the pneumoconiosis caused by inhalation of iron oxide particles produced in the welding process and is generally considered to be a benign form of lung disease. (Patel RR, et al. Systemic iron overload associated with welders siderosis. 2009 Am J Med Sciences 337(1):57-59).

Commentary: Pneumoconiosis is an occupational lung disease caused by small particle inhalation. It typically causes a restrictive lung disease pattern of injury. RS.

Question 73: What is the primary physiologic mechanism responsible for the phenomenon known as postmortem redistribution with regard to most drugs of abuse?

Answer: According to the cited reference, "Redistributive processes potentially affect the concentration of all drugs of abuse in postmortem cases as a result of diffusion of drug from higher concentration to a lower concentration following disruption of cellular membranes." (Drummer OH. Postmortem toxicology of drugs of abuse. 2004 For Sci Int 142:101-113).

Commentary: Postmortem redistribution may result in fluctuating whole blood and tissue concentrations. Understanding this phenomenon is important to avoid misinterpretation of postmortem drug levels. MK.

Question 74: In utero exposure to methadone may, in some cases, induce a well-described neonatal abstinence syndrome (NAS). What are the clinical characteristics of this NAS?

Answer: The NAS induced by in utero methadone exposure is characterized by central nervous system hyperirritability and autonomic nervous system dysfunction as well as gastrointestinal tract and respiratory system dysfunction. Untreated NAS can result in serious illness including diarrhea, feeding difficulties, weight loss, seizures and death. In most cases, methadone-associated NAS requires prolonged hospitalization, pharmacologic intervention, and continuous monitoring. (Jones HE, et al. Neonatal abstinence syndrome after methadone or buprenorphine exposure. 2010 NEJM 363(24): 2320-2331).

Commentary: NAS is an important disease in reproductive toxicology associated with adverse maternal and neonatal outcomes, as well as increased healthcare costs. The study cited above found both methadone and buprenorphine to be effective in the treatment of opioid dependence during pregnancy. RS.

Question 75: What is lathyrism and what chemical has been widely assumed to be causative of this disorder?

Answer: Lathyrism is a disorder associated with the ingestion of the grass pea (Lathyrus sativus). According to the cited reference, the main clinical sign is "a permanent, but not progressive, bilateral symmetric paraparesis which emerges in association with consumption of grass pea products as the main (or sole) food item for several weeks, due to the lack of availability of alternative foods." The authors go on to point out that "The association of lathyrism with grass pea (consumption) is firmly established, but the causative agents and pathogenic mechanisms remain doubtful. L. sativus seeds contain large amounts of b-N-oxalyl-L-a,b-diaminopropionic acid (ODAP), and this non-protein amino acid is widely accepted as the likely causative agent of lathyrism." (Llorens J et al A new unifying hypothesis for lathyrism, konzo and tropical ataxic neuropathy: Nitriles are the causative agents. 2011 Food and Chemical Toxicology 49:563-570).

Commentary: Lathyrism, konzo, and tropical ataxic neuropathy (TAN) are food-related toxicologic diseases. While lathyrism is associated with the grass pea, both konzo and TAN are associated with the cassava plant. The above cited reference states that the nitriles found in these plants may ultimately be responsible for these diseases. RS.

Question 76: The Japanese herbal remedy "dai-taiko-so" has been associated with the development of what hepatic disorder? This disorder has also been linked with a variety of viruses including hepatitis C, A and B as well as minocycline, nitrofurantoin, propylthiouracil and the statin drugs?

Answer: Autoimmune hepatitis. (Heneghan MA et al. "Autoimmune hepatitis" 2013 Lancet 382:1433-1444.

Commentary: Dai-taiko-so is commonly used in Japan for various medical illnesses predominantly gastrointestinal upset. It is likely that the risks of dai-taiko-so outweigh the potential benefits. MK.

Question 77: What are the risk factors for the development of bleomycin-induced pulmonary toxicity?

Answer: The cited reference reports: "The risk of developing bleomycin-induced pulmonary toxicity is increased by a number of factors, including increasing age, higher doses of the drug, impaired renal function (creatinine clearance < 35 ml/min), high concentration oxygen therapy and radiation therapy to the thorax. There are conflicting data as to whether concomitant granulocyte colony stimulating factor (G-CSF) therapy increases the risk of bleomycin-induced lung injury." (Fyfe AJ and McKay P. Toxicities associated with bleomycin. 2010 J R Coll Physicians Edinb 40:213-215).

Commentary: Bleomycin and busulfan may cause pulmonary fibrosis. Approximately 20-25% of patients taking bleomycin report febrile illness. Bleomycin may also cause anhidrosis, nail hyper-pigmentation, and irreversible hearing loss. MK.

Question 78: What chemical, used by some to promote weight loss and marketed via the internet under the names 'Dinosan', 'Dnoc', 'Solfo Black', 'Nitrophen', 'Aldifen' and 'Chemox' was first used by the French in munitions production during World War I?

Answer: Dinitrophenol (DNP), which acts by uncoupling oxidative phosphorylation, has been sold on internet sites under the names 'Dinosan', 'Dnoc', 'Solfo Black', 'Nitrophen', 'Aldifen' and 'Chemox' and marketed for weight loss purposes. It is important to note that the use of DNP for weight loss has resulted in significant and severe adverse effects including death. (Grundlingh J et al. 2,4-Dinitrophenol (DNP): A weight loss agent with significant acute toxicity and risk of death 2011 J Med Toxicol 7:205-212).

Commentary: Uncoupling oxidative phosphorylation is an important pathophysiologic concept commonly associated with salicylate toxicity. Uncoupling of oxidative phosphorylation disrupts the electrochemical proton gradient along the mitochondria, resulting in dissipation of heat. The reference states "heat production represents a failure in thermoregulatory homeostasis, leading to uncontrolled hyperthermia." RS.

Question 79: During the 2006–2007 time frame, an epidemic of severe contact dermatitis cases related to newly acquired sofas and chairs manufactured in China were reported. Buttocks, back, thighs, or arms were the initial locations of this severe dermatitis. What was determined to be the cause for this outbreak of dermatitis?

Answer: The cause for the so-called "Chinese sofa/chair dermatitis" epidemic was probably a contact allergy to the chemical dimethylfumarate (DMF), a potent contact sensitizer added to fabric as a mold inhibitor and biocide. (Rantanen T. The cause of Chinese sofa/chair dermatitis epidemic is likely to be contact allergy to dimethylfumarate, a novel potent contact sensitizer. 2008 Br J Dermatol 159: 218–221).

Commentary: Sofa dermatitis typically occurs on the back, buttocks, and posterior thighs. DMF is sometimes added to the furniture fabrics as a fungicide to protect from molds. It may cause type IV hypersensitivity reaction resulting into dermatitis that is relatively resistant to topical steroids. MK.

Question 80: What is the prevalence rate of use of antidepressant medication during pregnancy in the United States and what group of anti-depressants are the most commonly prescribed antidepressants during pregnancy?

Answer: According to the cited reference, the prevalence rate of use of antidepressant medication during pregnancy in the United States ranges from 8 to 13% and "Selective serotonin reuptake inhibitors (SSRIs) are the most commonly prescribed antidepressants during pregnancy." (Huybrechts KF et al. Antidepressant use in pregnancy and the risk of cardiac defects. 2014 NEJM 370(25): 2397-2407).

Commentary: More than 10% of pregnant patients suffer from a form of major depressive disorder. Intentional overdose of citalopram and escitalopram require a 24-hour observation for delayed toxicity. MK.

Question 81: What is green tobacco illness?

Answer: Green tobacco sickness (GTS) is an occupational disease caused by nicotine poisoning that occurs secondary to dermal absorption of dissolved nicotine on tobacco plants. This affliction may be seen in tobacco workers (including child workers) who come into direct contact with wet tobacco plants typically occurring during the process of tobacco harvesting. Individuals with GTS may present with a variety of symptoms consistent with nicotine poisoning including weakness, headache, nausea, vomiting, dizziness, crampy abdominal pain, difficulty breathing, pallor, diarrhea, chills, hypotension/hypertension, bradycardia/tachycardia, and increased perspiration and salivation. The onset of GTS ranges from 3 to17 hours after exposure and the duration of illness is typically from one to three days. (McBride J, et al. Green tobacco sickness. 1998 Tobacco Control 7:294-298).

Commentary: Increasing awareness of GTS and decreasing exposure to tobacco leaves, among at-risk populations is necessary for prevention. OSHA recommends that "employers should provide workers with information and training about nicotine hazards, GTS prevention, and appropriate personal protective equipment (PPE) before letting the workers handle tobacco leaves." However, there are currently no federal regulations requiring PPE for at-risk workers. (https://www.osha.gov/SLTC/green_tob_sickness/index.html) RS.

Question 82: Exposure to what toxicant is posited by some to be the cause of the deafness suffered by Ludwig Van Beethoven?

Answer: The cited reference points out "Recent analysis of his (Beethoven's) hair and bone has determined that he had lead poisoning". They further point out that "A lock of his hair removed at the time of his death, and stored in an airtight case, was analyzed in 2000 by researchers in Illinois. Beethoven's parietal skull bone was later analyzed in 2005. Both showed markedly elevated lead levels consistent with lead poisoning. As for the potential source for lead exposure in the case of Beethoven, the authors posit "It is well known that at that time lead was added illegally to inexpensive wine to improve the flavor. Beethoven was particularly fond of the adulterated or fortified Hungarian wine. It has been suggested that after the death of Beethoven's mother when he was 17 years old, he began to use wine to help deal with his loss." These authors have concluded that Beethoven's chronic consumption of wine tainted with lead is the best explanation for his hearing loss. (Stevens MH et al. Lead and the deafness of Ludwig Van Beethoven. 2013 The Laryngoscope 123:2854-2858).

Commentary: Chronic lead toxicity may have caused Beethoven's deafness. Sensory and autonomic findings with progressive hearing loss may raise suspicion for chronic low level lead exposure. MK.

Question 83: Indigenous U.S. coral snakes occur naturally in 11 states. Which states?

Answer: Micrurus fulvius occurs naturally in portions of North Carolina, South Carolina, Georgia, Florida, Alabama, Mississippi and Louisiana east of the Mississippi River. Micrurus tener occurs naturally in Louisiana west of the Mississippi River and in parts of Texas and Arkansas. Micruroides euryxanthus occurs naturally in parts of Arizona and New Mexico. (Walter F., et al. Temporal analysis of coral snakebite severity published in the American Association of Poison Control Centers' Annual Reports from 1983—2007. 2010 Clin Tox 48:72-78).

Commentary: Coral snake envenomations are potentially fatal. Identification of the culprit snake, in a patient that was bitten, is not always feasible. Physicians should be aware of the geographical distribution of venomous species to assist in identification and further management. RS.

Question 84: What is Samter's triad?

Answer: Samter's triad is a clinical syndrome characterized by aspirin sensitivity, nasal polyps, and bronchial asthma. The cited reference points out that this is also known as "aspirin exacerbated respiratory disease" or "aspirin sensitive asthma". The authors note that in this syndrome exposure to aspirin or other cyclooxygenase-I inhibitors results in a spectrum of bronchospasm, laryngospasm, rhinitis, and conjunctivitis. The mechanism for this aspirin intolerance has not been fully elucidated but likely relates to accumulation of leukotrienes and other inflammatory products resulting from dysfunction of the arachidonic acid metabolism pathway. (Shen J et al. Aural polyps in Samter's triad: Case report and literature review. 2012 Otology and Neurotology 33:774-778).

Commentary: This article reviews the literature and discusses the clinical features of Samter's triad. Inflammatory bilateral aural polyps are a special subset of aural polyps that are suggestive of Samter's triad. Aspirin desensitization has been shown to improve outcomes for asthma hospitalizations, sinus operations, and use of corticosteroids. MK.

Question 85: What is Otto Fuel II and what are its constituent chemicals?

Answer: Otto Fuel II is a distinct-smelling, reddish-orange, oily liquid that the U.S. Navy uses as a fuel for torpedoes and other weapon systems. It is a mixture of three synthetic substances: propylene glycol dinitrate (the major component), 2-nitrodiphenylamine, and dibutyl sebacate. Propylene glycol dinitrate, a colorless liquid with an unpleasant odor, is explosive. 2-Nitrodiphenylamine is an orange solid used to control the explosion of propylene glycol dinitrate. Dibutyl sebacate is a clear liquid used for making plastics, many of which are used for food packaging. It is also used to enhance flavor in some foods such as ice cream, candy, baked goods, and nonalcoholic drinks, and is found in some shaving creams. (http://www.atsdr.cdc.gov/substances/toxsubstance.asp?toxid=152.

Commentary: Workers at ammunition factories or military personnel handling the fuel are at risk of exposure. Headache is the most common reported symptom. RS.

Question 86: What is lepidopterism?

Answer: Some caterpillar members of the species Lepidoptera have larvae with poisonous hairs or "setae". These setae contain an urticating toxin that can cause skin and mucous membrane reactions on contact. The cited reference notes "Cutaneous reactions of lepidopterism are of three different types: weal and flare reaction, toxic irritant dermatitis, and persistent itchy papules. Other signs are conjunctivitis, pharyngitis, malaise, and upper respiratory tract symptoms including respiratory distress." Some cases involving life threatening anaphylactic reactions have been reported. (Gottschling S and Meyer S. An epidemic airborne disease caused by the oak processionary caterpillar. 2006 Pediatric Derm 23(1): 64-66).

Commentary: Lepidopterism is an unusual cause of allergic reaction, which may require topical or systemic corticosteroids. Lepidopterism should be included in the differential diagnosis in epidemic outbreaks of allergic reactions and dermatitis during the months of April – July, when these caterpillars are in the larval stages. MK.

Question 87: Synthetic cannabinoids such as K2, Spice, XLR-11 and others are related to delta-9-tetrahydrocannabinol, the active ingredient in marijuana but important clinical differences have been identified. What are the clinical differences seen associated with acute intoxication with the synthetic cannabinoids as compared with marijuana?

Answer: Synthetic cannabinoids are noted to be up to three times more likely to manifest sympathomimetic effects (i.e., tachycardia and hypertension), and roughly five times more likely to be associated with hallucinations. An increase in the occurrence of seizures has been reported with synthetic cannabinoid use. In addition, unanticipated acute renal injury has been reported in association with the abuse of synthetic cannabinoids. (Acute Kidney Injury Associated with Synthetic Cannabinoid Use — Multiple States, 2012. Morbidity and Mortality Weekly Report. February 15, 2013 / 62(06); 93-98).

Commentary: Synthetic cannabinoids (SC) remain an increasing public health concern and may cause life-threatening toxicity. Clinical effects may vary significantly given the variability of available SC preparations and constant synthesis of new formulas. Increasing public awareness of the potential serious effects of synthetic cannabinoids may deter future use. RS.

Question 88: What is NMAM?

Answer: NMAM is a collection of methods for sampling and analysis of contaminants in workplace air, and in the blood and urine of workers who are occupationally exposed. These methods have been developed or adapted by NIOSH or its partners and have been evaluated according to established experimental protocols and performance criteria. NMAM also includes chapters on quality assurance, sampling, portable instrumentation, etc.
(https://www.cdc.gov/niosh/nmam/).

Commentary: NIOSH Manual of Analytical Methods (NMAM) is a valuable resource in the evaluation of the workplace environment and potentially exposed workers. The use of established and validated protocols and adherence to quality measures is necessary to accurately assess occupational exposures. MK.

Question 89: What are the risk factors for the development of compartment syndrome following snakebite?

Answer: The cited reference notes that the following factors increase the risk for the development of increased intracompartmental pressures in patients envenomed following snakebite: 1-envenomations of small children; 2-envenomations of digits; 3-application of ice or cold packs; 4-delayed use of antivenin; 5-inadequate dosing of antivenin. (Cumpston KL. Is there a role for fasciotomy in Crotalinae envenomations in North America? 2011 Clin Tox 49:351-365).

Commentary: Compartment syndrome is a limb-threatening complication of a snakebite and early recognition of which patients are at-risk is crucial to preserve limb viability. The cited article states early and adequate administration of crotaline Fab

antivenin, rather than fasciotomy, is the preferred treatment for increased intracompartmental pressures following crotaline envenomation. RS.

Question 90: Acrylamide (ACR) is a water-soluble alkene used in the production of a variety of commercial polymers and gels. Polyacrylamide compounds are often used in the cosmetic, paper, and textile industries; in ore processing; and as soil conditioners and flocculants for wastewater treatment. During the 1950s it became apparent that occupational exposure to ACR had the potential to cause toxicity. Which organ system is involved and what characterizes the toxicity associated with ACR?

Answer: High-level, long duration, occupational ACR exposure has the potential, in some cases, to cause a neurotoxic syndrome characterized by ataxia, skeletal muscle weakness, cognitive impairment and numbness of the extremities. (LoPachin RM and Gavin T. Molecular mechanism of acrylamide neurotoxicity: Lessons learned from organic chemistry. 2012 Env Health Perspect 120:1650-1657).

Commentary: In the cited article, the authors provide evidence of impaired neurotransmission in peripheral and central nervous system associated with chronic ACR exposure. The alkenes may interact with various endogenous unsaturated aldehydes, thereby accelerating several disease processes where cellular oxidative stress is a contributing etiology such as diabetes mellitus, Alzheimer's disease, and atherosclerotic diseases. MK.

Question 91: Grayanotoxins, also known as andromedotoxin, acetylandromedol or rhodotoxin, are derived from the leaves, twigs or flowers of plants belonging to genera of the Ericaceae (heath) family, comprising among others the Rhododendron, Pieris, Agarista and Kalmia genera. What is the primary toxicity of grayanotoxin?

Answer: The cited article notes: "The toxicity of grayanotoxin lies in its ability to bind to the group II receptor site in voltage gated sodium channels within the cell." The authors further point out that "grayanotoxin binding modifies the channels configuration to such an extent that it prevents sodium channel inactivation, rendering the cell in a depolarized, and thus, activated state. Grayanotoxins bind to the channel only in its open state and, thereafter, the activation potential of the modified sodium channel is shifted in the direction of hyperpolarization." (Jansen SA et al. Grayanotoxin poisoning: 'Mad honey disease' and beyond. 2012 Cardiovasc Toxicol 12:208-215).

Commentary: In addition to intoxication and dizziness, consumption of grayanotoxin may cause atrioventricular block and hypotension, primarily by increasing the vagal tone by its ability to inhibit neural sodium channels activation and leaving them in an activated state. Cattle and pet poisoning by grayanotoxin may be fatal. Cases of honey consumption leading to grayanotoxin toxicity are most commonly reported in Turkey. The grayanotoxin intoxication is rarely fatal in humans, however herbal preparations with grayanotoxin should be avoided. MK.

Question 92: Atrazine is an "RUP" What is atrazine and what is an "RUP"?

Answer: Atrazine is the common name for an herbicide that is widely used to kill weeds. It is used mostly on farms. Pure atrazine-an odorless, white powder-is not very volatile, reactive, or flammable. It will dissolve in water. Atrazine is made in the laboratory and does not occur naturally. Atrazine is used on crops such as sugarcane, corn, pineapples, sorghum, and macadamia nuts, and on evergreen tree farms and for evergreen forest regrowth. It has also been used to keep weeds from growing on both highway and railroad rights-of-way. Atrazine can be sprayed on croplands before crops start growing and after they have emerged from the soil. Some of the trade names of atrazine are Aatrex®, Aatram®, Atratol®, and Gesaprim®. The scientific name for atrazine is 6-chloro-N-ethyl-N'-(1-methylethyl)-triazine-2,4-diamine. Atrazine is a Restricted Use Pesticide (RUP), which means that only certified herbicide users may purchase or use atrazine. Certification for the use of atrazine is obtained through the appropriate state office where the herbicide user is licensed. (http://www.atsdr.cdc.gov/phs/phs.asp?id=336&tid=59).

Commentary: Agricultural workers applying atrazine to crops and the general public living in the vicinity of such crops may be exposed to atrazine by water, air, or soil contamination but exposure to atrazine on a regular basis is not common. Atrazine is distributed widely in the body and primarily excreted in the urine in 24-48 hours. Atrazine is an RUP compound and a license is required to use the product. MK.

Question 93: Body piercing is a risk factor for the development of hypersensitivity to what material?

Answer: Body piercing is a risk factor for the development of hypersensitivity to nickel, which is commonly a major component of the jewelry used in body piercing. The cited reference notes that the prevalence of nickel hypersensitivity in the face of body piercing increases with increasing numbers of body piercings. Body piercings are thought to significantly contribute to the fact that the rate of nickel allergy appears to be increasing in North America. (Schram SE et al. Nickel hypersensitivity: a clinical review and call to action. 2010 Int J Derm 49:115-125).

Commentary: The incidence of nickel allergy and sensitivity is increasing annually in the United States. Interestingly, the above cited reference contends that this could carry significant future health risks, as nickel can be used as a material of vascular stents and artificial joint prostheses. RS.

Question 94: Talc retinopathy is related to intravenous drug use in some cases. What is the nature of this association?

Answer: According to the cited reference: "Talc is an inert filler in methylphenidate hydrochloride tablets, which are crushed for intravenous drug use. The talc is then unknowingly injected intravenously. Talc particles are usually fine and are distributed intravascularly and extravascularly in the retina in patients who chronically use intravenous drugs and in whom right-to-left cardiopulmonary shunting occurs through collateral vessels that may develop around sites of pulmonary infarction. However, in a patient with a patent foramen ovale, larger particles may cause retinal artery occlusions and severe vision loss." (Schoenberger SD and Agarwal A. Talc Retinopathy. 2013 NEJM 368:852).

Commentary: IV drug use may predispose a patient to specific ocular complications. In addition to talc retinopathy, other potential complications include infections, retinal infarcts, endopthalmitis, and corneal ulcers. Physicians should perform ophthalmic examinations in patients with history of IV drug use, as early recognition is crucial in treatment. RS.

Question 95: In what industries does one find the chemical para-nitroaniline, what is the primary toxicity of this chemical and what are the most important routes of exposure for this chemical?

Answer: Para-nitroaniline is frequently used as an intermediate in the manufacture of dyes. The cited reference also points out that it is used "in the production of rubber, gasoline, pesticides, paints and varnishes." Para-nitroaniline is acutely toxic to the hematopoietic system as a strong methemoglobin former. The authors of the cited reference also point out that para-nitroaniline is fat soluble and readily absorbed through intact skin. "Exposures most commonly occur via the skin and lungs although ingestion has also been reported." (Fagan K et al. Paranitroanaline poisoning: A failure in basic prevention? 2014 JOEM 56(1): 112-114.

Commentary: Para-nitroaniline exposure may result in methemoglobinemia. Appropriate selection of personal protective equipment, proper handling, and proper first aid may minimize the risk of clinical toxicity. MK.

Question 96: Chronically elevated serum levels of fluoride are associated with what radiological findings in the vertebral bodies as seen on plain x-ray?

Answer: Skeletal fluorosis may be associated with the so-called "rugger jersey sign", a pattern of vertical striations reflecting increased bone density in the upper and lower areas of the vertebral bodies. Skeletal fluorosis occurs in geographic areas where high levels of fluoride exist in drinking water. (Image Challenge 2013 NEJM March 14,2013 online at http://www.nejm.org/doi/full/10.1056/NEJMicm1200995#t=article).

Commentary: Skeletal fluorosis may be found in a variety of underdeveloped countries where fluoride levels in drinking water regularly exceed the safe limit. Interestingly, the author states that brewed tea has one of the highest fluoride concentrations of beverages commonly consumed in the United States. RS.

Question 97: What is aldicarb?

Answer: Aldicarb (propanal, 2-methyl-2-(methylthio)-O-[(methyl-amino) carbonyl] oxime) is a carbamate insecticide and nematocide marketed under the brand name Temik. As a carbamate, aldicarb is a potent but reversible cholinesterase inhibitor. (Proenca P et al. Aldicarb poisoning: one case report. 2004 For Sci Int 146S: S79-S81).

Commentary: The cited reference describes a case of a young male who was found dead after exposure to aldicarb. Carbamates reversibly inhibit acetylcholinesterase, which may result in a cholinergic toxidrome featuring miosis, bronchospasm, bronchorrhea, and bradycardia. MK.

Question 98: What is M8 detection paper?

Answer: M8 detection paper is used primarily by the military (and some first responder units) to detect liquid 'V', 'G' and 'H' agents. This paper contains two dyes and an acid-base (pH) indicator which changes to yellow when in contact with 'G' agents, green when in contact with liquid VX and red when in contact with liquid HD. The color change usually manifests within 30 seconds of exposure. Chemical detection papers, including the M8 paper, lacks specificity and may produce false positives. (Sferopoulos R. A review of chemical warfare agent (CWA) detector technologies and commercial-off-the shelf items. March 2009 Human Protection and Performance Division, Defense Science and Technology Organization, Australian Government Department of Defense. Accessed at: http://www.dtic.mil/cgi-bin/GetTRDoc?AD=ADA502856).

Commentary: Rapid detection of chemical warfare agents is advantageous from a military and public health perspective. M8 paper is typically distributed to soldiers for use in the field. It is important to be aware of the usefulness and limitations of chemical detector paper when interpreting results. RS.

Question 99: What are the clinical characteristics of envenomed bites of the Gaboon viper (Bitis gabonica) and what is the recommended treatment for these bites?

Answer: The cited reference notes that the usual symptoms associated with envenomation caused by Bitis gabonica include "rapid onset swelling of the bite area, later becoming very painful, bleeding and hemorrhagic edema at the bite site and finally, dyspnea and loss of consciousness with hematuria, hematemesis and local tissue necrosis." The treatment of choice for the envenomation by this snake is the timely administration of appropriate antivenom. (Marsh N et al. Gaboon viper (bitis gabonica) envenomation resulting from captive specimens- A review of five cases. 2007 Clin Tox 45(1):60-64).

Commentary: Envenomation by the Gaboon viper may result in local increased capillary permeability with resulting edema and systemic coagulopathy, which may lead to death. The mentioned article emphasizes the need for care that should be practiced while handling the Gaboon viper and the treatment for envenomation. MK.

Question 100: What was the so-called "Sevaso disaster"?

Answer: The Seveso, Italy, disaster resulted in TCDD (2,3,7,8-tetrachlorodibenzo-p-dioxin) exposure to a wide population in and around Seveso, Italy, on July 10, 1976. This environmental disaster took place in the trichlorophenol production department of a chemical plant located near the town of Seveso, approximately 25 km north of Milan, when a chemical cloud containing several kilograms of TCDD was released into the atmosphere. (Consonni D., et al. Mortality in a population exposed to dioxin after the Seveso, Italy, accident in 1976: 25 years of follow up. (2008 Am J Epidemiology 167(7): 847-858).

Commentary: It is important to study and learn from environmental disasters as they increase our knowledge of the involved exposure and can lead to prevention of similar events in the future. Other important gas disaster include carbon dioxide exposure in Cameroon, Africa in 1986 and methyl isocyanate exposure in Bhopal, India in 1984. RS.

Question 101: What toxin is causative of "bitter bottle gourd toxicity"? What is the clinical syndrome caused by this poisoning?

Answer: Bottle gourds are plants included in the Family Cucurbitaceae. These plants, especially when over-ripe, contain the substance cucurbitacin. Cucurbitacins are triterpenoids and, if ingested, reportedly increase capillary permeability causing severe capillary leak syndrome leading to hypotension. The authors of the cited article report that bottle gourds are usually consumed in South Asian countries and may be included with some Ayurvedic medicines. The ingestion of bottle gourds containing high concentrations of cucurbitacins, may result in severe GI effects within 60 minutes of ingestion. These effects include diarrhea, vomiting, GI bleeding and hypotension. Several outbreaks of cucurbitacin poisoning have been reported including a 1984 California outbreak of over 200 cases attributed to ingestion of bitter zucchini. (Ho CH et al. Bitter bottle gourd (Lagenaria siceraria) toxicity. 2014 J Emerg Med 46(6): 772-775).

Commentary: Bottle gourd toxicity should be considered in the differential diagnosis of acute gastroenteritis in countries where the plant is commonly consumed. Nausea, vomiting, GI bleeding, hemorrhage and resulting hypotension, which may require hospitalization. MK.

Question 102: The combination of which two drugs was at issue in the now infamous case involving Libby Zion?

Answer: The Libby Zion case reportedly involved the ill-advised combination of meperidine and phenelzine with the precipitation of a fatal serotonin syndrome (although some have suggested that cocaine and/or other drugs may also have been involved). (Asch DA and Parker RM. The Libby Zion Case. One step forward or two steps backward? 1988 NEJM 318(12): 771-775).

Commentary: This case is important not only because it was a medication error-related death but because it also had a significant impact on future physician training. This case initiated the Accreditation Council of Graduate Medical Education (ACGME) to reevaluate physician errors and fatigue and resulted in the 80 hour work week limit.

Question 103: What potentially harmful exposure may be associated with the breakage of CFL's?

Answer: CFLs are "compact fluorescent lamps". These light bulbs were introduced in the US with the intention of reducing domestic energy consumption. The cited reference notes that "an important disadvantage of fluorescent lamps is that CFLs contain milligram quantities of mercury." The authors go on to report that according to one recent study, "once a CFL breakage event occurs, mercury vapor, liquid mercury (if present) and mercury adsorbed onto the phosphorous powder is released." They further report that after a CFL breaks, indoor [mercury] air concentrations could potentially exceed regulatory thresholds of concern. (Sarigiannis DA et al. Exposure analysis of accidental release of mercury from compact fluorescent lamps (CFLs) 2012 Sci Tot Environ 435-436:306-315).

Commentary: Compact fluorescent lamp (CFL) breakage is a potential source for mercury toxicity. Infants and toddlers are particularly at risk due hand-to-mouth behaviors. MK.

Question 104: A "cock-walk" gait (also called "coq au pied") has been associated in the literature with extreme (high dose/ long duration) exposure to what heavy metal?

Answer: The so-called "cock-walk" gait has been described in association with manganese-induced neurotoxicity that may arise in association with extreme exposures to this metal. (Olanow CW. Manganese induced parkinsonism and Parkinson's Disease (PD. 2004 Ann NY Acad Sci 1021:209-223.).

Commentary: Manganese toxicity may have similar clinical features of Parkinson's Disease. The reference cited above highlights several key differences between Mn-induced PD and PD including the "absence of Lewy bodies (another hallmark of PD), the lack of therapeutic response to levodopa, failure to detect fluorodopa uptake by positron emission tomography (PET) studies, more frequent dystonia, and less resting tremor." RS.

Question 105: Guarana is a common additive found in a variety of so-called energy drinks. What is guarana?

Answer: The cited reference reports "Guarana, also known as Brazilian cocoa, is a South American plant that is commonly added to energy drinks. It contains a substance called guaranine, which is caffeine, with 1 g of guarana being equivalent to as much as 40 mg of caffeine." The authors go on to note "….when an energy drink lists its caffeine content, it is usually not taking into account the guarana, which has been reported to exert a more prolonged effect than an equivalent amount of caffeine. In reality, when a drink is said to contain caffeine plus guarana, it contains caffeine plus more caffeine. Guarana has not been evaluated by the FDA for safety, effectiveness, or purity." (Blankson KL et al. Energy drinks: What teenagers (and their doctors) should know. 2013 Pediatrics in Review 34(2):55-62).

Commentary: Consumers may not be aware of the additional caffeine contained in guarana. The effectiveness and safety of guarana has not been established by the FDA as the short and long term side effects of guarana and other additives caffeinated drinks are not completely understood. MK.

Question 106: What is the ATSDRs Rapid Response Registry (RRR)?21q.

Answer: The ATSDRs RRR helps local and state public health and disaster response agencies rapidly establish registries of persons who are exposed or potentially exposed to chemicals or other harmful agents during catastrophic events. ATSDR's RRR survey instrument gives local and state entities a tool to register responders and other persons exposed to chemical, biological, or nuclear agents from a disaster. The survey instrument is a two-page form that can be

distributed on paper or electronically. It can be implemented quickly to collect information rapidly to identify and locate victims and people displaced or affected by a disaster. For mass casualty events, ATSDR identified four critical fields that would be sufficient to establish an official registry record and require only about 90 seconds to complete for each registrant. These are the registrant's name, gender, home address, and telephone numbers. https://www.atsdr.cdc.gov/rapidresponse/index.html.

Commentary: The Rapid Response Registry collects information about disasters or mass casualty events. This registry records the basic information of the registrants and aids in the assessment of real-time and future needs for medical assistance, interventions, and health education for the purpose of public health planning. MK.

Question 107: What is alachlor? What is butachlor?

Answer: Alachlor (trade name "Lasso") is an aniline herbicide widely used in the USA, South America and Asia to control grasses and broad-leaf weeds. Butachlor is an analog of alchlor. Both are mucous membrane irritants that may, in some cases, cause severe neurological and cardiovascular effects if ingested in large quantities. (Lo Y, et al. Acute alachlor and butachlor herbicide poisoning. 2008 Clin Tox 46(8): 716-721).

Commentary: Alachlor and butachlor are commonly used herbicides. Inhalational exposure may result in local mucosal irritation, whereas severe neurological and cardiovascular effects have been reported following oral exposure. Poisonings typically result in minimal toxicity with gastrointestinal symptoms being the most prominent. MK.

Question 108: Carisoprodol (Soma, Soprodal, Vanadom) is a central nervous system depressant with sedative and skeletal muscle relaxant effects. What is the pharmacology of that accounts for the sedative effects of this drug?

Answer: The sedative as well as the adverse effects of carisoprodol are likely due to its metabolic conversion to meprobamate. Meprobamate induces sedation via action at gamma-aminobutyric acid A (GABA) receptors (Fass JA. Carisoprodol legal status and patterns of abuse. 2010 Ann Pharmacother, 44:1962-1967).

Commentary: Carisoprodol has the potential for abuse secondary to its potent sedative effects. Meprobamate is the active metabolite with its own sedative properties and longer half-life than the parent compound. Carisoprodol toxicity presents similarly to the benzodiazepine and barbiturate toxicity, as they all are GABA-A agonists. RS.

Question 109: What is the association, if any, between occupational lead exposure and amyotrophic lateral sclerosis (ALS)?

Answer: According to a recently published meta-analysis, "The risk of developing ALS among individuals with a history of exposure to lead was almost doubled (odds ratio, 1.81; 95% confidence interval, 1.39 to 2.36) on the basis of nine included case-control studies with specific lead exposure information, with no apparent heterogeneity across included studies ($I2 = 14\%$). The attributable risk of ALS because of exposure to lead was estimated to be 5%." The authors of this study concluded "Previous exposure to lead may be a risk factor for ALS." They further noted "Confirmation of the present findings in future studies would serve both to elucidate the causes of ALS, and to support risk mitigation actions to further reduce the risk of ALS because of exposure to lead from occupational and other sources." (Wang MD et al. A meta-analysis of observational studies of the association between chronic occupational exposure to lead and amyotrophic lateral sclerosis. 2014 JOEM 56 (12): 1235-1242).

Commentary: Lead may cause toxicity to motor neurons possibly by axonal degeneration and Schwann cell destruction. Lead toxicity may cause foot or wrist drop but the sensory system is typically spared. The cited meta-analysis reported an association between lead exposure and the development of amyotrophic lateral sclerosis. Further studies are needed to confirm this finding. MK.

Question 110: What is the Jarisch-Herxheimer reaction (JHR) and which patients are most susceptible to the development of this reaction?

Answer: JHRs have been reported in individuals receiving certain antibiotics (including tetracyclines, penicillins, bismuth, and sulfonamides) for treatment of a variety of spirochetal illnesses such as Lyme disease, leptospirosis, yaws, syphilis. JHR can occur as early as 2 hours after the first antibiotic dose with resolution usually complete by 24 hours. Patients may manifest fever and rigors, followed by diaphoresis as well as headache, myalgias and general malaise. Interestingly, the signs and symptoms of the treated disease may actually worsen during the course of any JHR. Jarisch-Herxheimer reactions have been reported more frequently in HIV infected patients. (See S et al. Penicillin-Induced JarischHerxheimer Reaction. 2005 Anns Pharmacotherapy, 39:2128-2130).

Commentary: Jarisch-Herxheimer reactions should be anticipated following administration of certain antibiotics for the treatment of treponemal diseases. Symptoms may be easily confused with drug allergy, however the underlying pathophysiology is different. RS.

Question 111: Male priapism is not an uncommon emergency. Female (clitoral) priapism, however, is a rare though non-emergent condition. Drug induced priapism in both sexes has been reported. Which drugs have been reported to be causative of female priapism?

Answer: The cited reference notes "Common causes of priapism in men and women are medications that cause alpha-adrenergic blockade such as certain antidepressants and psychotropic medications." These authors further note that female priapism specifically has been associated with the use of trazadone, bupropion and citalopram. (Unger CA and Walters MD. Female clitoral priapism: An over the counter option for management. 2014 J Sex Med 11:2354-2356).

Commentary: The most common cause of priapism world-wide is idiopathic. In the US, drugs used for erectile dysfunction mostly cause priapism. In pediatric population, sickle cell disease accounts for most cases of priapism in which case exchange transfusion may be necessary. High flow priapism may mandate urgent urologic consultation for surgical correction. MK.

Question 112: Levamisole is an antihelmintic drug specifically formulated for veterinary applications. Levamisole has recently become recognized as an additive in illicit cocaine purportedly used to enhance the euphoric effects of cocaine. When should a clinician consider the possibility that a patient has used cocaine contaminated with levamisole?

Answer: The cited reference notes that levamisole toxicity resulting from the use of adulterated cocaine may be an increasing problem and should be considered in a cocaine user with neutropenia and reticular purpura. (Trevor T., et al. Toxic effects of levamisole in a cocaine user. 2011 NEJM 364:e52June 16, 2011). RS.

Commentary: Toxicologic effects of additives to illicit drugs must be considered when a patient has unexpected clinical findings. Levamisole is a common potential additive to cocaine with distinct effects that must be recognized. RS.

Question 113: Which short-lived metabolite, when identified in urine, identifies recent heroin use?

Answer: The cited reference reports “6-acetylmorphine concentrations in urine were short-live ($<$ 7 hours) and highly variable, but were clearly associated with recent heroin exposure when present.” (Cone EJ et al. Forensic drug testing for opiates. VII. Urinary excretion profile of intranasal (snorted) heroin.1996 J Analytical Tox 20:379-392).

Commentary: Heroin (diacetylmorphine) is deacetylated to 6-acetylmorphine and then again to morphine. The deacetylation process is rapid which results in the short detection half-life for that metabolite. Morphine is not acetylated in vivo so detection of 6-am is consistent with heroin use rather than use of prescription opioid products. MK.

Question 114: What is the primary lethal pathophysiological factor in barium poisoning, what are the significant clinical manifestations and what treatment is expected to reverse the life threatening effects of barium?

Answer: According to the cited reference: “low serum potassium is the primary lethal pathophysiological factor in barium poisoning and is associated with arrhythmias, respiratory muscle paralysis and death. “Aggressive potassium administration has been shown to reverse barium toxicity.” (Yu D et al. Incorrigible hypokalemia caused by barium chloride ingestion. 2015 Am J Med Sci 349(3): 279-281).

Commentary: Barium toxicity may occur secondary to occupational exposure or intentional ingestion. Patients maintain consciousness even when severely intoxicated with barium. Clinical manifestations include vague gastrointestinal symptoms followed by profound hypokalemia that may occur within 2 hours of ingestion, resulting in skeletal and respiratory muscle paralysis. Barium blocks potassium channels and causes intracellular trapping of potassium ions. Prompt repletion of potassium is indicated. MK.

Question 115: An emergency physician wishes to treat a firefighter found unconscious on a fire ground empirically for cyanide toxicity but the pharmacy states they do not have hydroxocobalamin (or thiosulfate) available. The pharmacist instead recommends the use of vitamin B 12. Why is this advice seriously flawed?

Answer: The cited reference points out that hydroxocobalamin (vitamin B12a), the natural form of vitamin B12 , is a heme like molecule containing a complexed cobalt (Co) atom. Hydroxocobalamin acts as a cyanide antidote by direct binding to cyanide to form nontoxic cyanocobalamin that is excreted in the urine. Vitamin B 12 itself does not complex with cyanide nor does it increase the excretion of cyanide. Thus it does not act in the same way that hydroxocobalamin does. (Hall A, et al. Sodium Thiosulfate or Hydroxocobalamin for the Empiric Treatment of Cyanide Poisoning. 2007 Ann Emerg Med 49(6):806-813.

Commentary: Hydroxocobalamin is marketed under the name Cyanokit® and is one of three commercially available cyanide antidote kit used in the US. Hydroxocobalamin is a life-saving antidote in the setting of cyanide toxicity. RS.

Question 116: What was the Harrison Narcotic Act?

Answer: According to the cited reference, the Harrison Narcotic Act, enacted in 1915, required “anyone who imported, produced, sold, or dispensed “narcotics” (at that time meaning coca- as well as opium-based drugs) to register, pay a nominal tax, and keep detailed records”. The cited reference notes that through the Harrison Act “enforcement policies made it risky for [physicians] to regularly supply narcotics to addict, giving the law its reputation as a prohibition measure”. The Harrison Act was replaced by the 1970 Controlled Substances Act.

(Courtwright DT. Preventing and treating narcotic addiction-A century of federal drug control. 2015 NEJM 373:2095-2097).

Commentary: The Harrison Narcotic Act and Controlled Substances Act are two important laws for controlling the use of narcotics. The Harrison Narcotic Act of 1915 was put forward to control the marketing of narcotics. The Controlled Substance Act regulates the possession and distribution of all controlled substances including narcotics, hallucinogens, stimulants, and depressants. MK.

Question 117: Why is the vitreous humor (VH) often used for postmortem drug testing?

Answer: The vitreous is often used because it appears to be less susceptible than blood to postmortem redistributive changes. The cited reference notes that it is also a more simple environment than putrefied blood, containing 98.99% water. The reference states that VH may be the best substrate for measurement of postmortem drug concentrations "if the body has undergone considerable bleeding, decomposition, or burning". (Yarema MS and Becker C. Key Concepts in Postmortem Drug Redistribution. 2005 Clin Tox. 43:235-241).

Commentary: Postmortem redistribution may make interpreting postmortem drug testing complicated. Substrates, such as VH, that are less prone to redistribution may help toxicologists make more reliable determinations regarding the drug's role in the death. RS.

Question 118: What is the most common source for elevated carbon monoxide levels in indoor ice rinks?

Answer: The most common source for potentially dangerous elevated levels of CO in indoor ice rinks has been ice resurfacing machines that are powered by gas or propane, as opposed to electric motors. (Crewswell PD et al. Exposure to elevated carbon monoxide levels at an indoor ice arena- Wisconsin, 2014 MMWR November 20, 2015 / 64(45);1267-1270).

Commentary: Carbon monoxide is a colorless and odorless gas that has 250 times more binding affinity to hemoglobin than oxygen. While headache is the most commonly reported symptom, clinical manifestations may range from flu-like symptoms to coma. Prompt initiation of hyperbaric oxygen therapy may reduce the risk of permanent neurologic sequalae in selected cases. MK.

Question 119: Microvascular steatosis (MS) is a condition caused by impairment of mitochondrial function in which decreased fatty acid beta oxidation results in the accumulation of free fatty acids and triacylglycerol. What are the potential toxicological causes for MS?

Answer: Microvascular steatosis has been associated with aspirin (in Reyes syndrome), valproate, nucleoside analogues (e.g. didanosine and zidovudine), MDMA, tetracycline, Bacillus cereus emetic toxin, acute iron overload and/or acute iron toxicity. (Fearing MK, et al. Case 12-2011: A 9 month-old boy with acute liver failure. 2011 NEJM 364(16):1545-1556).

Commentary: Microvascular steatosis is a histological finding on liver biopsy that may be used to identify toxicologic causes of undifferentiated hepatic injury. RS.

Question 120: Ivabradine is a novel anti-anginal agent that has been reported to be associated with phosphenes. What are phosphenes?

Answer: The cited reference notes: "The visual sensations evoked by stimuli other than luminance changes are known as phosphenes. Phosphenes can be spontaneous or provoked in a number of ways including a gentle pressure on the eyelids…" Ivabradine has been reported to cause phosphene-like phenomena. (Cervetto L et al. Cellular mechanisms underlying the pharmacological induction of phosphenes. 2007 Br J Pharm 150:383-390).

Commentary: Phosphenes may be an early symptom of variety of retinal or visual diseases. The phosphene phenomenon has been reported by certain stimulant and depressant drugs. MK.

Question 121: What food/beverages increase the risk for gout? What food/beverages decrease the incident risk for gout?

Answer: The risk for gout is increased in persons with an increased intake of dietary purines (particularly meat and seafood), ethanol (particularly beer and spirits), soft drinks, and fructose and is decreased in those with an increased intake of coffee, dairy products, and vitamin C (which lower urate levels) (Neogi T. Gout. 2011 NEJM 364(5): 443-452).

Commentary: Gout is a common medical condition. Correct dietary recommendations may reduce the incidence of gout flares. RS.

Question 122: Which beta-blocking agent has been noted to cause false positive urine screening for amphetamines?

Answer: Labetalol has been noted to cause false positive urine screening for amphetamines. (Moeller KE et al. Urine drug screening: Practical guide for clinicians. 2008 Mayo Clin Proc 83(1):66-76).

Commentary: Labetalol is commonly used in the management of hypertension. Labetalol is moderately lipid soluble with a partition coefficient of 1.2. False positive amphetamine immunoassay results may occur due to cross-reactivity with labetalol as well as decongestants, ranitidine, sertraline, and bupropion. MK.

Question 123: What is the half-life and time to steady state for digoxin?

Answer: According to the cited reference "The half-life and time to steady-state varies by patient and is dependent on the renal function. In patients with normal renal function, the half-life ranges from 1.5 to 2 days. This is prolonged anywhere from 3.5 to 5 days in patients with moderate to severe renal dysfunction. Patients with normal renal function reach steady state in 5 to 7 days after initiation of therapy, whereas it may take up to 15 to 20 days in patients with impaired renal function." (Ehle M et al. Digoxin: Clinical Highlights: A review of digoxin and its use in contemporary medicine. 2011 Crit Pathways in Cardiol 10:93-98).

Commentary: Renal dosing modification is necessary in patients with renal dysfunction. Chronic digoxin toxicity may occur with therapeutic digoxin levels. Hyperkalemia in setting of acute digoxin toxicity is an indication for anti-digoxin antibodies. MK.

Question 124: What are the clinical manifestations of acute radiation sickness?

Answer: The major clinical manifestations of acute radiation sickness (ARS) are dependent upon the dose of radiation received. According to the cited reference, the major manifestations of ARS include signs of hematopoietic depression with concurrent infection and hemorrhage (hematopoietic syndrome). The intestinal, toxemia, and cerebral syndromes occur after large doses with signs of diarrhea, water loss, fever, arterial blood pressure drop, and changes of function and structure of the brain. Occasionally, with very high acute doses to the head or trunk, there may be loss of consciousness, which is sometimes referred to as transient incapacitation (or central nervous system) syndrome. (Mettler FA, et al. Health effects in those with acute radiation sickness from the Chernobyl accident. 2007 Health Physics, 93(5):462-469).

Commentary: The clinical findings of ARS can be predicted based on the dose of radiation received. There are 4 phases of ARS including a prodromal period, latent period, period of illness, and recovery or death. The period of illness will present as different syndromes (hematopoietic, gastrointestinal, and nervous) as the radiation dose increases. RS.

Question 125: Pain is present in more than 90% of the bites from pit vipers in the United States. What is the exception?

Answer: Bites from the Mojave rattlesnake (Crotalus scutulatus) often cause little to no pain. (Emergency Clinics of North America, 2004, 22:423-44).

Commentary: Identification of a snake following envenomation is often difficult. Mojave rattlesnake envenomations do not result in local pain and swelling which may lead physicians to falsely assume that the patient is not envenomated. RS.

Question 126: Marijuana use can increase heart rate, supine hypertension and postural hypotension. In addition, marijuana smoking has been said to be a trigger for myocardial infarction (MI). What are the characteristics that define the trigger risk for MI following the use of marijuana?

Answer: In order to evaluate if marijuana is a trigger of the onset of an acute MI, the authors of the cited study collected data on marijuana use in 3882 persons who sustained an acute MI. The cited reference reports "the risk of myocardial infarction onset was elevated 4.8 times over baseline (95% confidence interval, 2.4 to 9.5) in the 60 minutes after marijuana use." (Mittleman MA et al. Triggering myocardial infarction by marijuana. 2001 Circulation 103: 2805-2809).

Commentary: The use of synthetic cannabinoids is increasing and they are readily available on internet. In addition to an increased risk of acute myocardial infarction in the first 1 hour of use, synthetic cannabinoids may cause acute kidney injury. Marijuana is known to cause various arrhythmias and may precipitate a cardiac event in patients with previous history of CAD. MK.

Question 127: What is the half-life of carboxyhemoglobin in persons treated with 100% oxygen at atmospheric pressure?

Answer: One study of 93 carbon monoxide poisoned patients treated with 100% oxygen at atmospheric pressure reported the half-life of carboxyhemoglobin to be 74 +/- 25 minutes. These authors point out that some reports indicate the half-life of carboxyhemoglobin in patients treated with 100% oxygen to be as long as 130 +/- 130 minutes. In contrast, a frequently quoted average for the half-life of carboxyhemoglobin is 80 minutes in persons treated with 100% oxygen however this was based on a study of only two volunteers. (Weaver LK et al. Carboxyhemoglobin half-life in carbon monoxide poisoned patients treated with 100% oxygen at atmospheric pressure. 2000 Chest 117(3): 801-808).

Commentary: According to the CDC, there were 5149 carbon monoxide (CO)-related deaths reported in the US from 1999 to 2010. CO toxicity primarily affects organs with high oxygen consumption. Pulse oximetry is unreliable at detecting carboxyhemoglobin (CO-Hb) and therefore specific CO-Hb levels should be obtained in suspected CO poisoning. MK.

Question 128: What drug has been called "reverse marijuana"?

Answer: Rimonabant is a selective CB1 receptor antagonist, sometimes known as "reverse marijuana", has been shown to have anorexigenic effects (while cannabis is known to increase appetite) and has been widely investigated as a treatment for obesity. This drug was withdrawn from the US market in 2008 due to possible severe psychiatric adverse effects. However, as stated by the cited reference, rimonabant and the endocannabinoid system is "currently a top contender as a therapeutic target for the treatment of obesity". (Pataky Z et al. Efficacy of rimonabant in obese patients with binge eating disorder. 2013 Exp Clin Endocrinol Diabetes 121(01): 20-26).

Commentary: According to the CDC, 36.5% of the U.S. population is obese. An estimated health-care cost of $147 billion was linked to obesity in 2008. Rimonabant is an endocannabinoid receptor antagonist that is used in other countries for binge eating disorder. MK.

Question 129: What is the mechanism for the development of dapsone-induced methemoglobinemia?

Answer: The cited reference reports that dapsone undergoes N-hydroxylation by various hepatic P-450 enzymes to form N-hydroxy dapsone. It is this hydroxylamine metabolite (N-hydroxy dapsone), and not the parent drug dapsone, that induces the formation of methemoglobinemia. N-hydroxy dapsone mediates the oxidation of the iron moiety of the heme molecule to produce methemoglobin in a dose dependent fashion. (Pallais JC, et al. Case 7-2011: A 52 year old man with upper respiratory symptoms and low oxygen saturation levels. 2011 NEJM 364(10): 957-966).

Commentary: Dapsone is a common cause of iatrogenic methemoglobinemia. Methylene blue is the antidote for methemoglobinemia. Cimetidine, a CYP450 inhibitor, has been studied as a potential adjuvant therapeutic agent for preventing methemoglobinemia for patients taking dapsone. RS.

Question 130: Amyloidosis (amyloid A amyloidosis) with renal involvement has been reported to occur in some drug addicts. With what process has amyloidosis in addicts been linked?

Answer: Amyloidodisis has been reported in some addicts who engage in "skin popping" (subcutaneous injection) with concomitant development of chronic skin infections. (Bakir AA and Dunea G. Drugs of abuse and renal disease. 1996 Curr Opinion in Nephrol and Hypertension 5:122-126).

Commentary: Heroin abusers are at increased risk for skin infections due to skin popping. AA amyloidosis may occur in chronic heroin users and cause nephrotoxicity. Persistent serum amyloid A usually leads to end stage renal disease requiring dialysis and renal transplant. MK.

Question 131: The geometric mean blood lead level in children aged 1-5 years declined from 14.9 micrograms per deciliter in the late 1970s to 1.9 micrograms per deciliter in 2004. What is generally regarded as the primary cause for this decline in childhood blood lead levels?

Answer: Restrictions in the use of lead in paint and gasoline substantially reduced the amount of environmental lead resulting in important declines in children's blood lead levels from the 1970s to 2004. (MMWR, 60(3), January 28,2011).

Commentary: “Lead poisoning in children is a preventable public health problem that can adversely affect the developing nervous system and result in learning and behavior problems.” The above cited restrictions had a significant impact on incidence of the lead toxicity and are important historical regulations in the field of environmental toxicology. RS.

Question 132: What are the so-called “BTEX” compounds?

Answer: “BTEX” is an abbreviation that stands for the volatile organic compunds: “benzene, toluene, ethylbenzene and xylenes”. (Moolla R et al. Occupational exposure of diesel station workers to BTEX compounds at a bus depot. 2015 Int J Environ Res Public Health 12(4): 4101-4115.

Commentary: Diesel station attendants are at a particular risk for inhalational exposure to BTEX. Benzene is a known human carcinogen. MK.

Question 133: What is permethrin, what is the mechanism of action when used as a scabicide, and what is the basis for the selective neurotoxicity for this agent?

Answer: Permethrin is a synthetic pyrethroid agent usually used topically as a 5% cream for the treatment of scabies. Permethrin interrupts voltage-gated sodium channels of arthropods resulting in prolonged depolarization of nerve-cell membranes and disruption of neurotransmission. The selective neurotoxic effect of permethrin on invertebrates is due to structural differences in voltage-gated sodium channels between vertebrates and invertebrates. (Currie BJ and McCarthy JS. Permethrin and ivermectin for scabies. 2010 N Engl J Med 362:717-725).

Commentary: Permethrin is commonly prescribed to both adults and pediatrics for the treatment of scabies. Its selective neurotoxicity to invertebrates allows for its human applications. RS.

Question 134: What is the role of carbamazepine in treating alcohol withdrawal syndrome?

Answer: The cited reference notes "carbamazepine is superior to placebo and equal in efficacy to phenobarbital and oxazepam for patients with mild-to-moderate withdrawal symptoms". The authors also point out "it reduces emotional distress better and permits a faster return to work than does oxazepam". Finally carbamazepine is effective in preventing withdrawal seizures and has no potential for abuse. (Kosten TR and O'Connor PG. Management of drug and alcohol withdrawal. 2003 NEJM 348(18):1786-1795).

Commentary: Approximately 88,000 deaths annually are alcohol related in the US. Alcohol is a contributing factor in 31% of driving fatalities. The cited article reports carbamazepine is an effective treatment for mild-moderate alcohol withdrawal symptoms. MK.

Question 135: The compound 6-monoacetylmorphine (6-MAM) is a marker for exposure to what drug of abuse?

Answer: 6-monoacetylmorphine (6-MAM) is a marker for heroin use. Heroin is diacetylmorphine. Diacetylmorphone is rapidly hydrolyzed to 6-MAM in the early stages of heroin metabolism in humans. (Lintzeris N. Prescription of Heroin for the Management of Heroin Dependence: Current Status. 2009 CNS Drugs, 23(6):463-476).

Commentary: Opioid urine drug immunoassays cannot differentiate between codeine, morphine, and heroin. 6-MAM is a biomarker specific for heroin. It is rapidly metabolized and becomes undetectable within hours of heroin use. RS.

Question 136: Which antibiotics have been reported to cause false positive opiate urine drug screens?

Answer: Fluoroquinolones (with levofloxacin, ofloxacin and pefloxacin being the most common fluoroquinolones associated with such cross reactions) and rifampin have been reported to cause false positive urine drug screens for opiates by cross reactivity. (Shafiq Q and Mutgi A. Urine opiate screening: false positive result with levofloxacin. 2010 CMAJ 182(15): 1644-1645).

Commentary: Cross reactivity of various OTC medications and some prescription antibiotics may occur with urine immunoassays. The results of urine immunoassay are unlikely to have any significant impact on patient management. MK.

Question 137: What decrements in functional ability have been identified with regard to marijuana use and driving ability?

Answer: In driving studies, the strongest decrements were in the drivers’ abilities to concentrate and maintain attention, estimate time and distance, and demonstrate coordination on divided attention tasks, all important requirements for driving. (Huestis,MA. Estimating the Time of Last Cannabis Use from Plasma 9-Tetrahydrocannabinol and 11-nor-9- Carboxy-9-Tetrahydrocannabinol Concentrations. 2005 Clin Chem 51(12): 2289-2295).

Commentary: Marijuana use is increasing in the United States. Marijuana impairs driving ability and it is important to be aware of the public health risk associated with driving under its influence. RS.

Question 138: What is the death rate associated with delirium tremens (alcohol withdrawal delirium)?

Answer: The cited reference notes “Approximately 1 to 4% of hospitalized patients who have withdrawal delirium (DTs) die.” They go on to state that “this rate could be reduced if an appropriate and timely diagnosis were made and symptoms were adequately treated. (Schuckit MA. Recognition and management of withdrawal delirium (delirium tremens) 2014 NEJM 371:2109-2113).

Commentary: Delirium tremens (DT) is the most severe form of alcohol withdrawal. An estimated 5% of patients with alcohol withdrawal may experience DT. Early recognition and management is crucial as DT carries a mortality rate of up to 4% in hospitalized patients. Respiratory failure and cardiac dysrhythmias are the leading causes of death in DT. MK.

Question 139: The ingestion of concentrated hydrogen peroxide has been associated with a variety of serious clinical problems. What are these problems?

Answer: Venous and arterial gas embolism, hemorrhagic gastritis, GI bleeding, shock and death are the serious problems that may result from the ingestion of concentrated hydrogen peroxide.(French LK, et al Hydrogen peroxide ingestion associated with portal venous gas and treatment with hyperbaric oxygen: a case series and review of the literature. 2010 Clin Tox 48(6):533-538).

Commentary: Hydrogen peroxides' widespread availability lends it to be a frequent pediatric exploratory and adult intentional ingestion. The cited article reviews 11 cases of portal gas embolism resulting from hydrogen peroxide ingestion. Hyperbaric oxygen treatment completely resolved the portal gas embolisms in 9 out of the 11 patients. RS.

Question 140: What is the relationship between ingested acetaminophen dose and the development of nephrotoxicity?

Answer: The authors of the cited reference state, "The relationship between dose and nephrotoxicity is not as clearly delineated as with that of APAP-induced hepatotoxicity. APAP-induced nephrotoxicity may occur at lower doses than that seen with hepatotoxicity. In 1 of 2 limited poison center retrospective series, almost one third of patients developed renal insufficiency in the absence of significant hepatotoxicity." (Mazer M and Perrone J. Acetaminophen-induced nephrotoxicity: Pathophysiology, clinical manifestations and management. 2008 J Med Tox 4(1): 2-6 and Von Mach MA et al. Experiences of a poison center network with renal insufficiency in acetaminophen overdose: an analysis of 17 cases. 2005 Clin Tox 43: 31-37).

Commentary: The nephrotoxic effect of acetaminophen is reported in almost one third of patients who have no significant signs of hepatotoxicity. Nephrotoxicity occurs at a relatively lower dose compared to the hepatotoxic dose and N-acetylcysteine (NAC) is not reported to be an effective antidote for the kidney injury. MK.

Question 141: What is the so-called "grey baby syndrome" and what are the clinical characteristics of this syndrome?

Answer: The grey baby syndrome was first reported in 1959 in association with the use of the antibiotic chloramphenicol in infants. These babies developed abdominal distension, vomiting, cyanosis, cardiovascular collapse, irregular respirations and subsequent death shortly after initiation of therapy with chloramphenicol. Pharmacokinetic studies in neonates showed accumulation of chloramphenicol in plasma due to impaired drug metabolism. A reduction in the total daily dosage from 100 to 50 mg/kg prevented the development of the grey baby syndrome.(McIntyre J and Choonara I. Drug toxicity in the neonate. 2004 Biol of the Neonate 86:218-221).

Commentary: The cited article draws attention to the importance of "understanding the impact of developmental changes in drug disposition and metabolism," as evidenced by a reduction in the incidence of grey baby syndrome with a lower chloramphenicol dose. RS.

Question 142: What is the reported latent period between dermal exposure to sulfur mustard and the development of clinical signs and symptoms?

Answer: The development of clinical signs and symptoms following dermal exposure to sulfur mustard may be delayed from 2 to 24 hours. (Carroll LS. Sulfur mustard: cutaneous exposure. 2005 Clin Tox 43(1):55.

Commentary: Sulfur mustard is a blistering chemical warfare agent that typically causes severe irritation to skin and mucous membranes. Patients with exposure may initially be asymptomatic, however delayed cutaneous findings may occur. RS.

Question 143: What is the association between statin therapy and the development of pancreatitis?

Answer: A recently published pooled analysis of randomized trial data reported use of statin therapy was "associated with a lower risk of pancreatitis in patients with normal or mildly elevated triglyceride levels". (Preiss D et al. Lipid modifying therapies and risk of pancreatitis- am meta-analysis 2012 JAMA 308(8):804-811).

Commentary: While hypertriglyceridemia is an important cause of pancreatitis; gallstones and alcohol are more common causes world-wide. The cited meta-analysis shows a lower risk of pancreatitis with statins. Statins may however, cause myopathy and rhabdomyolysis in some patients. MK.

Question 144: What is the putative toxin associated with the blue-ringed octopus (Hapalochlaena sp)? What is characteristic of the bite of this marine animal and what situation is pathognomonic of the bite of the blue ringed octopus?

Answer: The toxin associated with the blue-ringed octopus is tetrodotoxin, a sodium channel-blocking chemical. The bite of this animal is typically painless and the pathognomonic situation is collapse with paralysis, on or near a beach, shortly after a minor bite. (Cavazonni E, et al. Blue-ringed octopus (Hapalochaena sp.) envenomation of a 4-year old boy: A case report. 2008 Clin Tox 46(8):760-761).

Commentary: A blue-ringed octopus envenomation is potentially lethal. There is no antivenom available and early supportive care is essential to prevent cardiopulmonary collapse. RS.

Question 145: What is the phenomenon known as the "K-hole" and what drug is commonly associated with the so-called K-hole?

Answer: The cited reference notes: "At low doses ketamine induces distortion of time and space, hallucinations and mild dissociative effects. However, at large doses (i.e. over 150 mg) ketamine induces more severe dissociation commonly referred to as a 'K hole', wherein the user experiences intense detachment to the point that their perceptions appear located

deep within their consciousness, thus causing reality to appear far off in the distance." (Muetzelfeldt L., et al. Journey through the K-hole: Phenomenological aspects of ketamine use. 2008 Drug and Alc Dependence. 95:219-229).

Commentary: Ketamine is usually abused in combination with other recreational drugs. Ketamine is amphophilic and therefore readily crosses the blood brain barrier, causing diverse psychomotor abnormalities. MK.

Question 146: Name the Kings College Criteria for acetaminophen-induced fulminant hepatic failure necessitating liver transplantation.

Answer: The criteria include a pH 100 seconds, creatinine >3.3 mg/dL, and grade III or IV encephalopathy. Since its inception, the additional criteria of a lactate >3.0 mmol after fluid resuscitation has come into use. (Makin AJ et al. A 7-year experience of severe acetaminophen-induced hepatotoxicity (1987-1993). Gastroenterol 1995;109:1907-1916.).

Commentary: The King's College Criteria is a useful tool for predicting the clinical outcome of hepatic failure secondary to acetaminophen. It is important to realize that while useful in monitoring hepatic injury, elevated transaminases (AST and ALT) are not part of the criteria. RS.

Question 147: Ondansetron is a commonly used antiemetic agent that acts by antagonizing serotonin at 5-hydroxytryptamine-3 receptors. The FDA has warned that ondansetron may induce fatal arrhythmias. What is the risk for arrhythmia induction following a single oral ondansetron dose?

Answer: A recently published postmarking analysis and systematic review reported "no reports describing an arrhythmia associated with single oral ondansetron dose administration." However, given the fact that this drug is frequently administered intravenously the authors of the cited study remind readers that high dose ondansetron given intravenously may prolong the QT interval and should be cautiously administered in patients with a significant medical history or who are also using any medication capable of causing QT prolongation.(Freedman SB et al. Ondansetron and the risk of cardiac arrhythmias: A systematic review and postmarketing analysis. 2014 Ann Emerg Med 64(1):19-25).

Commentary: Oral Disintegrating Tablets of ondansetron contain phenylalanine and should be cautiously prescribed to patients with phenylketonuria. Another major side effect of ondansetron is QT prolongation that may occur when thioridazine, pimozide and other QT prolonging medications are used with ondansetron. Profound hypotension and loss of consciousness may occur with concurrent use of apomorphine. MK.

Question 148: Vibration ($>$ 100 Hz) is considered by some to be an occupational "toxicant". More than 1.5 million individuals in the US engage in work that exposes them to "hand transmitted vibration" placing them at risk for the so-called "hand-arm vibration syndrome" (HAVS). What are the clinical characteristics of HAVS?

Answer: The cited reference indicates that HAVS is characterized by "dysfunction of the peripheral vascular and sensorineural systems" and points out that the most common findings associated with HAVS is cold induced vasospasm and digital blanching, sometimes called "vibration white finger". (Krajnak K, et al. Characterization of frequency dependent responses of the vascular system to repetitive vibration. 2010 JOEM, 52(6):584-594).

Commentary: HAVS can affect workers in multiple fields including construction, agriculture, forestry, ship-building, and mechanical engineering. RS.

Question 149: What is the pathophysiology of acute renal failure in ethylene glycol poisoning?

Answer: The cited reference notes "Although the "aldehyde" metabolites of ethylene glycol, glycolaldehyde and glyoxalate, have been suggested as the metabolites responsible, recent studies have shown definitively that the accumulation of calcium oxalate monohydrate (COM) crystals in the kidney tissue produces renal tubular necrosis that leads to kidney failure." (McMartin K. Are calcium oxalate crystals involves in the mechanism of acute renal failure in ethylene glycol poisoning? 2009 Clin Tox 47(9):859-869).

Commentary: Ethylene glycol is metabolized to glycolic acid, which primarily causes the anion gap metabolic acidosis and oxalic acid, which combines with calcium resulting in insoluble calcium oxalate. Calcium oxalate crystals are nephrotoxic and may lead to kidney injury. Dialysis may be indicated in cases of renal insufficiency and refractory metabolic acidosis. MK.

Question 150: When the action of the cytochrome CYP3A is inhibited by an interacting drug, how long does that inhibition typically last?

Answer: The inhibition of CYP3A by other drugs is usually reversible, typically within two to three days, once the interacting drug is discontinued. In the case of some inhibitors (e.g., diltiazem, macrolide antibiotics, mifepristone, and delavirdine), however, the effect may last much longer, because CYP3A is destroyed and new CYP3A enzyme must be synthesized. (Wilkinson GR. Drug metabolism and variability among patients in drug response, 2005 NEJM 352:2211-2221).

Commentary: Drug-drug interactions are of significant clinical importance for both patients and healthcare providers. Many drugs undergo metabolism via CYP3A and there is increased potential for drug-drug interactions. RS.

Question 151: What was the original rationale for the development of the drug carisoprodol?

Answer: The cited reference notes that carisoprodol was introduced in the late 1950s "as an alternative to meprobamate, hoping that it would have less sedative and better muscle relaxing properties. However, the drugs turned out to have many clinical similarities, possibly explained by the fact that carisoprodol is almost completely metabolized to meprobamate by dealkylation. (Brames JG and Morland J. Carisoprodol intoxications and serotonergic features. 2005 Clin Tox 43(1): 39-45).

Commentary: Carisoprodol, like baclofen, is a muscle relaxant that acts as a GABA receptor agonist. Increased muscle tone, hyperreflexia and spastic encephalopathy may be seen in carisoprodol toxicity. The active metabolite of carisoprodol, meprobomate, may cause profound hypotension secondary to myocardial depression. MK.

Question 152: In the past, outbreaks of so-called "beer-drinkers' cardiomyopathy" have been reported. What toxicant has been implicated in this syndrome and what are the clinical manifestations associated with this problem?

Answer: This syndrome has been reported in individuals consuming large quantities of cobalt fortified beer. This syndrome is characterized by pericardial effusion, elevated hemoglobin concentrations, and congestive heart failure. (Barceloux D. Cobalt. 1999 J Tox Clin Tox. 37(2):201-206).

Commentary: "Beer-drinkers' cardiomyopathy" is different than so-called "holiday heart." The latter term is used to describe acute heart failure in the setting of binge drinking (typically on holidays) and is thought to be secondary to direct effects of ethanol on the heart. (Tonelo D, et al. Holiday Heart Syndrome Revisited after 34 Years. Arquivos brasileiros de cardiologia. 2013;101(2):183-189.) RS.

Question 153: What are the three main toxic syndromes associated with organophosphate poisoning?

Answer: The three main toxic syndromes associated with organophosphate poisoning are 1- acute cholinergic syndrome, 2- intermediate syndrome, and 3- organophosphate induced delayed polyneuropathy (OPIDN). (Jayawardane P, et al. Electrophysiological correlates of intermediate syndrome following acute organophosphate poisoning. 2009 Clin Tox 47(3):193-205).

Commentary: Most healthcare providers are familiar with the cholinergic toxidrome (bradycardia, bronchospasm, bronchorrhea, diarrhea, lacrimation, and urination) associated with organophosphate poisoning, however the intermediate syndrome (IMS) is of equal importance. IMS can develop 1-4 days following organophosphate exposure and may lead to severe muscle paralysis requiring ventilatory support. RS.

Question 154: Benzo[a]pyrene is an aromatic hydrocarbon that has been identified as a carcinogen. What is the primary source for this chemical and what cancer types (by organ) have been linked to benzo[a]pyrene exposure?

Answer: Benzo[a]pyrene is found in cigarette smoke, coal tar, and certain roofing materials. Benzo[a]pyrene exposure has been causally linked to cancer of the stomach, skin and lung. (Luch A. Nature and nurture-Lessons from chemical carcinogenesis. 2005 Nature Reviews, 5:113-125).

Commentary: It is important to be aware of known environmental carcinogens to increase patient education and prevention. RS.

Question 155: What health concerns regarding the use of so-called "Chinese dry wall" emerged during the year 2008?

Answer: According to the cited reference "The health concerns involved possible health implications from exposure to sulfur gases emitted from Chinese-manufactured drywall. According to ATSDR based on the limited number of drywall samples tested, exposures to the estimated levels of hydrogen sulfide and sulfur dioxide from drywall samples manufactured in China between 2005 and 2006 were a public health concern. Short-term exposures might result in effects seen in both clinical and human epidemiologic studies. These include exacerbation of pre-existing respiratory conditions, eye and nasal irritation, headache, changes in vision, and weakness. Although less certain, longer term exposures may have increased the risk of damage to nasal tissue. Exposure to the estimated contaminant concentrations could diminish a resident's quality of life by triggering irritant (eye, nose, and throat) and physical (respiratory, gastrointestinal) symptoms, leading to negative mood states, and altering daily activities." (http://www.atsdr.cdc.gov/drywall/docs/Drywall_HC_05-02-2014_508.pdf, accessed September 2014).

Commentary: Drywall manufactured in China and imported to the U.S for construction purposes, from 2001 to 2008, off-gassed sulfur containing volatile compounds. Adverse health effects and reduced quality of life were attributed to the hydrogen sulfide and other sulfur containing compounds emitted by the drywall. MK.

Question 156: What is the Household Products Database?

Answer: The Household Products Database is sponsored by the National Library of Medicine and is based on the Consumer Product Information Database. This database links over 14,000 consumer brands to health effects from Material Safety Data Sheets (MSDS) provided by manufacturers and allows scientists and consumers to research products based on chemical ingredients. The database is designed to help answer the following typical questions: What are the chemical ingredients and their percentage in specific brands? Which products contain specific chemical ingredients? Who manufactures a specific brand? How do I contact this manufacturer? What are the acute and chronic effects of chemical ingredients in a specific brand? What other information is available about chemicals in the toxicology-related databases of the National Library of Medicine? (http://hpd.nlm.nih.gov/about.htm; accessed September, 2014).

Commentary: Household products are common toxicologic exposures, especially among pediatric patients. Numerous brands and formulations can exist for each specific product making identification of the chemical ingredients more difficult. This database provides an excellent resource for both parents and healthcare professionals. RS.

Question 157: What percent of patients poisoned with carbon monoxide (CO) will manifest MRI evidence of basal ganglia lesions within 6 months of exposure?

Answer: The cited study notes that the literature quotes an extremely wide variation of incidence for basal ganglia lesions with reported incidences ranging from 4% to 88%. However these authors studied 73 CO poisoned patients who

underwent MR scanning on day 1, 2 weeks and 6 months post exposure. They report only one patient from this cohort manifesting globus pallidus lesions and they concluded "Basal ganglia lesions, including lesions of the globus pallidus, may be less common than previously reported." (Hopkins R O et al. Basal ganglia lesions following carbon monoxide poisoning. 2006 Brain Injury 20(3): 273-281).

Commentary: Basal ganglia lesions may occur in the setting of carbon monoxide poisoning. The cited article is a prospective cohort study of 73 cases with literature review and concludes that basal ganglia lesions are found less commonly than previously reported in the literature. MK.

Question 158: What was the toxicant involved in the so-called Massengil tragedy?

Answer: The Massengil tragedy occurred in 1937 when more than 100 deaths were documented related to the use of sulphanilamide elixir suspended in diethylene glycol. "Massengil" refers to the Massengil Company of Bristol, Tennessee. This incident hastened the enactment of the 1938 Federal Food Drug and Cosmetic Act, the statue that remains the basis for FDA regulation of these products. (Alfred S et al. Delayed neurologic sequelae resulting from epidemic diethylene glycol poisoning. 2005 Clin Tox 43(3):155-159).

Commentary: The Massengil tragedy is an important toxicologic disaster that is responsible for the FDA's current role in regulation of products. There have been a number of other DEG epidemics in other countries, resulting in many deaths. RS.

Question 159: What is locust bean gum, what is it used for and what is the safety profile for this material when applied for its intended use?

Answer: According to the cited reference locust bean gum (LBG) is "a galactomannan polysaccharide (from the endosperm seed of the locust/carob tree (Ceratonia siliqua (L.) Taub) of the plant family of Leguminosae.) used as thickener in infant formulas with the therapeutic aim to treat uncomplicated gastroesophageal reflux". The cited reference provides an integrated review of relevant toxicological databases as well as clinical evidence. The authors have determined that LBG was "not associated with any adverse toxic or nutritional effects in healthy term infants, while there are limited case-reports of possible adverse effects in preterms receiving the thickener inappropriately. Altogether, it can be concluded that LBG is safe for its intended therapeutic use in term-born infants to treat uncomplicated regurgitation from birth onwards." (Meunier L et al. Locust bean gum safety in neonates and young infants. 2014 70(1):155-169).

Commentary: Locust bean gum (LBG) is used in infant formula to thicken it and to treat infant gastroesophageal reflux. The cited article concludes LBG is a safe and non-toxic substance that may be added to formula feed of term infants under medical supervision. It should not be mixed in the formula of pre-term and low birthweight infants. MK.

Question 160: The risk for congenital anomalies in pregnant females taking lithium is generally considered to be high. Which congenital cardiac anomaly has been reported to be associated with a 400-fold increased risk in pregnancies where the mother took lithium for a substantial portion of their pregnancy?

Answer: A 400-fold increased risk for Ebstein's anomaly has been reported when lithium was taken during pregnancy. (Nora JJ, et al. Lithium, Ebsteins anomaly, and other congenital heart defects. 1974 Lancet, 304: 594–95 as cited in McKnight R et al. Lithium toxicity profile: a systematic review and meta-analysis. 2012 Lancet, 379:721-728).

Commentary: Adverse maternal and fetal health effects must be considered when prescribing medications to pregnant women. Ebstein's anomaly poses a significant risk to the neonate, and lithium should be avoided in pregnant women. RS.

Question 161: What is the most likely cause for the cardiac arrhythmias and muscle weakness often associated with barium poisoning?

Answer: According to the cited reference, "Barium is a potent, non-specific inhibitor of the potassium IRC current and affects all types of muscle at micromolar concentrations. Gastrointestinal symptoms frequently occur early in the course of barium poisoning. Hypokalemia resulting from an intracellular shift of potassium and the direct effect of barium at the potassium channels explain the cardiac arrhythmias and muscle weakness which commonly occur in barium poisoning." (Bhoelan BS et al. Barium toxicity and the role of the potassium inward rectifier current. 2014 Clin Tox 52:584-593).

Commentary: Barium poisoning may cause a variety of symptoms ranging from gastrointestinal disturbance and muscle weakness to respiratory and cardiovascular compromise. The cited article reviews the literature for morbidity and mortality due to barium poisoning. MK.

Question 162: Case reports have appeared in the medical literature describing a pink colored sediment in the urine of patients who have recently received propofol anesthesia. What is the proposed mechanism for the formation of pink urine associated with propofol anesthesia?

Answer: The cited reference notes "pink urine syndrome" is "a rare condition described after surgery and propofol anesthesia." The authors go on to describe that "uric acid excretion in urine is increased by propofol and by V1 receptor stimulation associated with postoperative inappropriate antidiuretic hormone secretion. Low urinary pH decreases uric acid solubility, promoting the formation of amorphous uric acid crystals, which exhibit a characteristic pink color. Increasing the urinary pH dissolves the crystals thereby restoring normal urine color." The condition is noted to be benign. (Potton L et al. Pink urine. 2013 Intensive Care Med 39:389-390).

Commentary: Propofol is a common therapeutic infusion used for sedation. Propofol infusion syndrome has been reported following prolonged use of this medication, particularly in pediatric populations, and features metabolic acidosis, liver dysfunction, and is potentially fatal. RS.

Question 163: Acrylonitrile is a colorless liquid chemical with a "sharp, onion or garlic-like odor. It is used in the manufacture of plastics, acrylic fibers and synthetic rubber. What is the potentially harmful metabolic breakdown product of acrylonitrile?

Answer: Acrylonitrile is metabolized to cyanide (among other metabolites) and signs of cyanide toxicity have been reported in some cases following occupational exposure to this chemical. (Toxicological profile for acrylonitrile. 1990 ATSDR, http://www.atsdr.cdc.gov/substances/toxsubstance.asp?toxid=78; accessed December 2014).

Commentary: Workers in the plastics industry are at risk for exposure to acrylonitrile. Physicians should be aware of the potential for development of cyanide toxicity in patients with occupational exposure to this substance. MK.

Question 164: What is the so-called Holiday Heart Syndrome (HHS) and what arrhythmias characterize this disorder?

Answer: The cited reference notes "The term [HHS] was officially introduced in 1978 (by Ettinger et. al.) for describing the occurrence of an acute cardiac rhythm disturbance in apparently healthy people after an episode of heavy drinking, i.e., "binge drinking." This disturbance disappeared with subsequent abstinence, leaving no residual heart disease. These occurrences had the particularity of being more frequent after weekends or holidays like Christmas or New Year's Eve, which are known to be associated with increased alcohol ingestion, hence the name." The authors further point out "HHS is mainly associated with supra ventricular arrhythmias, with AF being the most common cardiac arrhythmia in this syndrome. However, other less frequent types of arrhythmias can also occur, such as atrial flutter, paroxysmal atrial tachycardia, and isolated ventricular premature beats." (Tonelo D et al. Holiday heart syndrome revisited after 34 years. 2013 Arq Bras Cardiol 101(2): 183-189.

Commentary: Atrial fibrillation is the most commonly reported arrhythmia in Holiday Heart Syndrome. Prompt recognition of HHS in patients with arrhythmias, where evident heart diseases are ruled out, is important. An appropriate counselling of the patient may prevent further episodes. MK.

Question 165: What is the FDA's "FAERS" system?

Answer: The FAERs system is the FDA Adverse Event Reporting System. This supports the FDA's post-marketing safety surveillance program for all approved drug and therapeutic biologic products. It contains adverse drug reaction reports FDA has received from manufacturers as required by regulation. (http://www.fda.gov/Drugs/InformationOnDrugs/ucm135151.htm; accessed February 2015).

Commentary: FAERS data is used to ensure drug safety and to identify any health hazards associated with the drug. Entries are voluntary by consumers or healthcare professionals. Based on an evaluation of the potential safety concern, "the FDA may take regulatory actions to improve product safety and protect the public health, such as updating a product's labeling information, restricting the use of the drug, communicating new safety information to the public, or, in rare cases, removing a product from the market." RS.

Question 166: What structural changes reportedly occur in the brains of children who have been exposed to methamphetamine in utero?

Answer: The findings reported in the cited study reveal "significant structural changes mainly of striatal, parietal and temporal areas" in children exposed prenatally to methamphetamine "compared to controls in 1) volumes, 2) cortical thickness and 3) group by gender interactions of volumes and cortical thickness." The authors further state "Future prospective longitudinal studies are needed to address the precise trajectories of changes in brain volumes and cortical thickness over time, and their associated neuropsychological and neurodevelopmental impact." (Roos A., et al. Structural brain changes in prenatal methamphetamine-exposed children. 2014 Metab Brain Dis 29:341-349).

Commentary: Reproductive toxicology is an emerging field of medicine that still requires further research. Studies, such as the one cited, are important to increase our knowledge of a drug's effects on both mother and fetus. Methamphetamine use is widely prevalent so its reproductive effects are of particular concern. RS.

Question 167: What are kretek cigarettes?

Answer: The cited reference notes "Kretek cigarettes contain clove buds in addition to tobacco in the filler (up to 40%) that gives them their unique taste and smell. In addition to the clove buds they also contain flavor ingredients according to the smoking preferences of the different consumer groups." (Roemer E. et al. Toxicological assessment of kretek cigarettes Part 6: The impact of ingredients added to kretek cigarettes on smoke chemistry and in vitro toxicity. Regul. Toxicol. Pharmacol. (2014), http://dx.doi.org/10.1016/j.yrtph.2014.11.016).

Commentary: The cited article describes in depth the constituents of kretek cigarettes and the fact that these constituents do not change the toxicity profile of the mainstream smoke. MK.

Question 168: Tens of thousands of US workers may be exposed to asphalt fumes in the roofing, road building, paving and asphalt manufacturing industries. What biomarkers have been used as indicators of exposure to or effects of asphalt fumes?

Answer: Urinary thioether excretion, glucaric acid metabolites in urine, detection of mutagens in urine, sister chromatid exchange and primary DNA damage in lymphocytes, urinary 1-hydroxypyrene, and DNA or protein adducts have been described as indicators of exposure to or effects of asphalt fumes. (NIOSH hazard Review. Health Effects of Occupational Exposure to Asphalt. 2000. http://www.cdc.gov/niosh/docs/2001-110/pdfs/2001-110.pdf; accessed November 2014).

Commentary: Construction workers are at possible risk for exposure to asphalt fumes. The cited article describes in detail the biomarkers that are used to detect such an exposure. MK.

Question 169: What is the so-called palmar-plantar erythrodysesthesia syndrome (PPES)?

Answer: Palmar-plantar erythrodysesthesia syndrome, also known as "hand-foot syndrome", is a painful syndrome involving dermal toxicity with redness and tingling dysesthesias of the palms and soles progressing to painful swelling. The cited reference notes "The syndrome is associated with several chemotherapeutic agents, including methotrexate, mercaptopurine, cytarabine, fluorouracil, epirubicin, daunorubicin and doxorubicin. The occurrence of PPES appears to depend on peak drug level and total cumulative dose. In other words, it tends to be more common with bolus infusion than with continuous low-dose infusion, and in later cycles of chemotherapy than in the first cycle. However, not all patients experience this dose dependent phenomenon." The mechanism for PPES is not known. (Hui YK and Cortes JE. Plamar-plantar erythrodysesthesia syndrome associated with liposomal daunorubicin. 2000 Pharmacotherapy 20(1):1221-1223).

Commentary: PPES may be misdiagnosed as a cellulitis. Topical anesthetics, such as lidocaine, may provide symptomatic relief. RS.

Question 170: What is tea tree oil and what has this substance been used for in complementary and alternative medicine practices? What are the potential toxicities of this oil?

Answer: Tea tree oil (TTO) is a volatile essential oil derived from the Australian plant Melaleuca alternifolia. According to the cited reference "TTO is composed of terpene hydrocarbons, mainly monoterpenes, sesquiterpenes and their associated alcohols". These authors go on to state that TTO is "employed largely for its antimicrobial properties" and " as the active ingredient in many topical formulations used to treat cutaneous infections." It is widely available over the counter the world over. Topical exposure to TTO may result in irritant and/or allergic reactions. TTO can be harmful if ingested however no cases of human deaths have been reported. (Carson CF et al. Melaleuca alternifolia (Tea Tree) oil: A review of antimicrobial and other medicinal properties. 2006 Clin Micro Rev. 19(1): 50-62).

Commentary: Tea tree oil is one of the most widely used essential oils for cutaneous infections. Largely because of its anti-inflammatory and antibacterial properties, it is available as an over-the-counter formulation worldwide. Adverse effects may occur after topical application or oral ingestion and is treated mainly by supportive care. MK.

Question 171: What is the "ACE" Program?

Answer: The ACE Program is the Assessment of Chemical Exposures (ACE) Program and it falls under the National Toxic Substances Incidents Program of the ATSDR. ACE provides training on how to perform an epidemiologic assessment after a chemical incident. The ACE Toolkit is a helpful resource to assist local authorities in responding to or preparing for a chemical release. The toolkit contains materials that can quickly be modified to meet the needs of a local team performing an epidemiologic assessment, including: Surveys; Consent forms; Medical chart abstraction form; Interviewer training manual; Epi Info™7 databases to enter and analyze the data. When an incident occurs ACE provides technical assistance by forming a multi-disciplinary, often multi-agency, team to assist the state and local health department. Team members may assist from ATSDR headquarters in Atlanta, Georgia or deploy to the scene. Other support the ACE team can provide is: GIS mapping and assistance with sample methodologies; Clinical testing, if appropriate; Liaising with other federal agencies. (http://www.atsdr.cdc.gov/ntsip/ace.html; accessed February 2015).

Commentary: In the event of a mass chemical exposure, it is important to be aware of what resources are available to assist local authorities and healthcare professionals. Their website (cited above) lists examples of previous ACE investigations including ammonia release at a refrigeration facility, chlorine release at a poultry processing facility, and vinyl chloride release from a train derailment. RS.

Question 172: What is the epidemiology of death due to alcohol poisoning in the US?

Answer: During 2010–2012, there was an annual average of 2221 alcohol poisoning deaths, an age-adjusted rate of 8.8 deaths per 1 million population, among persons aged $\geq$ 15 years in the United States. Of these deaths, 1681 (75.7%) were among adults aged 35–64 years, and 1696 (76.4%) were among men. The highest death rate from alcohol poisoning was among men aged 45–54 years (25.6 deaths per 1 million). Although non-Hispanic whites accounted for the majority of alcohol poisoning deaths (67.5%; 1500 deaths), the highest age-adjusted alcohol poisoning death rate was among American Indians/Alaska Natives (49.1 deaths per 1 million). A total annual average of 44 deaths (2.0%) involved persons aged 15–20 years, who were under the legal drinking age of 21. The age-adjusted alcohol poisoning death rate in states ranged from 5.3 per 1 million in Alabama to 46.5 per 1 million in Alaska. Twenty states had alcohol poisoning death rates greater than the overall national rate of 8.8 per 1 million, and two states (Alaska and New Mexico) had alcohol poisoning death rates $>$ 30 per 1 million. States with the highest death rates were located mostly in the Great Plains and western United States, but also included two New England states (Rhode Island and Massachusetts). Alcohol dependence was listed as a contributing cause of death in an annual average of 677 (30.4%) of the deaths from alcohol poisoning, and hypothermia was listed as a contributing cause of death in an annual average of 134 (6.0%) deaths. Drug poisoning and drug use mental disorders were listed as contributing causes of death in an annual average of 62 (2.8%) and 86 (3.9%) deaths from alcohol poisoning, respectively. (MMWR. Alcohol poisoning deaths-United States, 2010-2012, January 6, 2015 63 (early release):1-5).

Commentary: Alcohol poisoning accounts for six deaths daily in the US and death rates differ significantly by each state. The cited article discusses alcohol poisoning deaths by state. MK.

Question 173: What is hexamethylene diisocyanate (HDI) and what are the adverse health effects that may be associated with chronic, high dose exposure to this chemical?

Answer: Hexamethylene diisocyanate is a pale yellow liquid with a strong odor. It is an industrial chemical that is not known to occur naturally. It is also commonly known as HDI, 1,6-hexamethylene diisocyanate, 1,6-diisocyanatohexane, Mondur HX, and Desmodur H. Hexamethylene diisocyanate is mainly used to make polyurethane foams and coatings. It is also used as a hardener in automobile and airplane paints. According to the cited reference: [some] "People exposed to hexamethylene diisocyanate for a long time (a few months to a few years) have shown an allergic, asthma-like syndrome. The symptoms consist of shortness of breath, wheezing, bronchitis, and coughing. These symptoms are not usually seen when the person is not using a product that contains hexamethylene diisocyanate, but will start up again when they begin to use hexamethylene diisocyanate products again." (https://www.atsdr.cdc.gov/toxprofiles/TP.asp?id=874&tid=170).

Commentary: Occupational asthma is a common work-related lung disease. Automotive refinishers and painters that manually mix two-compartment polyurethane paint systems are at an increased risk of disease.

Question 174: What ocular problems may result from occupational exposure to optical radiation in glassblowers?

Answer: The cited reference notes, "The harmful effects of long term ocular exposure to cumulative levels of radiation in glassblowing have been recognized since the late 19th century. These effects include cataracts, pterygia, keratitis, and chronic dry eye problems." (Oriowo OM et al. Eye exposure to optical radiation in the glassblowing industry: An investigation in southern Ontario. 2000 Can J Pub Health 91(6): 471-474).

Commentary: Several ocular side effects are reported from exposure to optical radiation in the glassblowing industry. A survey of workers demonstrated that many are unaware of the proper personal protective equipment. MK.

Question 175: Historically, the topical application of silver sulfadiazine has been avoided in very young infants. What is the reason for this?

Answer: According to the cited reference, "Historically, treatment with silver sulfadiazine was regarded with caution due to its association with kernicterus. The sulfur component in these older products binds with albumin, resulting in excess unbound bilirubin that readily crosses the blood brain barrier. However some argue that these complications may be exacerbated by the chlorhexidine component of the silver sulfadiazine dressing causing additional toxicity." (Rustogi R. et al. The use of Acticoat in neonatal burns. 2005 Burns 31(7): 878-882 as cited in August DL et al. Silver based dressing in an extremely low birth weight infant. 2015 J Wound Ostomy Continence Nurs 42(3): 290-293).

Commentary: The efficacy of silver sulfadiazine treatment in burns is controversial, however its use should be avoided in neonates as it may have significant health consequences. (Aziz Z, Abu SF, Chong NJ. A systematic review of silver-containing dressings and topical silver agents (used with dressings) for burn wounds. Burns. 2012;38:307–18. doi: 10.1016/j.burns.2011.09.020.) RS.

Question 176: What is the number one cause of lung cancer in people who have never smoked?

Answer: Residential radon is the number one cause of lung cancer in people who have never smoked. According to the EPA, radon causes approximately 21,000 lung cancer deaths annually and about 10% of these are diagnosed in people who have never smoked. (https://www.epa.gov/radon/health-risk-radon).

Commentary: Radon is overall the second leading cause of lung cancer after cigarette smoking. It is, however, the most common cause in persons who have never smoked. MK.

Question 177: Antimony toxicity usually occurs as a result of occupational exposures or during treatment with drugs containing antimony. Antimony is used in the treatment of which disorders and what toxicities have been reported as a result of the therapeutic use of antimony compounds?

Answer: The cited reference notes "As a therapeutic, antimony has been mostly used for the treatment of leishmaniasis and schistosomiasis. The major toxic side-effects of antimonials as a result of therapy are cardiotoxicity (~9% of patients) and pancreatitis, which is seen commonly in HIV and visceral leishmaniasis co-infections." (Sundar S and Chakravarty J. Antimony toxicity. 2010 Int J Env Res Public Health 7:4267-4277).

Commentary: Cases of antimony toxicity were identified while treating HIV and visceral leishmaniasis with sodium stibogluconate. Major cardiovascular side effects were reported and the drug was discontinued due to safety issues. MK.

Question 178: The mushroom Pleurotus ostreatus contains the toxin ostreolysin. What is the mechanism of toxicity for this toxin?

Answer: The cited reference notes that ostreolysin is a 16-kDa acidic protein and is a member of the aegerolysin protein family. The authors note that the mechanism of toxicity for ostreolysin is "Transient increase in arterial blood pressure and then a progressive fall to mid-circulatory pressure accompanied by bradycardia, myocardial ischemia, and ventricular extrasystoles. The hyperkalemia resulting from the hemolytic activity probably plays an important role in its toxicity." (Jo WS et al. Toxicological profiles of poisonous, edible, and medicinal mushrooms. 2014 Mycobiology 42(3):215-220).

Commentary: Pleurotus ostreatus, also known as the oyster mushroom, is an edible mushroom grown commercially for food. Sporadic local intoxications following ingestions of large quantities of the fresh mushroom have been reported and are thought to be due to ostreolysin. MK.

Question 179: What is the so-called “pine mouth syndrome” (PMS)?

Answer: The “pine mouth syndrome” is also known as the “pine nut syndrome” and is reportedly associated with the ingestion of pine nuts. Possible etiologies included ingestion of rancid nuts, unknown toxins / fungi, or possible adulterants. According to the cited article “A clinically compatible case of PMS must include a complaint of a taste disturbance, usually characterized as bitter or metallic. This taste disturbance must follow the ingestion of affected pine nuts, usually by 1 to 3 days. Affected nuts would appear to include all, or some portion, of nuts harvested from species Pinus armandii, but could include nuts from other species. The taste disturbance must resolve (without treatment) within one month, and usually within 1 to 2 weeks. Patients must not present with any other related neurologic deficits except for mild headache. Patients should have no other obvious explanation for cacogeusia or metallogeusia, such as the recent ingestion of medications known to cause these symptoms.” (Munk MD. Pine mouth (pine nut) syndrome: description of the toxidrome, preliminary case definition, and best evidence regarding an apparent etiology. 2012 Sem in Neurol 32(5): 525-527).

Commentary: This question discusses a relatively new clinical entity, “pine mouth syndrome”. No clinical case definition of PMS has been published to date but the cited article describes what a clinically compatible case should be like. MK.

Question 180: What are the constituents of concentrated laundry detergent packs currently marketed in the U.S.?

Answer: According to the cited reference, “US products may contain anionic surfactants (15%-60%), nonionic surfactants (10%-30%), benzenesulfonic acid derivatives (0%-30%), propylene glycol (0%-15%), and polymers (3% -7%). U.S. product formulations vary by brand. (Yin S et al. Laundry pack exposures in children 0-5 years evaluated at a single pediatric institution. 2015 J Emerg Med 48(5): 566-572.

Commentary: Laundry detergent packs, also known as pods, are a common pediatric ingestion with more associated health hazards than liquid detergent. Pod ingestions may cause more systemic toxicity, including CNS depression, than detergent although the exact mechanism is unclear. RS.

Question 181: What is the so-called “Jack Rabbit” field experiment?

Answer: The “Jack Rabbit” field experiment, conducted at the Dugway Proving Ground in 2010, involved controlled releases of pressurized liquefied chlorine and ammonia into a depression in the ground. The dispersion characteristics of the resultant chemical plumes were studied and described. These experiments provide important modeling information with regard to chemical releases from both accidental and intentional events. (Hanna S et al. The Jack Rabbit chlorine release experiments: implications of dense gas removal from a depression and downwind concentrations. 2012 J Hazardous Materials 213-214:406-4.

Commentary: Chlorine is typically transported in large volumes (50-100 tons) by train. Historically, railcar accidents have resulted in massive chlorine release and casualties from resultant exposure. The purpose of this experiment was to predict chlorine concentrations after chlorine dispersion in an attempt to better calculate potential exposures following a mass chlorine emission. RS.

Question 182: What is “NASPER”?

Answer: “NASPER” is the National All Schedules Prescription Electronic Reporting Act. This Act was passed in 2005 with the aim of providing Federal support to states for prescription monitoring programs (PMPs). It is the only statutorily authorized program to assist states in combating prescription drug abuse of controlled substances through a prescription monitoring program. To date 38 states have PMPs, but there is a significant difference in the manner and frequency with which the data is collected. (http://nasper.org/Documents/FactSheet-DrugAbuse-2011.pdf; accessed June 2015).

Commentary: Prescription drug abuse is a significant cause of morbidity and mortality and growing public health concern. Prescription monitoring programs are a useful tool for healthcare providers to identify patients at risk for abuse. RS.

Question 183: The cited reference notes that “Marchiafava–Bignami disease (MBD) was originally described as a rare, fatal disease affecting wine drinkers.” What is the pathophysiology of MBD?

Answer: The cited reference notes that MBD is “Characterized by demyelination and necrosis of the corpus callosum, it has long been considered to be of either a toxic or nutritional etiology.” The authors go on to state that “Marchiafava–Bignami disease (MBD) is a rare condition mainly associated with alcoholism, although it may be mimicked by several other disorders that cause corpus callosum lesions” and “As thiamine deficiency is frequently associated with alcoholism, malnutrition and prolonged vomiting; we recommend prompt treatment of MBD with parenteral thiamine in such subjects.” (Hillbom M, et al. Diagnosis and management of Marchiafava-Bignami disease: A review of CT/MRI confirmed cases. 2014 J Neurol Neurosurg Psych 85:168-173).

Commentary: Thiamine is considered the first-line treatment for treatment of some diseases associated with alcoholism such as Wernicke’s encephalopathy and Korsakoff’s syndome. Wernicke’s encephalopathy may present as the classic triad of confusion, ataxia, and mystagmus. RS.

Question 184: What is the toxin contained in the seeds of the so-called Pong-Pong or “suicide” tree?

Answer: Cerberin is the toxin contained in the seeds of the so-called Pong-Pong or “suicide” tree. This toxin is reported to cause classic cardiac glycoside toxicity.(Gaillard Y et al. Cerbera odollam: a “suicide tree” and cause of death in the state of Kerala, India. 2004 J Ethnopharm 95:123-126 and Wermuth M et al. Two deaths from intentional ingestion of non-native Pong-Pong tree (Cerebra odollam) seeds. Poster presentation at NACCT 2016, Boston, MA).

Commentary: The Cerbera tree is native to India and South Asia, growing primarily in swampy and marshy areas. It has been used for both homicide and suicide in India, with more than 500 cases of fatal poisonings being reported in a ten-year period in one Indian state. MK.

Question 185: What is the common name for the organism Physalia physallis? What is the primary toxin delivered by this organism and what is the mechanism of toxicity?

Answer: Physalia physallis is commonly known as the Portuguese man-of war. The cited reference points out "The main toxin of the man-of-war venom is a glycoprotein of 240 kDa which is called Physaliatoxin (potent cytotoxic and haemolytic toxicity), but numerous other components (enzymes, proteins) have been isolated from this venom. The mechanism of its neurotoxic and cardiotoxic action is still unclear." (Albadie M et al. Portuguese man-of war (Physalia physallis) envenomation on the Aquitaine coast of France: An emergency health risk. 2012 Clin Tox 50(7): 567-570).

Commentary: Portuguese man-of-war (Physalia physallis) envenomation primarily causes hemolysis and cytotoxicity. It is still unclear how physaliatoxin causes the neurotoxicity and cardiotoxicity that is seen in these cases. MK.

Question 186: Which non-selective herbicide, often used for vegetation control along roadsides, is characterized by the formation of methemoglobinemia, hemolysis, DIC and renal failure following ingestion?

Answer: Sodium chlorate is the non-selective herbicide, often used for vegetation control along roadsides and is characterized by the formation of methemoglobinemia, hemolysis, DIC and renal failure following ingestion. With regard to the associated renal failure, the cited reference notes the "nephrotoxicity of chlorate is mediated by methemoglobinuria along with a vasoconstriction due to intravascular hemolysis that results in tubular damage. In addition, it must be considered a direct toxic effect on the proximal tubule of chlorate itself. Interestingly, sodium chlorate-dependent renal failure is characterized by the same histological lesions (fibrin deposition in afferent arterioles and glomerular capillaries) as those described in hemolytic uremic syndrome." (Ranghino A et al. A case of acute sodium chlorate self-poisoning successfully treated without conventional therapy. 2006 Nephrol Dial Transplant 21:2971-2974).

Commentary: Sodium chlorate is a hygroscopic substance that is used for bleaching paper, as a non-selective herbicide, and for chemical oxygen generation. Ingestion may result in acute severe hemolysis with ensuing DIC and renal failure. It is still available in the US, but it has been banned as an herbicide in the EU. MK.

Question 187: What is the best method for decontamination of the skin following dermal exposure to phenol?

Answer: The cited reference notes: "Removing a person from phenol exposure is the most important method for reducing toxic effects of phenol. This is especially important following dermal exposure, after which speed in removing phenol from the skin is important. Because a study has shown that dilution in water increases the dermal absorption of phenol, it has been recommended that polyethylene be used to remove dermal contamination with phenol. Because water is readily available, others believe that its use is more appropriate for the decontamination of skin following phenol exposure. A study is available that evaluated several strategies to decontaminate the skin of pigs following acute dermal exposure to phenol. The study showed that polyethylene glycol (PEG 400) and 70% isopropanol were superior to other treatments and equal effective in reducing skin damage induced by phenol." (http://www.atsdr.cdc.gov/toxprofiles/tp115-c3.pdf; accessed May 2015).

Commentary: Phenol is typically used as a disinfectant and can be found in several consumer products. Dermal exposure to phenol may result in significant skin burns (https://www.atsdr.cdc.gov/toxfaqs/tf.asp?id=147&tid=27) RS.

Question 188: Describe signs and symptoms of camphor intoxication.

Answer: Camphor intoxication can involve nausea/vomiting, burning of the mouth/throat, and cyanosis of the lips in severe cases. Neurologic symptoms predominate, and include irritability, hyper-reflexia, tonic muscular contraction, myoclonic jerks, confusion, coma, and apnea. Seizures are common in significant intoxication and are often the presenting sign. (Love JN et al. Are one or two dangerous? Camphor exposure in toddlers. J Emerg Med. 2004 Jul;27(1):49-54).

Commentary: Camphor is readily available in non-prescription "cold" medications. Ingestion of as little as 500mg of camphor may lead to toxicity. The efficacy of camphor is largely unproven. MK.

Question 189: What is the metabolite responsible for hepatotoxicity in acute valproate overdose?

Answer: 4-en-VPA, a byproduct of omega oxidation, is the toxic metabolite that accumulates in acute valproate overdose once carnitine depletion occurs. 4-en-VPA is responsible for hyperammonemia seen in toxicity. (Lheureux PE et al. Science review: carnitine in the treatment of valproic acid-induced toxicity - what is the evidence? Crit Care. 2005 Oct 5;9(5):431-40).

Commentary: Acute valproate overdose leads to the formation of 2-propyl-4-pentenoic acid (4-en-VPA), a byproduct of ω-oxidation of valproate that causes hepatotoxicity and is the primary toxic metabolite in valproate toxicity. Oral or intravenous L-carnitine is the primary treatment for valproate hepatotoxicity. MK.

Question 190: Oral naltrexone is often recommended for the treatment of alcohol use disorders. What are the contraindications for the use of oral naltrexone in treating these problems?

Answer: According to the cited reference "Oral naltrexone is contraindicated for patients with acute hepatitis or liver failure (and has precautions for other hepatic disease) and for those currently using opioids or with anticipated need for opioids, and it can precipitate severe withdrawal for patient dependent on opioids." Interestingly the prescribing information for injectable naltrexone does not include contraindications for patients with acute hepatitis or liver failure. ("Pharmacotherapy for Adults with Alcohol-Use Disorders in Outpatient Settings: A monograph". 2015 Agency for Healthcare Research and Quality. www.ahrq.gov. accessed September 2015).

Commentary: Alcohol abuse is a common disease frequently encountered by healthcare professionals. Naltrexone can be a beneficial treatment option, however, it is important to be aware of associated adverse drug effects and contraindications. Naltrexone-precipitated opioid withdrawal may occur rapidly and be severe. RS.

Question 191: What is the potential utility of the Chinese herbal root known as kudzu?

Answer: Kudzu is a derivative of the plant Pueraria lobata that contains high concentrations of isoflavones. The cited reference notes: “Although the mechanism of action remains unclear it is widely accepted that the isoflavones found in kudzu are effective in reducing alcohol intake in a number of nonhuman mammalian models.” The cited reference reports their study population demonstrated “significant reduction in the number of beers consumed that was paralleled by an increase in the number of sips and the time to consume each beer and a decrease in the volume of each sip” but without an effect in the urge to drink alcohol. (Lukas SE et al. An extract of the Chinese herbal root kudzu reduces alcohol drinking by heavy drinkers in a naturalistic setting. 2005 Alcohol Clin Exp Res 2995): 756-762).

Commentary: Alcoholism is a common disease with high morbidity and mortality. Further research into the utility of kudzu in the treatment of alcoholism is necessary. There are only several FDA-approved medications (naltrexone, disulfiram, and acamprosate) available for the treatment of alcohol dependence in the United States. RS.

Question 192: What is the half-life and time to steady state for digoxin?

Answer: According to the cited reference “The half-life and time to steady-state varies by patient and is dependent on the renal function. In patients with normal renal function, the half-life ranges from 1.5 to 2 days. This is prolonged anywhere from 3.5 to 5 days in patients with moderate to severe renal dysfunction. Patients with normal renal function reach steady state in 5 to 7 days after initiation of therapy, whereas it may take up to 15 to 20 days in patients with impaired renal function.” (Ehle M et al. Digoxin: Clinical Highlights: A review of digoxin and its use in contemporary medicine. 2011 Crit Pathways in Cardiol 10:93-98.

Commentary: Chronic digoxin toxicity is a potentially lethal complication of digoxin use in the elderly. Patients with renal insufficiency are at increased risk of toxicity. Chronic toxicity may present with non-specific signs and symptoms including weakness, anorexia, confusion, or visual disturbances. RS.

Question 193: What is the most serious complication of ingestion of Ginkgo biloba seeds, what is the compound responsible for this effect, and what is the recommended treatment?

Answer: Seizures following ingestion of Ginkgo biloba seeds appear to be caused by 4-methoxypyridoxine (MPN) and should be treated by the administration of pyridoxal phosphate and a benzodiazepine such as diazepam. (Pediatrics, 2002 Feb, 109(2):325-7).

Commentary: Ginkgo biloba is commonly used as a dietary supplement with manufacturer’s claiming that it enhances cognitive function. Clinical toxicity following overdose is uncommon but rarely can be serious. MK.

Question 194: Propylene glycol accumulation, as reflected by a hyperosmolar anion gap metabolic acidosis, may be observed in critically ill adults receiving continuous high-dose infusion of what drug for more than 48 hrs.

Answer: Lorazepam (Arroliga et al. Relationship of continuous infusion of lorazepam to serum propylene glycol concentration in critically ill adults. 2004. Crit Care Med. 32(8):1709-1714).

Commentary: Prolonged high-dose infusion of lorazepam, which may occur in the ICU setting, has been reported to leading to propylene glycol toxicity. Propylene glycol toxicity features a metabolic anion gap acidosis, hypotension, and tachycardia. MK.

Question 195: Finding trichloroethanol on autopsy toxicology tests suggests abuse of what drug?

Answer: Chloral hydrate is metabolized to trichloroethanol and commonly causes positive trichloroethanol levels at autopsy. (Jones GR, Singer PP. An unusual trichloroethanol fatality attributed to sniffing trichloroethylene. J Anal Toxicol. 2008 Mar;32(2):183-6.).

Commentary: Poisoning with choral hydrate, sometimes referred to as a Mickey Finn, has historically been used to incapacitate victims. Detection of trichloroethanol on autopsy may be indicative of poisoning secondary to chloral hydrate. MK.

Question 196: What is the so-called “cinnamon challenge”?

Answer: According to the cited article, the “cinnamon challenge”, an evolving adolescent fad, involves “swallowing a tablespoon of ground cinnamon in 60 seconds without drinking fluids. However, as stated on www.cinnamonchallenge.com, this challenge is practically impossible, decidedly unpleasant, and potentially harmful.” The authors further point out that ingesting cinnamon powder may increase the risk for aspiration and that cinnamon inhalation may result in pulmonary inflammation and thus to airway damage and potentially aspiration pneumonitis. (Grant-Alfieri A, Schaechter J and Lipshultz S E. Ingesting and aspirating dry cinnamon by children and adolescents: The 'Cinnamon Challenge'. 2013 Pediatrics 131(5): 833-835).

Commentary: This question highlights a “pop-culture” toxicological exposure with the potential to affect a large population. This particular fad was popularized by social media and one video of the “cinnamon challenge” acquired over 19 million views. The average person attempting this challenge is most likely unaware of the potential health risks. It is important to be aware of social trending phenomenon with public health risks. RS.

Question 197: What potentially dangerous substance is contained in the product known as Red Flower Oil?

Answer: Red Flower Oil contains up to approximately 67% methyl salicylate. (Davis JE. Are one or two dangerous? Methyl salicylate exposure in toddlers. 2007 J Emerg Med 32(1): 63-69).

Commentary: Methyl salicylate exposure can be fatal in pediatric patients. A relatively small volume such as a mouthful can be life-threatening. Methyl salicylate exposure is typically associated with oil of wintergreen but it is important to be aware of additional sources such as Red Flower oil. RS.

Question 198: What skin lesions are associated with chronic exposure to arsenic?

Answer: The skin lesions associated with chronic exposure to arsenic include “raindrop” hyperpigmentation, nonspecific hyperpigmentation, hyperkeratosis, squamous cell carcinoma, basal cell carcinoma, and Bowen’s disease. (Syed EH et al. Arsenic exposure and oral cavity lesions in Bangladesh. 2013 J Occ Env Med 55(1): 59-66).

Commentary: Chronic exposure to arsenic by contaminated groundwater is worldwide public health concern, the article cited above states it “affects 150 million in people in more than 70 countries including the United States.” The International Agency for Research on Cancer (IARC) classifies arsenic as a known human carcinogen. RS.

Question 199: What are the risk factors for SILENT (Syndrome of Irreversible Lithium-Effectuated Neurotoxicity)?

Answer: The risk factors for SILENT include: age (mean age 48 years of age), gender (female prevalence), dose (wide range but can occur even at therapeutic doses), psychiatric diagnoses (more prevalent in patients with marked psychotic symptoms), neurologic status (seizure prone patients may be at greater risk), and misc. factors (infection, dehydration, poor renal function. (Adityanjee et al. The syndrome of irreversible lithium-effectuated neurotoxicity. 2005 Clin Neuropharmacol 28(1):38-49).

Commentary: SILENT is an uncommon complication of chronic lithium poisoning, it features altered mental status, tremor, ataxia, and other neuropsychiatric symptoms. Although the syndrome acronym contains the term “irreversible,” patients may recover over a period of months to years. MK.

Question 200: What is Chan Su?

Answer: Chan Su is a traditional Chinese medicine derived from the secretion of the skin and auricular glands of Chinese toads (Bufo melanostictus Schneider or Bufo bufo gargarzinas Gantor). It has been identified as an important component of various herbals and medicines used in Asia and elsewhere. Administration of Chan Su, traditonally given in small doses, is often aimed at stimulation of myocardial contraction and for the treatment of heart disease. It is also sometimes given as an analgesic and for the reduction of inflammation. The cardiac effects of Chan Su probably result from its constituent bufadienolides, including bufalin. The cited reference reports: "Bufalin blocks vasodilatation and increases vasoconstriction, vascular resistance, and blood pressure by inhibiting Na, K-ATPase". Chan Su has also been reported to interfere with some serum digoxin assays. (Reyes MA et al. Effect of Chinese Medicines Chan Su and Lu-Shen-Wan on Serum Digoxin Measurement by Digoxin III, a New Digoxin Immunoassay. 2008 Ther Drug Monitoring 30(1):95-99).

Commentary: Chan Su is a traditional medicine readily available in the US. It is used as a topical anesthetic and cardiac medication. It has a mechanism of action similar to that of the cardiac glycosides. MK.

Question 201: The mainstay of treatment for ethylene glycol poisoning involves inhibition of alcohol dehydrogenase using fomepizole in conjunction with hemodialysis. What is the elimination half-life of ethylene glycol in humans treated with fomepizole but who have not received hemodialysis?

Answer: The study cited below reported that the mean elimination half-life of ethylene glycol in humans treated with fomepizole but who have not received hemodialysis was 14.2 hours (SD 3.7 hours; 95% CI 13.1 to 15.3 hours) Levine M. et al. Ethylene glycol elimination kinetics and outcomes in patients managed without hemodialysis. 2012 Ann Emerg Med 59:527-531).

Commentary: Ethylene glycol is an important cause of toxic alcohol poisoning in the US and internationally. The relatively short half-life of ethylene glycol when treated with ethanol or fomepizole has lead toxicologists to conclude that hemodialysis may be avoided in cases of mild poisonings that are treated in a timely fashion. MK.

Question 202: The inhalation of carbon nanotubules has become a concern in the occupational setting with regard to the potential for generating pulmonary injury. What form of pulmonary injury is the primary concern regarding the inhalation of carbon nanotubules?

Answer: The primary concern regarding the inhalation of carbon nanotubules is the ability for these nanoparticles to generate fibrotic reactions in the lung parenchyma. (Shevedova AA et al. Inhalalation versus aspiration of single walled carbon nanotubes in C57/ Bl6 mice: Inflammation, fibrosis, oxidative stress and mutagenesis 2008 Am J Physiol Lung Cell Mol Physiol 295: L552-L565 as quoted in Donaldson K and Seaton A. A short history of the toxicology of inhaled particles. 2012 Particle and Fibre Toxicology 9:1-12).

Commentary: Nanoparticle use is emerging as a product in the manufacturing of “electronics, aerospace devices, computers, and chemical, polymer, and pharmaceutical industries.” Their health risk is still being studied and represents a future area of monitoring for occupational toxicology. RS.

Question 203: In some welding processes workers may be exposed to manganese containing fumes and some have suggested that manganese exposure may lead to the development of an atypical form of Parkinsonism. Are welders at higher risk for the development of the common form of Parkinson disease?

Answer: The cited reference reports a meta-analysis of 13 studies and concludes that welding and manganese exposure are not associated with an increased risk for the common form of Parkinson disease (PD). (Mortimer JA et al. Associations of welding and manganese exposure with Parkinson disease. 2012 Neurology 79:1174-1180).

Commentary: Manganese exposure has been previously associated with atypical Parkinsonism features (manganism) but its association with PD was less clear. The cited reference is the first published meta-analysis on this topic. RS.

Question 204: What is the difference in the chest x-ray findings usually seen in cadmium related pneumonitis versus metal fume fever?

Answer: The chest x-ray in metal fume fever is typically normal while the chest x-ray in cases of cadmium pneumonitis is frequently abnormal, often with bilateral interstitial infiltrates. (Barnhart S and Rosenstock L. Cadmium chemical pneumonitis. 1964 Chest 86(5): 789-791).

Commentary: Metal fume fever is an occupational illness in welders that is secondary to exposure to fumes from different metals, most commonly zinc. Cadmium pneumonitis, conversely, occurs following welding of cadmium containing compounds and results in a potentially fatal ARDS-like clinical syndrome. MK.

Question 205: What percentage of elevated blood lead levels reported among adults in the US are work-related?

Answer: Approximately 95% of all elevated BLLs reported among adults in the United States are work-related. (CDC. Adult blood lead epidemiology and surveillance—United States, 2008–2009. MMWR 2006;60(25): 841-845).

Commentary: While childhood exposure due to contaminated water supplies, old lead based paints attract the most public attention, occupational lead exposure remains an important public health problem. OSHA has specific regulations in place to protect workers, but it is unclear whether these are adequate. MK.

Question 206: What is radon?

Answer: The cited reference answers this question as follows: “Radon is a naturally occurring, radioactive noble gas with the atomic number 86. It is odorless, tasteless, colorless, and chemically nearly inert. It is found in the radioactive decay series of uranium and thorium, in which it is formed from its mother nuclide, radium. The very long-lived parent nuclei and their breakdown products are natural components of rock and soil. A number of isotopes of radon are known, of which radon-222 is the most stable: it decays to polonium-218 with a half-life of 3.8 days”. (Schmid K, et al. Radon in indoor spaces- An underestimated risk factor for lung cancer in environmental medicine. 2010 Disch Aztebl Int 107(11):181-186).

Commentary: Radon is a radioactive gas that is reported to cause 20,000 lung cancer deaths per year in the US. According to EPA, radon levels were found above the recommended limits in 1 in 3 homes in seven different states. It is a leading cause of lung cancer in patients who have never smoked. Necessary measures and interventions should be practiced to prevent the environmental and occupational radon exposure. MK.

Question 207: What are so-called "asbestos bodies" and what is their clinical significance?

Answer: The cited reference notes that asbestos bodies are “inhaled asbestos fibers that have been coated with hemosiderin by alveolar macrophages. Asbestos bodies in bronchoalveolar lavage fluid may be reliable markers of asbestos exposure, and can be present as early as 10 months alter exposure.” (Vathesatogkit P, et al. Clinical correlation of asbestos bodies in BAL fluid. 2004 Chest 126:966-971).

Commentary: Asbestos exposure does not always correlate with clinical findings or symptoms. Prior to the cited study, “asbsestos bodies” (AB) were strictly markers of asbestos exposure. This study found an association between AB and “parenchymal abnormalities, respiratory symptoms, and reduced pulmonary function.” RS.

Question 208: Nickel carbonyl or nickel tetracarbonyl, is a potentially harmful, colorless, volatile, and flammable liquid formed when carbon monoxide contacts nickel. What are the industrial uses for nickel carbonyl?

Answer: The cited reference notes that “Nickel carbonyl is used in the extraction of nickel (Mond process), gas plating, and as a catalyst and reactant in chemical synthesis, and is usually encountered as a vapor that is rapidly absorbed after inhalation.” (Gan Sl, et al. .Inhalational nickel carbonyl poisoning in waste processing workers 2005 Chest 128:424-429).

Commentary: Nickel carbonyl exposure may cause acute respiratory distress syndrome (ARDS) and interstitial pneumonitis. It has been associated with high mortality. Occupations at risk to nickel carbonyl exposure are miners, nickel refiners, glass and metal plating workers. RS.

Question 209: What are the differences in effects on lung function due to cannabis smoking compared with tobacco smoking?

Answer: The authors performed a population based cohort study (n = 1037) of the problem. These authors report “Cannabis appears to have different effects on lung function from those of tobacco. Cannabis use was associated with higher lung volumes, suggesting hyperinflation and increased large-airways resistance, but there was little evidence for airflow obstruction or impairment of gas transfer.” (Hancox RJ et al. Effects of cannabis on lung function: a population-based cohort study. 2010 Eur Respir J 35:42-47).(Tashkin, D. P. (2013). Effects of marijuana smoking on the lung. Annals of the American Thoracic Society, 10(3), 239-247).

Commentary: As marijuana continues to become more widely available in the United States, it is important to be aware of its associated health effects. The authors conclude that “overall, the risks of pulmonary complications of regular use of marijuana appear to be relative small and far lower than those of tobacco smoking.” RS.

Question 210: What biomarkers have been used in occupationally based studies investigating the chronic effects of the chemical styrene?

Answer: The cited reference notes that in the occupational studies that are the basis for quantifying the relationship between chronic styrene exposure and health effects, end-of-shift or next-morning urine levels of mandelic acid and phenylglyoxylic acid may be used. Additional styrene biomarkers include urinary styrene and mercapturic acid levels as well as phenylglycine and 4-vinylphenol conjugates. (Rueff J, et al. Genetic effects and biotoxicity monitoring of occupational styrene exposure. 2009 Clinica Chimica Acta 399:8-23).

Commentary: Styrene is a colorless liquid with a sweet odor. Chronic exposure to styrene may affect the ocular, respiratory, hepatic and neurological systems. Urinary mandelic acid and phenylglyoxylic (PGA) are the most widely used markers for occupational exposure of styrene. MK.

Question 211: Most cadmium in the human body is bound to a small, cysteine-rich metal binding protein. What is that protein and what role does it play with regard to the potential for cadmium toxicity?

Answer: The protein is metallothionein (MT) and the cited reference points out that "MT functions in Cd detoxification primarily through the high affinity binding of the metal to MT, thus [fostering] sequestration of Cd away from critical macromolecules." (Klaassen CD, et al. Metallothionein protection of cadmium toxicity. 2009 Tox Appl Pharm 238:215-220).

Commentary: Cadmium toxicity may occur due to occupational and environmental exposure. It was first reported to cause "Itai-Itai" disease in post-menopausal Japanese females who were exposed to high environmental cadmium. The cited article discusses the protective effect of metallothionein in cadmium toxicity, which International Agency for Research on Cancer has classified as a known human carcinogen. MK.

Question 212: Acute gout is often treated with the drug colchicine. This drug has also been used in the treatment of Behcet's disease, familial Mediterranean fever, amyloidosis, psoriasis as well as recurrent pericarditis of unknown etiology. From where is colchicine derived?

Answer: Colchicine is derived from the plant Colchicum autumnale also known as the autumn crocus, meadow saffron or naked lady. (Mullins M, et al. Unrecognized fatalities related to colchicine in hospitalized patients. 2011 Clin Tox, 49(7):648-652).

Commentary: In addition to C. autumnale, colchicine is also derived from Gloriosa superba, which is also a member of the Liliaceae family. The concentration of colchicine in the plant is highest in the summer. Poisoning due to colchicine initially manifests as gastrointestinal distress followed by bone marrow suppression that may last for several days to weeks. MK.

Question 213: What is RDX?

Answer: "RDX", also known as cyclonite, stands for Royal Demolition eXplosive. It is also known as cyclonite or hexogen. The chemical name for RDX is 1,3,5-trinitro-1,3,5-triazine. It is a white powder and is very explosive. RDX is used as an explosive and is also used in combination with other ingredients in explosives. C-4 explosive is approximately 91% RDX) Its odor and taste are unknown. It is a synthetic product that does not occur naturally in the environment. It creates fumes when it is burned with other substances. Limited studies have shown adverse gastrointestinal, hematological, hepatic, and renal effects in workers exposed to C-4 (an explosive composed of 91% RDX) or RDX dusts via inhalation. (http://www.atsdr.cdc.gov/substances/toxsubstance.asp?toxid=72).

Commentary: Exposure to RDX occurs in areas near ammunition factories or military bases, where water or soil may become contaminated. RDX can affect several organ systems however the central nervous system is the most susceptible, and both seizures and tremors have been reported (http://www.atsdr.cdc.gov/toxguides/toxguide-78.pdf). RS.

Question 214: The seeds of some fruit trees contain cyanogenic glycosides that may liberate cyanide when digested. What fruit trees are included in this group?

Answer: Malus (apple), Prunus (cherry, plum, peach, apricot) as well as Hydrangea contains cyanogenic glycosides. (Petersen DD. Common plant toxicology: A comparison of national and Southwest Ohio data trends on plant poisonings in the 21st century. 2011 Tox Appl Pharm 254:148-153).

Commentary: Cyanide blocks oxidative phosphorylation by inhibiting multiple enzymes, primarily cytochrome oxidase. Exposure may occur due to combustion of certain organic materials, ingestion of cyanogenic compounds found in plants, or iatrogenically by the use of nitroprusside. MK.

Question 215: What are the most common infectious complications associated with the use of black tar heroin?

Answer: Clostridial infections, including wound botulism, tetanus, and necrotizing fasciitis as well as polymicrobial infections and Staph aureus (including MRSA) infections are the most common infectious complications associated with the use of black tar heroin.(Dunbar NM, et al. Necrotizing Fasciitis: Manifestations, Microbiology and Connection with Black Tar Heroin. 2007 J Forensic Sci. 52(4):920-923).

Commentary: Black tar heroin is a crude form of heroin. Intravenous injections of black tar heroin carry a high risk of thrombophlebitis while subcutaneous injections may lead to polymicrobial infections. Proper antimicrobial coverage is warranted in these infections. MK.

Question 216: Which drugs are known to predispose to heat illness?

Answer: The cited reference notes that the following drugs predispose individuals to heat illness: All typical antipsychotics, all atypical antipsychotics, all tricyclic antidepressants, atropine, benztropine, cyclobenzaprine,

diphenhydramine, hydrochlorothiazide, furosemide, metoclopramide, methylphenidate, oxybutynin, prochlorperazine, promethazine, scopolamine, spironolactone, amphetamines, cocaine,. (Levine M et al. Influence of drug use on morbidity and mortality in heatstroke. 2012 J Med Tox 8(3): 252-257).

Commentary: The above listed medications alter thermo-regulation by a number of mechanism including increased endogenous heat production, impaired heat dissipation and altered behavioral responses to warm environments. MK.

Question 217: What is Krokodil, what is its primary component chemical, and what are the characteristics of this core chemical?

Answer: Known as Crocodile, Krok or Croc, Krokodil is a mixture of several substances with the core component being the chemical desomorphine. Krokodil first emerged in the Russian drug scene in late 2002. Desomorphoine is an opioid analogue first synthesized in the US in 1932. This substance reportedly creates a higher dependence profile than morphine with an analgesic potency 8-10 higher than morphine and a more rapid onset of action with a shorter elimination half life. (Gahr M et al. Desomorphone goes "crocodile". 2012 J Addictive Dis 31:407-412).

Commentary: Desomorphine is primarily synthesized using codeine. Its use is more prevalent in Eastern Europe as codeine is more widely available and more accessible than alternative opioids. RS.

Question 218: Gasoline is a complex mixture of hydrocarbons and additives and contains roughly 60% to 70% alkanes, 25% to 30% aromatics, and 6% to 9% alkenes. What is the primary cause of morbidity and mortality associated with the ingestion of gasoline?

Answer: The primary cause of morbidity and mortality associated with the ingestion of gasoline is related to pulmonary aspiration. (Rahman I., et al. Gasoline ingestion: A rare cause of pancytopenia. 2009 Am J Med Sci 338(5): 433-434).

Commentary: Gasoline contains a mixture of hydrocarbons, which are responsible for the toxic pulmonary effects. Low viscosity and low surface tension increase the aspiration risk. Pulmonary aspiration of hydrocarbons may lead to pneumonitis, pulmonary edema, bronchospasm, atelectasis, and ARDS. RS.

Question 219: What is the so-called "CFR Title 49, Part 40"?

Answer:The Code of Federal Regulations (CFR) annual edition is the codification of the general and permanent rules published in the Federal Register by the departments and agencies of the Federal Government. Title 49, Part 40 specifically defines "procedures for transportation workplace drug and alcohol testing programs" (http://www.dot.gov/sites/dot.dev/files/docs/PART40_2012.pdf, accessed May, 2014).

Commentary: The cited reference provides detailed information regarding the Department of Transportation workplace drug and alcohol testing. The resource is useful for healthcare professionals, employers, and employees. RS.

Question 220: The so-called Daubert standard is used to help determine the admissibility of scientific evidence in federal courts of law in the United States. What were the allegations in the landmark case that established the Daubert standard?

Answer: The cited reference notes that in the landmark case (Daubert v Merrell Dow Pharmaceuticals, 1993), the Plaintiffs alleged that Bendectin, an anti-nausea drug prescribed for pregnant females, was teratogenic. Two specific Plaintiffs, Jason Daubert and Eric Schuller, alleged that they were born with limb reduction defects induced by Bendectin taken by their respective mothers. (Fung F. Demystifying the role of expert witness for clinical toxicolgists. 2012 Clin Tox 50&7):539-545).

Commentary: The Daubert and Frye standards determine the admissibility of expert testimony in litigations in various jurisdictions in the U.S. The intent of the standards is to prevent experts from providing a biased or unscientific testimony. MK.

Question 221: Colchicine has been used to treat gout for hundreds of years. However the drug is known to have a narrow therapeutic range. The recognized maximum cumulative IV dose is 4 mg for a single course of therapy, with a 7-day colchicine-free interval after each full IV course. However, deaths have been reported with cumulative doses as low as 5.5 mg. Which subset of patients have been identified as being a higher risk for toxicity and death due to the use of IV colchicine?

Answer: Older adults, patients with preexisting renal and hepatic failure, and patients with concomitant use of nonsteroidal anti-inflammatory drugs or oral colchicine might have a higher risk for toxicity and death from IV cholchicine. (Bonnel RA et al. Deaths associated with inappropriate intravenous colchicine administration. 2002 J Emerg Med 22:385-387 as cited in Centers for Disease Control and Prevention. Deaths from Intravenous Colchicine Resulting from a Compounding Pharmacy Error — Oregon and Washington, 2007 MMWR Oct 12,2007 56(40):1050-1052).

Commentary: The dosing of colchicine must be adjusted for renal and hepatic disease. Colchicine is metabolized by CYP3A4 and toxicity may occur with concurrent use of CYP3A4 inhibitors. Treatment for colchicine toxicity is mainly supportive. MK.

Question 222: How does HF (hydrofluoric acid) cause the destruction of tissue?

Answer: The cited reference describes two general mechanisms for tissue destruction related to HF. The authors point out that "the hydrogen ions cause a corrosive burn similar to other acid burns. This damage occurs immediately and results in visible tissue destruction." They go on to point out "The second mechanism of tissue injury is liquefaction necrosis of deeper tissues. This occurs as the highly lipophilic fluoride ions penetrate tissue and alter cellular metabolism." The latter type of damage is of greater clinical importance as it may continue for up to several days if untreated. (Stuke LE et al. Hydrofluoric acid burns: A 15-year experience.2008 29:893– 896).

Commentary: Hydrofluoric acid is used commercially in glass etching, metal cleaning, and as a rust remover. The severity of local toxicity is mainly determined by the amount, contact time and concentration of the acid. Exposure to high

concentration products may lead to systemic toxicity. Manifestations of hypocalcemia (prolonged QT interval) and hyperkalemia (peaked T waves) may be evident on EKG in cases of systemic toxicity. MK.

Question 223: In 1997, 48-year-old chemistry professor Karen Wetterhahn died as a result of a minimal skin (with or without concomitant possible inhalational) exposure to what mercury-containing compound often said to be "supertoxic"?

Answer: Several months following an inadvertent laboratory accident, Dr. Wetterhahn succumbed to mercury toxicity following exposure to a very small amount of dimethylmercury. (Nierenberg DW et al. Delayed cerebellar disease and death after accidental exposure to dimethylmercury. 1998 NEJM 338(23):1672-1676).

Commentary: This famous and unfortunate toxicologic case describes the clinical course of dimethylmercury exposure. The case ultimately resulted in death even though the patient was only exposed to a drop of dimethylmercury. RS.

Question 224: Is clinically significant methanol toxicity possible following inhalational exposure to products containing methanol?

Answer: A number of reports have demonstrated that methanol toxicity can result from intentional inhalational exposure and can range from a relatively benign clinical course to death. Some have suggested that lower levels of serum methanol are achieved through inhalation versus ingestion however the cited reference reports serum methanol levels ≥ 50 mg/dL in 28% (n = 19) of the admitted cases of inhalation exposure to methanol they report. (Wallace EA and Green AS. Methanol toxicity secondary to inhalant abuse in adult men. 2009 Clin Tox 47: 239-242).

Commentary: Methanol and ethylene glycol are commonly encountered toxic alcohols that may result in significant morbidity and mortality. While many differences exist between them, only methanol has the potential to cause human poisoning following an inhalational exposure. Clinicians should be aware of the potential for significant methanol toxicity following inhalation in the absence of ingestion. RS.

Question 225: What is CSF lavage and under what circumstances might this procedure be useful in treating a poisoned patient?

Answer: CSF lavage is a procedure whereby 20-30 mL of CSF is removed and replaced with 30–40 mL of preservative-free normal saline or lactated Ringer's solution via an epidural catheter. This procedure may be considered (in conjunction with the use of appropriate reversal agents such as naloxone) in the face of serious opioid toxicity following therapeutic overdose due to intrathecal pump malfunction. CSF lavage has also been used to treat accidental therapeutic vincristine overdose. (Boyer EW. Management of opioid analgesic overdose. 2012 NEJM 367(2):146-155 and Tsui BC et al. Reversal of an unintentional spinal anesthetic by cerebrospinal lavage. 2004 Anesth Anag 98:434-436).

Commentary: CSF lavage may be considered as a treatment for opioid toxicity secondary to intrathecal opioid pump malfunction. In addition to the aforementioned uses, it may also be used following inadvertent intrathecal, rather than epidural, administration of analgesia in obstetric cases. MK.

Question 226: Clenbuterol is a beta 2 adrenergic agonist agent that has been noted as an adulterant in heroin and other street drugs. Why has this drug also been abused by bodybuilders?

Answer: Bodybuilders have reportedly used clenbuterol because, as the cited reference points out, this agent has "specific anabolic activity and increased lipolysis that is not seen with other beta agonists" with the ultimate goal of increasing lean muscle mass. (Yen M and Burns Ewald M. Toxicity of weight loss agents. 2012 J Med Toxicol 8(2):145-152).

Commentary: Clenbuterol is approved in the U.S. for veterinary use. Suspicion of clenbuterol abuse in bodybuilders is important since it is a long-acting beta-2 agonist with reported half-life of up to 39 hours. MK.

Question 227: Following death, does fentanyl continue to be released into the circulation from pre-mortem, cutaneous placed, transdermal fentanyl patches?

Answer: The cited reference states "There are no data to support continued postmortem release of fentanyl from TD patches from one part of the body (e.g.,the shoulder) causing an increase in blood fentanyl concentration in a distant anatomic site (e.g., the femoral vessels)." The author further points out "in the absence of circulation, there is no thermodynamic force to drive such a continued release. The movement of drug from the patch into the skin and subsequent systemic delivery requires continual uptake of fentanyl by the circulating blood. In the absence of circulatory uptake, the depot of drug in the skin will simply remain in equilibrium with the drug in the patch resulting in a net-zero transfer." (Palmer RB. Fentanyl in postmortem forensic toxicology. 2010 Clin Tox 48(8):771-784).

Commentary: Fentanyl has a higher affinity for opioid receptors than morphine. Fentanyl patches provide sustained release of drug and pain control but it may take 13-24 hours to reach therapeutic serum concentrations. Drug absorption through the skin depends on a number of factors, including core body temperature. MK.

Question 228: What is rigor mortis and how might the presence of rigor mortis assist in the determination of the precise time of death?

Answer: Rigor mortis (RM) is simply the postmortem stiffening of muscles thought to be related to buildup of lactate and phosphate in muscle tissue leading to an acidic microenvironment that promotes the binding of actin and myosin to yield stiff muscles. RM occurs uniformly throughout the body but is first visible in the face and neck at 1 to 4 hours after death and in the rest of the body by 12 hours post death. RM begins to disappear at about 24 hours post death. In most cases

however, the presence or absence of RM cannot be used to precisely determine the time of death. (Reddy K and Lowenstein EJ. Forensics in dermatology: Part I. 2011 J Am Acad Derm; 64:801-808).

Commentary: An accurate determination of time of death is often an important issue in forensic toxicology. RM cannot always be reliably used for determining timing of death. RS.

Question 229: What chemical may be used in the treatment of both thallium toxicity and toxicity due to cesium-137?

Answer: Prussian blue may be used in the treatment of both thallium toxicity and toxicity due to cesium-137. (Thompson DF and Callen ED. Soluble or insoluble Prussian blue for radiocesium and thallium poisoning? 2004 Anns Pharmacotherapy 38:1509-1514).

Commentary: Constipation is a common adverse health associated with Prussian blue. Patients may be given a bowel regimen during Prussian blue administration to counteract this adverse effect. RS.

Question 230: What is "gas eye"?

Answer: "Gas eye" is a form of keratoconjunctivitis that may be seen in some workers who may be exposed to low levels of hydrogen sulfide (e.g in some sour gas plants). The cited reference discusses an interesting aspect of this problem in that it "can be associated with reversible chromatic distortion and visual changes. This effect is sometimes accompanied by blepharospasm, tearing and photophobia". (Guidotti TL. Hydrogen sulphide. 1996 Occ Med 46(5):367-371).

Commentary: Mucosal irritation, including of the eye, may be the first clinical sign of hydrogen sulfide exposure. Increasing levels of exposure can result in a sudden loss of consciousness, pulmonary edema, and death. Olfactory recognition of the "rotten eggs" smell is unreliable for detecting hydrogen sulfide secondary to olfactory nerve paralysis and fatigue. RS.

Question 231: Toxicity related to which heavy metal should be included in the differential diagnosis of Guillain-Barre syndrome?

Answer: Arsenic should be included in the differential diagnosis of Guillain-Barre syndrome. As the cited reference points out arsenic neurotoxicity "is usually a symmetrical sensori-motor neuropathy, often resembling the Guillain–Barré syndrome". Arsenic related neuropathy is usually an ascending phenomenon, similar to what is often seen in the Guillain–Barré syndrome. (Vahidnia A ety al. Arsenic neurotoxicity-A review. 2007 Human & Experimental Toxicology 26: 823–832).

Commentary: In addition to Gullain-Barre syndrome, ascending paralysis may be caused by tick borne infections, hyperkalemia and arsenic poisoning. The presence of ocular signs may differentiate tick paralysis from GBS. While the peripheral neuropathy in arsenic poisoning is usually long standing, ascending weakness may be rapid and may require mechanical ventilation in extreme cases. MK.

Question 232: Chewing the leaves of the Catha edulis (Khat) plant results in the release of cathinone, (an amphetamine-like compound). The chewing of Khat, as a stimulant, is especially popular in some countries in northern Africa and the Middle East. Khat chewing is also practiced by some individuals who have immigrated to the US from these areas. Chronic chewing of Khat has been associated with an increased risk for what specific medical problems?

Answer: Chewing Khat has been associated with an increased risk for myocardial infarction, dilated cardiomyopathy and duodenal ulcers. (Al-Motarreb A, et al. Khat chewing, cardiovascular disease and other internal medical problems; the current situation and directions for future research. 2010 J Ethnopharmacol 132:540–548 as cited in Prosser JM and Nelson LS. The toxicology of bath salts: A review of synthetic cathinones. 2012 J Med Toxicol 8:33-42).

Commentary: Khat contains an amphetamine like stimulant and induces sympathomimetic symptoms on consumption. The use of Khat is most prevalent in Yemen. In addition to gastrointestinal and cardiovascular being the most commonly affected systems, there is reported association between khat use and psychosis. MK.

Question 233: What is the pathologic mechanism of caterpillar-associated skin rashes?

Answer: The pathologic mechanism of caterpillar-associated rash is not understood entirely and depends on the caterpillar species. The mechanism is thought to involve exposure to chemicals on caterpillar or cocoon hairs (spicules) or mechanical irritation. Additionally, when caterpillars and cocoons are in high density, particularly susceptible persons can develop a rash when the hairs become airborne. In these situations, the rash might not occur on the area of the skin where caterpillar or cocoon contact occurred. (MMWR. Caterpillar-associated rashes in children. March 30,2012 61(12):209-211).

Commentary: Spines in certain species of caterpillars contain an urticarial toxin that is thought to produce the skin rash in these exposures. Dermal and eye exposure may occur in seasons when the insect is in the larval form. Adhesive tap may be applied to remove the caterpillar hair and spicules. The area should be washed with soap and water and topical steroids may be used for symptom control. MK.

Question 234: What biomarkers have been used in occupationally based studies investigating the chronic effects of the chemical styrene?

Answer: The cited reference notes that in the occupational studies that are the basis for quantifying the relationship between chronic styrene exposure and health effects, end-of-shift or next-morning urine levels of mandelic acid and phenylglyoxylic acid may be used. Additional styrene biomarkers include urinary styrene and mercapturic acid levels as well as phenylglycine and 4-vinylphenol conjugates. (Rueff J, et al. Genetic effects and biotoxicity monitoring of occupational styrene exposure. 2009 Clinica Chimica Acta 399:8-23).

Commentary: Occupational styrene exposure typically occurs via inhalation among workers in the reinforced plastics industry. Biomarkers can be used to identify chronic exposure when it is suspected. RS.

Question 235: The Australian platypus (Ornithorhynchus anatinus) is one of only two mammalian species possessing a functional venom delivery apparatus. What is the nature of platypus venom and how is it delivered?

Answer: The first cited reference below notes that venom from the platypus is injected through spurs located on the hind legs that are connected to venom ducts. Interestingly, Only the male platypus possesses this apparatus. Five types of proteins and peptides have been isolated and identified from platypus venom, namely: defensin-like peptides (DLPs); Ornithorhynchus venom C-type natriuretic peptides (OvCNPs); Ornithorhynchus nerve growth factor; hyaluronidase; and l-to-d-peptide isomerase. (Hodgson WC Pharmacological action of Australian animal venoms. 1997 Clin Exp Pharm Physiol 24:10-17 and Koh JM, et al Platypus venom: source of novel compounds. 2009 Aust J Zoology 57(4):203-210).

Commentary: The venom concentration in male platypus peaks during the late winter and spring, the breeding season. Handling a male platypus or platypus of uncertain origin should be avoided as the venom contains several aforementioned enzymes. The pain secondary to platypus envenomation is intense and long lasting and is typically refractory to conventional analgesics. MK.

Question 236: What is CCA pressure treated wood?

Answer: “CCA” stands for chromated copper arsenate. This material is used as a wood preservative and is impregnated, under high pressure, into certain wood products intended for outdoor use to protect the wood from development of fungus, rot and destruction by insects. Chromium, arsenic and copper may become bioavailable specifically when CCA treated woods are burned, cut, or sanded. Under these circumstances (depending on exposure and dose parameters) unprotected exposure to these metals could be clinically important. In 2004, the US EPA banned the use of CCA in wood in residential products including wood used in play structures, decks, picnic tables, landscape timbers, residential fences, patios, walkways and boardwalks. (Decker P, et al. Exposure to wood dust and heavy metals in workers using CCA pressure treated wood. 2002 Am Ind Hyg Assoc J 63:166-171 and Katz SA and Salem H. Chemistry and toxicology of building timbers pressure treated with chromated copper arsenate: a review. 2005 J Applied Tox 25:1-7).

Commentary: Proper personal equipment should be worn while sawing or handling CCA treated wood. Children should be discouraged from eating while on CCA treated wood used in playgrounds and decks. Application of bleach and other harsh cleaning solutions on CCA treated wood should be avoided. MK.

Question 237: Rituximab (Rituxan) (RTX) is a biologic agent, B cell depleting antibody, now widely used in a variety of conditions including non-Hodgkin’s lymphoma and rheumatoid arthritis. What is the predominate toxicity (organ system) that has been reported in patients taking this agent?

Answer: According to the cited reference, "respiratory events have been reported in up to 38% of patients receiving RTX and include cough, bronchospasm, dyspnea, sinusitis and rhinitis. Likewise respiratory tract infections have been reported in up to 10% of the patients." More serious pulmonary complications reported include bronchiolitis organizing pneumonia, interstitial lung disease and pulmonary fibrosis. (Hadjinicolaou AV et al. Non-infectious pulmonary toxicity of rituximab: a systematic review. 2012 Rheumatology).

Commentary: Rituximab is an increasingly important medication in the treatment of a variety of cancers. Patients receiving Rituximab typically have significant co-morbidities making any signs of toxicity potentially worrisome. The authors conclude that “RTX-induced interstitial lung disease should be considered in any patient who develops respiratory symptoms or new radiographic changes while receiving this biologic agent.” RS.

Question 238: Emtricitabine/tenofovir (Truvada) is a combination preparation containing the drugs emtricitabine and tenofovir. This combination was first approved to treat HIV-1 infection and currently is also approved as pre-exposure prophylaxis to prevent HIV-1 infection in individuals of high risk. What are the safety concerns associated with the use of this drug?

Answer: According to the cited reference: “The drug must not be prescribed if the patient’s creatinine clearance is less than 60 mL per minute per 1.73 m2 (1.00 mL per second per m2) because its use has been associated with renal failure and Fanconi syndrome. Although rare and not reported in premarketing studies, lactic acidosis and severe hepatomegaly with steatosis are possible in patients at risk of liver disease, according to the drug’s manufacturer. Because both emtricitabine and tenofovir are active against hepatitis B virus, and because of the risk of rebound hepatitis following discontinuation of therapy, this combination should be used with caution in patients coinfected with hepatitis B virus.” (Coutinho B and Prasad R. Emtricitabine/tenofovir (Truvada) for HIV prophylaxis. 2013 Am Fam Physician 88(8):535-540).

Commentary: 70-90% of HIV-infected patients in the United States have evidence of past or active infection with Hepatitis B. (Rodríguez-Méndez ML et al. Prevalence, patterns, and course of past hepatitis B virus infection in intravenous drug users with HIV-1 infection. 200 Am J Gastroenterol. 95(5):1316-22). RS.

Question 239: What is Captagon?

Answer: Captagon is a “brand name for the drug fenethylline. It is not commercially available but rather is produced illicitly and is reportedly widely used in the Near and Middle East. The cited reference notes “Fenethylline is an N-alkylated amphetamine derivative and is metabolized to amphetamine and theophylline….”. Captagon has been recently noted in the lay press as a drug probably used by Daash terrorists for its sympathomimetic effects. (Ulucay A et al. Acute myocardial infarction associated with

captagon use. 2012 Anadoly Kardiol Derg 12:181-186 and http://timesofindia.indiatimes.com/world/middle-east/Turkey-seizes-11-million-pills-of-Syria-war-drug-reports/articleshow/49860478.cms; accessed November 2015).

Commentary: Illicit drugs such as fenethylline, while not commonly found in the US, may be trafficked into the US. The cited article states products mimicking Captogen may contain "amphetamine, caffeine, ephedrine, quinine, theophylline, acetaminophen, diphenhydramine and lactose or a combination of these substances." There are several reported cases of acute myocardial infarction associated with amphetamine and ephedrine use. RS.

Question 240: Tularemia is a CDC designated "Category A bioterrorism agent". In other words, it is considered to be a high-priority organism that poses a risk to national security because: (1) it can be easily disseminated or transmitted from person to person; (2) it may result in high mortality rates and have the potential for major public health impact; (3) it might cause public panic and social disruption; and (4) it may require special action for public health preparedness. What is the causative organism for tularemia and what are the natural reservoirs for this organism in the US?

Answer: According to the cited reference, tularemia is "a zoonotic infection caused by the small, aerobic, pleomorphic Gram negative coccobacillus Francisella tularensis to which humans are a highly susceptible host". The authors also point out that "In the US, rabbits, hares, and ticks are among the most important natural reservoirs for the organism, and infection is most commonly transmitted by tick, deerfly, flea or by direct contact with infected animal products". While tularemia does have an incidence of natural occurrence in some parts of the US, "a diagnosis of tularemia, in a non-endemic area, should alert the clinician to possible bioterrorism exposure". (Guffey MB, et al Ulceroglandular tularemia in a nonendemic area. 2007 So Med J 100(3):304-308).

Commentary: In addition to direct contact with infected animal products, tularemia may spread through contaminated water and inhalation of contaminated aerosolized material. Pneumonic tularemia carries the highest risk of mortality. Streptomycin is considered as the antibiotic of choice for active tularemia infection. MK.

Question 241: What was the Hawk's Nest Tunnel Disaster?

Answer: The Hawk's Nest Tunnel was a hydroelectric power project constructed by blasting into massive natural rock formations in the area of Gauley Bridge, West Virginia (undertaken during the 1930s). When the drilling and blasting phase of the Hawks Nest project was complete, an epidemic of silicosis was identified among men who had worked at the Gauley Bridge site. Four hundred drillers died, and lung-related disabilities were reported in the majority of surviving workers. This has been noted as one of the worst occupational health and public health disasters in the history of the United States. (Greenberg MI, et al Silicosis: a review. 2007 Disease Month 53: 394-416).

Commentary: Silicosis remains an important occupational disease in the US. There are three generally recognized forms of silicosis: acute, chronic and accelerated. Workers from mines, foundries, sandblasting, and glass manufacturing are potentially at risk. MK.

Question 242: An occupational disorder known as acro-osteolysis was first described in 1950 in a blacksmith. What is acro-osteolysis? Exposure to what chemical has been causally associated with this disorder?

Answer: Occupationally derived acro-osteolysis is a reversible disorder characterized by bony destructive lesions of the distal phalanges of one or more fingers (most frequently involving the thumbs). Acro-osteolysis has been recognized in a very small percentage of workers (less than 2%) involved with the polymerization of vinyl chloride. (Gama C, et al. Occupational acro-osteolysis. 1978 J Bone Joint Surg 60-A(1):86-90).

Commentary: A band like pattern of acro-osteolysis may develop due to exposure to vinyl chloride. It is a reversible disorder that is thought to occur secondary to obstruction of small peripheral arteries causing bony destruction of terminal parts of distal phalanges. MK.

Question 243: Over 200 million people worldwide are afflicted with schistosomiasis (S. mansoni, S japonicum or S hematobium). Which drug provides low cost high cure rate treatment for this infection and what is the probable mechanism of action for this agent?

Answer: Praziquantel is the drug of choice for schistosomiasis and provides low cost/ high cure rate treatment. The cited reference reports: "Targeting the cellular $Ca2+$ channels and pumps that underpin parasite $Ca2+$ homeostasis may realize novel antihelmintic agents. Indeed, the antischistosomal drug praziquantel (PZQ) is a key clinical agent that has been proposed to work in this manner. Heterologous expression data has implicated an action of PZQ on voltage-operated $Ca2+$ channels, although the relevant in vivo target of this drug has remained undefined over three decades of clinical use." (Chan JD et al. Ca $2+$ channels and praziquantel: A view from the free world. 2013 Parasitol Intl 62:619-628).

Commentary: Praziquantel is a widely used treatment for schistosomiasis worldwide. The cited reference highlights that its mechanism of action may be useful in the development of new anthelmintic agents. RS.

Question 244: Should osteoporosis (anti-resorptive) therapy (e.g.bisphosphonates) be stopped prior to dental procedures?

Answer: According to the cited reference: "The American Dental Association in 2011 recommended that osteoporosis therapy does not require alteration before dental procedures. A recent review suggested that before major, invasive dental surgery, consideration should be given to stopping antiresorptive therapy; the review also emphasized the importance of good dental hygiene in reducing risk." (Black DM and Rosen CJ. Postmenopausal osteoporosis. 2016 NEJM 374: 254-262 and Khan AA et al. Diagnosis and management of osteonecrosis of the jaw: a systematic review and international consensus. 2015 J Bone Miner Res 30:3-23).

Commentary: Osteonecrosis of the jaw most commonly occurs after a dental extraction. Many patients are prescribed bisphosphonates for the treatment of osteoporosis, so it is important to be aware of the recommendations above. RS.

Question 245: What are the major sources of exposure to perfluoroalkyls including PFOA (perfluorooctanoic acid) and PFOS (perfluorooctane sulfonic acid)?

Answer: Contaminated drinking water and contaminated food are the primary sources of exposure for perfluoroalkyls. However industrial releases of these chemicals into ambient air or surface water may also be important sources. The cited reference notes: “The general population may also be exposed to PFOS from mill treated carpets and to PFOA from migration from paper packaging and wrapping into food and inhalation from impregnated clothes.” (ATSDR 2015. Toxicological Profile for Perfluoroalkyls (Draft for Public Comment) Atlanta Georgia: US Dept of HHS, PHS).

Commentary: PFOA and PFOS exposure is widespread among the general population and may be associated with adverse health effects such as high cholesterol and hypertension. The International Agency for Research on Cancer (IARC) has not yet evaluated the carcinogenicity of perfluoroalkyls. RS.

Question 246: Hydrogen sulfide is a flammable, colorless gas with a characteristic odor of rotten eggs. Hydrogen sulfide may be found associated with a number of industrial activities, such as food processing, coke ovens, paper mills, tanneries, and petroleum refineries. It also occurs naturally in a variety of settings; what are they?

Answer: Hydrogen sulfide (H2S) occurs naturally in crude petroleum, natural gas, volcanic gases, and hot springs. It can also result from bacterial breakdown of organic matter. It is also produced by human and animal wastes. (ATSDR, Toxic Substances Portal, available at http://www.atsdr.cdc.gov/substances/toxsubstance.asp?toxid=67).

Commentary: Hydrogen sulfide inhibits cytochrome oxidase and may lead to high anion gap metabolic acidosis. Suicide attempts by hydrogen sulfide carry a high mortality rate. A “suicide craze in Japan” was reported in 2008 when a bath additive with lime sulfur was mixed with toilet detergent to produce H2S. Poisoning by H2S may be evident by discoloration of copper coins around the victim or in victim’s pockets. MK.

Question 247: What is diisopropyl methylphosphonate?

Answer: Diisopropyl methylphosphonate, also known as DIMP, diisopropyl methane-phosphonate, phosphonic acid, and methyl-bis-(1-methylethyl)ester is a chemical by-product resulting from the manufacture of Sarin (GB), a well-known chemical nerve agent. A chemical by-product is a chemical that is formed while making another substance. Sarin was produced and stored only in the Rocky Mountain Arsenal outside of Denver, Colorado. Production of Sarin in the United States was discontinued in 1957. Diisopropyl methylphosphonate is not known to occur naturally in the environment. It is not likely to be produced in the United States in the future because of the signing of a chemical treaty that bans the use, production, and stockpiling of poison gases. Diisopropyl methylphosphonate is a colorless liquid.(http://www.atsdr.cdc.gov/substances/toxsubstance.asp?toxid=203).

Commentary: According to ATSDR, exposure of the general population to DIMP is anticipated to be low. Exposure is most likely to occur from drinking or showering with DIMP contaminated water near the Rocky Mountain Arsenal or through ingestion of fruits and vegetables that have been irrigated with such water. MK.

Question 248: Allergic reactions to local anesthetics are not common however local anesthetics are indeed capable of causing potentially serious allergic reactions. What is the basis for the antigenicity of procaine and the ester local anesthetic agents that might cause allergic reactions?

Answer: The antigenicity of procaine and the amino ester agents is “most often related to the para-aminobenzoic acid (PABA) component of ester anesthetics, a decidedly antigenic compound.” PABA results from the metabolism of the ester agents. PABA does not form due to the metabolism of the amide agents. (Speca SJ et al. Allergic reactions to local anesthetic formulations. 2010 Dent Clin N Amer 54:655-664).

Commentary: Local anesthetics (LA) are broadly classified into ester and amide groups. While ester class LA are hydrolyzed by plasma cholinesterase and have short half-lives, the drugs in the latter group are metabolized by the liver and have longer duration of effect. MK.

Question 249: What is “MBOCA”?

Answer: MBOCA is a synthetic chemical used primarily to make polyurethane products. Pure MBOCA is a colorless, crystalline solid, but the commonly used form is usually yellow, tan, or brown pellets. It has no smell or taste. Examples of these products include gears, gaskets, sport boots, roller skate wheels, shoe soles, rolls and belt drives in cameras, computers and copy machines, wheels and pulleys for escalators and elevators, components in home appliances, and various military applications. It is also used as a coating in chemical reactions to "set" glues, plastics, and adhesives. Because plastics have many uses, MBOCA is widely used. Other names for MBOCA include 4,4'-methylenebis(2-chloroaniline), methylene-bis-ortho-chloro-aniline, bis-amine, DACPM, MCA, and MOCA. (http://www.atsdr.cdc.gov/substances/toxsubstance.asp?toxid=209; accessed February 2016.

Commentary: MBOCA is a component used to make a large variety of products. Exposure can occur via direct dermal absorption among workers or ingestion of contaminated soil. MBOCA is classified as a known human carcinogen by IARC (group 1). RS.

Question 250: What is the pathophysiology of cadmium induced nephropathy?

Answer: Roughly 30% of absorbed cadmium is stored in the kidneys, where it persists with a biologic half-life of up to 30 years. The cited reference notes: "In chronic cadmium exposure much of the plasma cadmium is bound to metallothionein (MT). Due to its small molecular size, cadmium–MT, in contrast to the cadmium–albumin complex, is efficiently filtered through the glomerular membrane and reabsorbed by renal tubular cells through pinocytosis. The cadmium–MT complex is then metabolized within lysosomes and cadmium ion is released. Cadmium nephropathy presents as tubular proteinuria that can be quantified by measuring low molecular weight proteins including beta-2 microglobulin and retinol binding protein. With continued cadmium exposure this tubular dysfunction progresses and ultimately glomerular damage characterized by a decreased glomerular filtration rate may emerge. Several studies have documented that in almost all cases, this cadmium-induced tubular proteinuria and damage is irreversible even if exposure ends." (Wittman R and Hu H. Cadmium exposure and nephropathy in a 28-year-old female metals worker. 2002 Environ Health Perspect 110:1261-1266.

Commentary: Nephrotoxicity is a clinical feature of chronic cadmium exposure, and the most common clinical finding of chronic cadmium toxicity is low-molecular weight proteinuria. Examples of occupational cadmium exposure sources include nickel-cadmium battery manufacturing, zinc refining/cadmium smelting, and metal plating. RS.

Question 251: What is tetryl?

Answer: The chemical name for tetryl is 2,4,6-trinitrophenyl-n-methylnitramine. Some commonly used names are nitramine, tetralite, and tetril. Tetryl is an odorless, synthetic, yellow crystal-like solid that is not found naturally in the environment. Under certain conditions, tetryl can exist as dust in air. It dissolves slightly in water and in other liquids. Tetryl was used to make explosives, mostly during World Wars I and II. It is no longer manufactured or used in the United States. Stocks of tetryl are found in storage at military installations and are being destroyed by the Department of Defense (DOD). According to the cited reference, "Exposure to tetryl occurs around military installations where it was made, used, or stored. Workers who breathed tetryl-laden dust complained of coughs, fatigue, headaches, eye irritation, lack of appetite, nosebleeds, nausea, and vomiting." (http://www.atsdr.cdc.gov/substances/toxsubstance.asp?toxid=216; accessed March 2016).

Commentary: Tetryl is a potential occupational toxicologic exposure among military personnel. It is becoming increasingly rare in the United States as it is no longer being produced. The quantity of tetryl or geographical distribution among military storage facilities is unknown. RS.

Question 252: What was "Koremlu"?

Answer: "Koremlu" was a thallium acetate-containing, topically applied, depilatory used in the past (1920s–1930s). This now discontinued commercial product contained approximately 7% (or more) thallium acetate and was historically responsible for numerous cases of severe thallium intoxication including some deaths. (Severe thallium acetate intoxication caused by the use of a depilatory called "Koremlu". Rudy A. 1932 NEJM 207(25): 1151-1152).

Commentary: Thallium toxicity may initially present with vague symptoms but alopecia and ascending peripheral neuropathy are the most distinctive features. The "Thallium Craze" from Australia was reported in 1950s where thallium was used for homicidal purposes. Thallium was once an important component in rodenticide. Exposure to thallium may be inhalational, dermal or by oral ingestion. Proper decontamination is crucial when managing patients with suspected or proven thallium toxicity. MK.

Question 253: What is the mechanism for the QT interval prolongation that can occur due to methadone and by what percent is the QTc generally increased following the initiation of methadone therapy?

Answer: According to the cited reference, "Methadone as well as its derivative levacetylmethadol prolong the QT interval by inhibition of the rapid component of the delayed rectifier potassium ion current." One study cited by these authors reported "…an 8% increase of the QTc interval after initiation of methadone." (Sticherling C et al. Methadone-induced torsade de pointes tachycardias. 2015 Swiss Medical Weekly. 135(19-20):282-285).

Commentary: Methadone is frequently used in the drug maintenance programs for heroin addicts and the treatment of chronic pain. S-enantiomer of methadone causes more QTc prolongation compared to the R-enantiomer. An EKG should be done prior to initiation of methadone and subsequent EKG should be done at 30 days and yearly. Severe methadone overdose may require IV infusion of naloxone for respiratory support. MK.

Question 254: What is so-called "crumb rubber", what are the major uses for this material and what are the health concerns that have been raised with regard to this material?

Answer: According to the US EPA, the term "crumb rubber": "Refers to ground rubber pieces the size of sand or silt used in rubber or plastic products, or processed further into reclaimed rubber or asphalt products." Approximately 30% of crumb rubber goes to the production of other rubber products, 31 % goes to playground mulch, 17% goes to the production of sports surfaces, 7% to the asphalt production industry and 6% goes to use in the automotive industry. One concern voiced by some is that exposure to crumb rubber may increase the risk of developing a variety of cancers. This notion has never been proven but research related to this question is ongoing. (https://ofmpub.epa.gov/sor_internet/registry/termreg/searchandretrieve/glossariesandkeywordlists/search.do?details=&glossaryName=Recycling%20-%20State%20and%20Local; accessed June 2016 and (https://www.epa.gov/chemical-research/tire-crumb-questions-and-answers; accessed June 2016).

Commentary: The use of crumb rubber on playing fields and playgrounds and potential associated health risk is an ongoing concern. “The U.S. Environmental Protection Agency (EPA), the Centers for Disease Control and Prevention/Agency for Toxic Substances and Disease Registry (ATSDR), and the U.S. Consumer Product Safety Commission (CPSC) launched a multi-agency action plan [in 2016] to study key environmental human health questions.” https://www.epa.gov/chemical-research/federal-research-recycled-tire-crumb-used-playing-fields. RS.

Question 255: Which drug is sometimes referred to as “poor man’s” methadone?

Answer: Loperamide has been referred to by some as the “poor man’s methadone”. The cited study “suggests that loperamide is being used extra-medically to self-treat opioid withdrawal symptoms. There is a growing demand among people who are opioid dependent for drugs to control withdrawal symptoms, and loperamide appears to fit that role. The study also highlights the potential of the Web as a “leading edge” data source in identifying emerging drug use practices.” (Daniulaityte R. “I just wanted to tell you that loperamide WILL WORK”: A web-based study of extra-medical use of loperamide. 2013 Drug and Alcohol Dependence 130: 241–244).

Commentary: Loperamide is an over-the-counter antidiarrheal that is a meperidine analog. Loperamide overdose may cause opioid-like toxic effects. The FDA issued a warning in June 2016 against overuse and abuse of loperamide as it may cause arrhythmias, QTc prolongation and sudden cardiac death. The safety of loperamide use is not established in children less than 2 years of age. MK.

Question 256: Based on its structure, the popular muscle relaxant cyclobenzaprine (Flexeril) sometimes creates a false positive drug test with regard to which class of drugs?

Answer: The tricyclic structure of the drug cyclobenzaprine, makes this drug structurally very similar to the tricyclic antidepressants. The cited author point out: “In addition to common structural aspects, cyclobenzaprine also shares a similar, although less severe, anticholinergic and cardiac overdose adverse effect profile with tricyclic antidepressants”. (Van Hoey NM. Effect of cyclobenzaprine on tricyclic antidepressant assays. 2005 Ann Pharmacother 39:1314-1317).

Commentary: It is important to understand the limitations of urine drug immunoassays and possible social, economic, and legal ramifications of a false positive result. Diphenhydramine and carbamazepine may also cause a false-positive TCA result. RS.

Question 257: Is it safe to use cephalosporin antibiotics for patients with a history of penicillin allergy?

Answer: The cited references notes “ ……a myth persists that approximately 10% of patients with a history of penicillin allergy will have an allergic reaction if given a cephalosporin…….the overall cross-reactivity rate is actually approximately 1% when using first generation cephalosporins or cephalosporins with similar R1 side chains. For penicillin-allergic patients, the use of 3rd or 4th generation cephalosporins or cephalosporins with dissimilar side chains than the offending penicillin carries a negligible risk of cross allergy.” (Campagna JD et al. The use of cephalosporins in penicillin allergic patients: A literature review. 2012 J Emerg Med 42(5):612-620).

Commentary: Prescribing cephalosporin antibiotics to a patient with a reported penicillin allergy is a common clinical dilemma among physicians. Healthcare providers should be aware of the small risk of cross-reactivity of first-generation cephalosporins, and the negligible risk with third or fourth generation cephalosporins. RS.

Question 258: How long might the paralysis associated with botulism be expected to persist?

Answer: The cited reference points out “Paralysis from botulism can be long lasting, and is toxin dependent. Mechanical ventilation may be required for 2 to 8 weeks or longer with food borne botulism and paralysis may continue for as long as 7 months. Symptoms of cranial nerve dysfunction and dysautonomia may persist for more than 12 months.” (Dembek Z et al. Botulism: Cause, Effects, Diagnosis, Clinical and Laboratory Identification, and Treatment Modalities 2007 Disaster Med Pub Health Preparedness 1:122-134).

Commentary: Physicians should understand the typical progression of the disease to anticipate and monitor the recovery process, as well as educate their patients. RS.

Question 259: With regard to the current epidemic of street drugs, what does the abbreviation “IMF” stand for?

Answer: The cited reference notes: “IMF” is "illegally manufactured fentanyl", obtained through illicit drug markets, includes fentanyl analogs, and is commonly mixed with or sold as heroin. Starting in 2013, the production and distribution of IMF increased to unprecedented levels, fueled by increases in the global supply, processing, and distribution of fentanyl and fentanyl-precursor chemicals by criminal organizations.” (Gladden RM et al. Fentanyl law enforcement submissions and increases in synthetic opioid–involved overdose deaths — 27 States, 2013–2014.August 26, 2016 MMWR 65(33): 837-

Commentary: The EPA and CDC issued alerts in 2015 based on an increased number of deaths in Florida and Ohio secondary to fentanyl products, including IMF. Fentanyl is 100 hundred times more potent than morphine. Rapid administration of naloxone as an antidote is crucial while managing these patients. MK.

Question 260: What is the association between frequent acetaminophen use and asthma related complications in children?

Answer: A recent multicenter, prospective, randomized, double-blind, parallel-group trial involving 300 children (age range 12-59 months) concluded “Among young children with mild persistent asthma, as-needed use of acetaminophen was not shown to be associated with a higher incidence of asthma exacerbations…” (Sheehan WJ et al Acetaminophen versus ibuprofen in young children with mild persistent asthma. 2016 NEJM 375: 619-630).

Commentary: Several adult and pediatric observational studies have reported an association between poor asthma control and the use of acetaminophen. The results from the cited double-blind multicenter study, suggest that using acetaminophen for pain and fever control in asthmatic children is safe. MK.

Question 261: Clomiphene citrate (CC) has been used as a first line drug for the treatment of subfertility. Which birth defects have been associated with the use of clomiphene citrate?

Answer: According to the cited reference, CC use was reported by 1.4% of control mothers (94/6500). Among 36 case-groups assessed, increased adjusted odds ratios (aOR) were found [all: aOR, 95% confidence interval (CI)] for anencephaly (2.3, 1.1–4.7), Dandy–Walker malformation (4.4, 1.7–11.6), septal heart defects (1.6, 1.1–2.2), muscular ventricular septal defect (4.9, 1.4–16.8), coarctation of aorta (1.8, 1.1–3.0), esophageal atresia (2.3, 1.3–4.0), cloacal exstrophy (5.4, 1.6–19.3), craniosynostosis (1.9, 1.2–3.0) and omphalocele (2.2, 1.1–4.5)." These authors concluded: "Several associations between CC use and birth defects were observed. However, because of the small number of cases, inconsistency of some findings with previous reports, and the fact that we cannot assess the CC effect separately from that of the subfertility, these associations should be interpreted cautiously." (Reefhuis J et al. Use of clomiphene citrate and birth defects, National Birth Defects Prevenetion Study, 1997-2005) 2010 Human Repro 26(2): 451-457).

Commentary: Clomiphene citrate is a selective estrogen receptor modulator that is used in fertility clinics and in patients with polycystic ovarian syndrome. The use of clomiphene citrate is contraindicated in patients with liver disease, endometrial cancer, and during pregnancy. Patients may experience nausea, vomiting, abdominal discomfort, hot flushes and visual symptoms. MK.

Question 262: Amiodarone is an antiarrhythmic drug that may be useful for both atrial and ventricular arrhythmias. It exhibits a combination of calcium channel blockade, beta blockade and class III antiarrhythmic effects. Amiodarone has been associated with multiple potentially serious systemic adverse effects; what are they?

Answer: Amiodarone has been associated with bradycardia, hypo- or hyperthyroidism, pulmonary toxicity, ocular deposits, and abnormalities of hepatic function. (Doyle JF et al. Benefits and risks of long-term amiodarone therapy for persistent atrial fibrillation: A meta-analysis. 2009 Mayo Clin Proc.84(3):234-242).

Commentary: Amiodarone is a commonly prescribed antiarrhythmic with many reported adverse drug effects that require monitoring. Approximately 15% of patients started on amiodarone will experience an adverse drug effect within the first year. Less than 20% of patients will need to discontinue amiodarone secondary to adverse effects Goldschlager N et al. Practical guidelines for clinicians who treat patients with amiodarone. 2000 Practice Guidelines Subcommittee, North American Society of Pacing and Electrophysiology. Archives of internal medicine. 160(12):1741-1748.) RS.

Question 263: Occupational exposure to what substance has been reported to be associated with the development of a greenish discoloration of the tongue?

Answer: Occupational exposure to vanadium and vanadium containing compounds has been reported to be associated with the development of a greenish discoloration of the tongue. (Venkataraman BV and Sudha S. Vanadium Toxicity 2005 Asian J Exp Sci 19(2):127-134).

Commentary: Vanadium is a transition metal used in the production of steel alloys and as a catalyst for the production of sulfuric acid. RS.

Question 264: Recent reports indicate an increase in cyclospora-related illness in humans. Ingestion of which foods have been associated with US outbreaks of cyclospora-related illness over the past decade?

Answer: Ingestion of imported fresh produce, including fresh cilantro, pre-packaged salad mix, raspberries, strawberries, basil, snow peas and mesclun lettuce have been involved in US outbreaks of cyclospora-related illness over the past decade. (Vignes-Kendrick et al. Outbreaks of cyclosporiasis- United States, June- August 2013. MMWR 62(43): 862).

Commentary: Cyclospora infection usually presents with dehydration secondary to explosive watery diarrhea and vomiting. It usually resolves in 6-7 weeks but prolonged infection may occur in HIV infected patients. According to CDC, there is no reported death due to cyclospora infection. While trimethoprim-sulfamethoxazole is the drug of choice, aggressive IV fluid replacement should be promptly instituted while managing these patients. MK.

Question 265: SGLT2 inhibitors may predispose some diabetic patients to the development of ketoacidosis. Patients with which form of diabetes (type I or Type II) are subject to this risk?

Answer: The cited reference points out that SGLT2 inhibitors may increase the risk of ketoacidosis in patients with both type I and Type II diabetes. (Taylor SI et al. SGLT2 inhibitors may predispose to ketoacidosis. 2015 J Clin Endocrinol Metab 100(8): 2849-2852).

Commentary: SGLT-2 inhibitors are recently approved for the treatment of diabetes mellitus type II. Seventy-three cases of ketoacidosis were reported to FDA Adverse Event Reporting System (FAERS) from March 2013 to May 2015. SGLT-2 inhibitors should be prescribed cautiously and patients should be educated about the risk of ketoacidosis while on this medication. The efficacy and safety of SGLT-2 inhibitors in DM type 1 is not yet established. MK.

Question 266: Which plant, consumed throughout the world for its stimulant effects and as an opioid substitute, is typically brewed into a tea, chewed, smoked or ingested in capsules and is also known as Thang, Kakuam, Thom, Ketum and Biak?

Answer: Kratom (Mitrayna speciosa) is consumed throughout the world for its stimulant effects and as an opioid substitute, is typically brewed into a tea, chewed, smoked or ingested in capsules and is also known as Thang, Kakuam, Thom,

Ketum and Biak. Some published case reports have associated kratom exposure with psychosis, seizures and death. (Anwar M et al.Notes from the Field: Kratom (Mitragyna speciosa) Exposures Reported to Poison Centers — United States, 2010–2015. MMWR July 29, 2016, 65(29):748-749).

Commentary: Kratom plant grows naturally in some countries in the Southeast Asia. It has stimulant and sedative affects. While stimulant effects appear in low doses, opioid-like effects may occur in moderate to high doses. The FDA has issued warning that the availability of kratom is recently increasing in the US. The US poison control centers received 660 cases of Kratom exposure from January 2010 to December 2015. MK.

Question 267: There have been 12 methylene chloride related deaths associated with professional bathtub refinishing operations during the years 2000–2011. What makes this profession especially vulnerable to the adverse effects of methylene chloride?

Answer: Methylene chloride is a highly volatile, colorless, potentially dangerous chemical that is widely used as a degreaser, process catalyst, and paint remover. Bathtub refinishers frequently use stripper compounds that contain this chemical. They often work in poorly ventilated small bathrooms and often do not wear appropriate respiratory protective gear. In addition, methylene chloride vapors are heavier than air and they likely remain in the bathtub after application. Further, the 1997 OSHA standard for methylene chloride requires air monitoring, medical surveillance, hazard communication, and personal protective equipment be in place where methylene chloride is used. The bathtub refinishing industry, in some cases, has fallen behind in maintaining this standard. (MMWR February 24,2012, 61(07):119-122).

Commentary: Methylene chloride is metabolized in the liver to form carbon monoxide and exposure may lead to carbon monoxide poisoning. The odor of methylene chloride is unreliable to detect its presence. RS.

Question 268: What is acrodynia and what are the clinical symptoms associated with this problem?

Answer: Acrodynia is a childhood affliction with symptoms that may include painful, red, swollen fingers and toes. One or all of these symptoms may occur in conjunction with photophobia, irritability, asthenia and hypertension. Acrodynia is believed to be a hypersensitivity reaction to mercury that was, in the past, usually caused by exposure to mercuric and mercurous salts. (Clarkson TW, et al. The toxicology of mercury- Current exposures and clinical manifestations. 2003 NEJM 349(18):1731-1737.).

Commentary: Acrodynia serves as a historical reminder of the childhood effects of mercury poisoning, as it is not commonly seen today. RS.

Question 269: What spider is known as the most dangerous spider in the world based on lethal dose studies conducted in animals?

Answer: The Australian funnel-web spiders (Atrax and Hadronyche spp., Hexathelidae) are known as the most dangerous spider in the world based on lethal dose studies conducted in animals. (Vetter RS and Isbister GK. Medical aspects of spider bites. 2008 Annu Rev Entomol, 53:409-429).

Commentary: Spider envenomations are common so it is worth knowing the most lethal envenomation (Australian funnel-web spider) and geographical distribution (Australia). RS.

Question 270: Mesenteric venous thrombosis (MVT) is a known cause of intestinal ischemia and accounts for roughly 15% of all cases of mesenteric ischemia. In approximately 75% of cases of MVT, a prothrombotic state can be identified with coagulation disorders, neoplasia, intra-abdominal inflammatory states and portal hypertension among the most commonly reported causes. While MVT is most common in the 6 th to 7th decade of life, young women have been reported to suffer from this disorder as well. Which pharmacological agents have been associated with the development of MVT in young women?

Answer: In young females, the use of oral (as well as transdermal patch and vaginal ring) contraceptives reportedly accounts for up to 18% of cases of MVT. (Eilbert W et al. Acute mesenteric venous thrombosis with a vaginal ring contraceptive. 2014 Western J Med 15(4): 395-397).

Commentary: MVT symptoms are usually present for a longer duration as compared to typical acute mesenteric ischemia. Prompt initiation of heparin to halt further thrombus formation may increase survival.

Question 271: What is “snake wine”?

Answer: According to the cited reference, “snake wine” is a beverage that “contains more than 45% ethanol and whole venomous snakes”. These authors further note: “Snake wine is generally preserved in an airtight, sealed container before it is drunk. Snake wine is consumed in certain Asian countries, including South Korea, for its presumed effect of invigorating ones energy level.” The cited reference reports on severe coagulopathy after the ingestion of “snake wine”. (Moon JM and Chun BJ. Severe coagulopathy after the ingestion of “snake wine” 2016 J Emerg Med 50(6): 848-851).

Commentary: Snake wine is used for traditional medicinal purposes and enhancing sexual performance. It is commonly thought that the snake venom would be denatured by the presence of 45% ethanol and gastric acid. MK.

Question 272: What are the clinical hallmarks of acyclovir-induced neurotoxicity and how is the diagnosis confirmed?

Answer: According to the cited reference the “Presenting symptoms are neuropsychiatric and include disturbances in consciousness, myoclonus, seizures, coma, and death delusions. Most commonly, patients have had a preceding herpes zoster infection that has been treated with dosages of oral acyclovir or valacyclovir that were not properly calculated based

on their level of renal dysfunction. Symptoms typically occur after the third or fourth dose and are rapidly progressive, especially if drug administration continues." These authors further point out that.

"Once acyclovir-induced neurotoxicity is suspected, the diagnosis can be confirmed by identifying elevated cerebrospinal fluid levels of the acyclovir metabolite 9- carboxymethoxymethylguanine (9-CMMG). (Gentry JL and Peterson C. Death delusions and myoclonus: Acyclovir toxicity. 2015 Am J Med 128(7): 692-694).

Commentary: Phlebitis may occur secondary to IV administration of acyclovir. Renal dosing adjustment is mandatory in patients with renal dysfunction as high-dose chronic therapy may cause crystalluria. In April 2013, muco-adhesive acyclovir tablets were approved by the FDA for recurrent herpes libialis. MK.

Question 273: The ingestion of multiple small magnets (or toys containing magnets) can lead to a number of important gastrointestinal complications. What are they?

Answer: Following ingestion of multiple small magnets the cited reference notes "When aligned, the force between magnets pulls bowel walls together, exerting pressure and causing obstruction, necrosis, fistula, and peritonitis from perforation". (Brown DJ. Small bowel perforation caused by multiple magnet ingestion. 2010 J Emerg Med 39(4):497-498).

Commentary: Single magnet ingestions are relatively benign, however a multiple magnet ingestion has the potential for severe complications. RS.

Question 274: Black pigmentation of the tongue has been reported to be associated with which drug used to treat dyspepsia? What is the mechanism for the production of this black pigmentation and how does this drug-related hyperpigmentation differ from so-called "black hairy tongue"?

Answer: Bismuth subsalicylate use has been reported to cause black pigmentation of the tongue. According to the cited reference "Anaerobic bacteria in the mouth are able to produce hydrogen sulfide. Bismuth subsalicylate can react with the hydrogen sulfide to produce bismuth sulfide. Bismuth sulfide is a highly insoluble black salt that is responsible for producing the darkening of the tongue in these individuals." This drug related lingual hyperpigmentation differs from "black hairy tongue" in that acquired (due to drugs) black tongue does not involve enlargement of the filiform papillae of the tongue that is typical of black hairy tongue. (Cohen PR. Black tongue secondary to bismuth subsalicylate: Case report and review of exogenous causes of macular lingual pigmentation. 2009 J Drugs Derm 8(12): 1132-1137).

Commentary: Bismuth salicylate is found in Pepto Bismol, a common over-the-counter antidiarrheal medication in the US. Reyes syndrome is a potential complication that may occur following bismuth salicylate administration during a viral illness in children. MK.

Question 275: What are erabutoxins?

Answer: Erabutoxins are neurotoxins isolated from the venom of certain sea snakes including the sea snake Laticuada semifasciata. The cited reference notes "The short neurotoxins to which erabutoxins belong act by blocking the nicotinic acetylcholine receptor on the post synaptic membrane in a manner similar to that of curare." (Tamiya N and Yagi T. Studies on sea snake venom.2011 Proc Jpn Acad Ser B 87(3): 41-52).

Commentary: Sea snakes belong to the family Hydrophidae. These snakes should be handled with caution since the venomous bite may be painless. Envenomation may cause myotoxicity and neurotoxicity. Symptoms may be delayed for up to 6 hours. Prompt consultation with a toxicologist should be made as administration of antivenom may be necessary. MK.

Question 276: What is the probable cause for the green colored urine that can sometimes be seen in patients who have received the drug propofol?

Answer: According to the cited reference: "Propofol is metabolized in the liver and excreted in the urine predominantly as the 1-glucuronide, 4-glucuronide and 4-sulfate conjugates of 2,6- diisopropyl-1,4 quinol. Green discoloration of urine is attributed to the presence of these phenolic metabolites." These authors also note "In addition to urine, reports of green discoloration of the hair and liver after propofol administration implicate these phenols." (Blakey SA and Hixson-Wallace JA. Clinical significance of rare and benign side effects: propofol and green urine. 2000 Pharmacotherapy 20(9): 1120-1122).

Commentary: Green discoloration of urine may be caused by some commonly used medications that include indomethacin, metoclopramide and amitriptyline. Propofol has also been reported to cause pink and white discoloration of urine. MK.

Question 277: Some resources recommend the topical application of vinegar to treat jellyfish stings in North America and Hawaii. Why may this not represent optimal therapy?

Answer: A recent systematic review of the treatment of jellyfish stings in North America and Hawaii suggests "vinegar may not be an ideal agent because it causes pain exacerbation or nematocyst discharge in most species except Physalia". The authors report that the application of lidocaine and hot water are the better treatment alternative but point out that these modalities may not always be available in the field. (Ward N, et al. Evidence-based treatment of jellyfish stings in North America and Hawaii. 2012 Ann Emerg Med 60(4):399-414).

Commentary: Jellyfish stings are common in North America and may be painful. Tentacles may be removed using a firm flat surface tool such as credit card or a razor. RS.

Question 278: What is "mad honey poisoning"?

Answer: According to the cited reference "mad honey poisoning" is little known outside of the country Turkey, but it is a well-described condition presenting with incapacitating and sometimes life threatening bradycardia, hypotension,

respiratory depression and altered mental status. Poisoning occurs when grayanotoxin from the pollen and nectar of certain members of the family Ericaceae, especially Rhododendron L. species, enters the human food supply as “deli bah” (in Turkish) or “mad honey”. (Gunduz A, et al. Clinical review of grayanotoxin/mad honey poisoning past and present. 2008 Clin Tox 46(5):437-442).

Commentary: Grayanotoxin is the toxin responsible for causing “mad honey poisoning. It prevents the inactivation of sodium ion channels that leads to the toxic effects. RS.

Question 279: What is a NIOSH “Health Hazard Evaluation” (HHE)? Who is permitted to request such an evaluation?

Answer: An HHE is a study of a workplace. It is done to learn whether workers are exposed to hazardous materials or harmful conditions. In private sector and Federal workplaces an employee can request an HHE if he or she is currently an employee at the workplace of concern and has the signatures of two other employees. If the workplace has three or fewer employees, the signature of only one employee is enough. An officer of a labor union that represents employees for collective bargaining can request an HHE. Any management official may request an HHE on behalf of the employer. When the workplace is part of a State or local government, NIOSH authority is more limited than for the private and Federal sectors. The cooperation of the employer may be necessary before NIOSH can do an evaluation. (http://www.cdc.gov/niosh/hhe/HHEprogram.html; accessed January, 2015).

Commentary: HHE’s are an important tool to identify and help control any work-related health hazards. The HHE Program is not an enforcement or rule-making program and does not issue fines or citations to workplaces. It does however generate a public report including recommendations on ways to reduce or eliminate any identified hazards. RS.

Question 280: What is the HSDB database?

Answer: HSDB is the Hazardous Substances Data Bank. It is a toxicology database that focuses on the toxicology of potentially hazardous chemicals. It provides information on human exposure, industrial hygiene, emergency handling procedures, environmental fate, regulatory requirements, nanomaterials, and related areas. The information in HSDB has been assessed by a Scientific Review Panel. The HSDB Scientific Review Panel meets several times yearly to review selected substances, add new records, and update records, as needed(http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB; accessed March 2015).

Commentary: This database is a free, useful resource for healthcare professionals to utilize for patient care. Users can search by chemical or other name, chemical name fragment, Chemical Abstracts Service Registry Number (RN), and/or subject terms. RS.

Question 281: The over-ingestion of black tea has been reported to be causative of acute renal failure. What is the basis for this potential association?

Answer: According to the cited reference, “Black tea is a rich source of oxalate, containing 50-100 mg per mL”. These authors point out that more than 80% of tea consumed in the United States is black tea. They report a case of acute renal failure in an individual who consumed 16 cups of black tea daily and they posit that this excessive intake of black tea caused oxalate-induced acute renal failure in a 56-year-old male. (Syed F and Mena-Gutierrez A. A case of iced-tea nephropathy. 2015 NEJM 371(14): 1377-1378).

Commentary: Other dietary causes of acute oxalate nephropathy include Averrhoa carambola (star fruit), A. bilimbi (cucumber tree fruit), rhubarb, and peanuts. Gastric bypass surgery, absorbic acid, and ethylene glycol are also associated with hyperoxaluria. RS.

Question 282: What is the likely pathophysiology of vancomycin-related “red man syndrome” (RMS)?

Answer: According to the cited reference: “RMS is believed to be an anaphylactoid type of reaction due to vancomycin-induced direct mast cell degranulation. It has been shown to be associated with a rise in blood histamine level in some studies, however conflicting data exist. Increasing evidence suggest that altered histamine metabolism may contribute to the pathogenesis of hypersensitivity reactions including RMS.” (Myers AL et al. Defining risk factors for red man syndrome in children and adults. 2013 Pediatr Infect Dis 31:464-468).

Commentary: Vancomycin is nephrotoxic and ototoxic. Serial serum levels should be done to avoid toxic effects. Pretreatment with anti-histamine may decrease the incidence of RMS. Treatment for RMS includes slowing the IV infusion. MK.

Question 283: Tick paralysis results from the secretion of a neurotoxin and is not an infectious disease. Which species of tick have been associated with the development of tick paralysis in humans and how long after initial attachment does this paralysis usually have its onset?

Answer: A number of tick species have been associated with the development of paralysis in humans including Dermacentor, Amblyomma and Ixodes. According to the cited reference, paralysis usually begins within 48 hours to 6 days following attachment of the tick. (Pecina CA Tick paralysis. 2012 Semin Neurol 32(5): 531-532 and Green WL and Millsap WG Tick-borne illness. 2016 Crit Dec in Emerg Med30(1):3-9).

Commentary: The neurotoxicity in tick paralysis occurs secondary to ixobotoxin that inhibits the acetylcholine release at neuromuscular junction. Similar to Guillian-Barre Syndrome, ascending paralysis with respiratory insufficiency may occur but ocular findings distinguish tick paralysis from GBS. The definitive treatment is removal of the tick. MK.

Question 284: The epidemic use of opioids is widely discussed with regard to prescription opioids. However the use of raw opium is also widespread and has been estimated to be used by at least four million people worldwide. The use of raw opium has been associated with the development of which forms of cancer?

Answer: According to the cited systematic review, "Opium use was associated with an increased risk of cancers of the oesophagus, stomach, larynx, lung, and urinary bladder." These authors point out "Although the present evidence suggests that these associations are possibly causal, further epidemiological studies (particularly prospective studies that collect detailed data about lifetime opium use and control for a broad range of potential confounders) are needed." (Kamangar F. et al. Opium use: an emerging risk for cancer. 2014 Lancet Oncol 15: e69-77).

Commentary: Medicinal and recreational use of opium is widespread in other countries. Little is known about the carcinogenic effect of raw opium. MK.

Question 285: What are so-called "burn pits"? What are the potential adverse health consequences associate with burn pits?

Answer: Burn pits are open-air waste burning location often used by deployed military personnel when other waste disposal options are not available. The U.S. military has utilized burn pits in both Afghanistan and Iraq until their use was restricted in 2009. However burn pits continue to be used in Afghanistan as recently as January 2011. Due to the potential for generation of toxic pyrolysis products and the potential for human exposure, the Institute of Medicine has recently studied burn pit exposures for military personnel. The US Army Public Health Command recently reported that the "risks of acute health effects of all chemicals detected, except coarse particulate matter (PM) was low and that long term health risks were "acceptable". ("Featured for the Institute of Medicine": Long-term health consequences of exposure to burn pits in Iraq and Afghanistan. 2015 Military Medicine 180(6): 601-603).

Commentary: "Burn pits" are an important occupational toxicological exposure among military personnel. The cited reference concluded that "studies did not yield conclusive results about long-term health effects associated with exposure to combustion products in the populations studied, but several health outcomes [such as respiratory, neurological, and cardiovascular outcomes] deserve further investigation." RS.

Question 286: What is Stoddard Solvent?

Answer: Stoddard solvent is a colorless, flammable liquid that smells and tastes like kerosene. It will turn into a vapor at temperatures of 150-200°C. Stoddard solvent is a petroleum mixture that is also known as dry cleaning safety solvent, petroleum solvent, and varnoline; its registered trade names are Texsolve S® and Varsol 1®. It is a chemical mixture that is similar to white spirits. Stoddard solvent is used as a paint thinner; in some types of photocopier toners, printing inks, and adhesives; as a dry cleaning solvent; and as a general cleaner and degreaser. (http://www.atsdr.cdc.gov/substances/toxsubstance.asp?toxid=73;accessed March 2016).

Commentary: Exposure to Stoddard solvent may cause mucosal irritation and CNS findings such as dizziness or headaches. RS.

Question 287: Blue cohosh (Caulophyllum thalictroides (L.) Michx.; C. giganteum (Farw.) Loconte &W.H. Blackw; Family Berber- idaceae) is a plant that has been used by Native Americans, midwives and herbal medicine practitioners. What potential therapeutic actions have traditionally been ascribed to the use of blue cohosh?

Answer: The therapeutic actions that have traditionally been ascribed to the use of blue cohosh include use as: an abortifacient, emetic, anti- inflammatory, emmenagogue, anti-pyretic, diuretic, expectorant, hypoglycemic, spasmogenic, uterotonic, and vaso-constrictor, among many others. (radder JI and Pawar RS. Primary constituents of blue cohosh: quantification in dietary supplements and potential for toxicity. 2013 Anal Bioanal Chem 405:4409-4417).

Commentary: Blue cohosh, also called squaw root or papoose root, is endemic to the eastern United States. RS.

Question 288: What is the "MOTHER project"?

Answer: The MOTHER project (Maternal Opioid Treatment: Human Experimental Research project) is a multi-center, randomized, double-blind, double-dummy, flexible-dosing, parallel-group clinical trial examining the comparative safety and efficacy of methadone and buprenorphine for the treatment of opioid dependence in pregnant women and their neonates. One of the conclusions of the MOTHER project as published in the cited reference is that the "results are consistent with the use of buprenorphine as an acceptable treatment for opioid dependence in pregnant women." (Jones HE, et al. Neonatal abstinence syndrome after methadone or buprenorphine exposure. 2010 NEJM 363:2320-2331).

Commentary: Neonatal abstinence syndrome (NAS) is a potential complication in opioid-dependent mothers. Symptoms include irritability, seizures, and tremors. MK.

Question 289: What is microcystin toxin?

Answer: Microcystin is a hepatoxin released by cyanobacteria in certain harmful algal blooms. Exposure to microcystin has been associated with gastrointestinal and hepatic illness in both humans and animals. (McCarty CL et al. Community Needs Assessment After Microcystin Toxin Contamination of a Municipal Water Supply — Lucas County, Ohio, September 2014. MMWR September 9, 2016, 65(35): 925-929).

Commentary: Harmful algal blooms and the microcystin toxin they produce may contaminate water and cause hepatotoxicity. Prompt public health communication and awareness should be provided in case of community water contamination with these toxins. MK.

Question 290: Para-phenylenediamine (PPD) is often added to henna temporary tattoo solutions in order to decrease application time and to intensify the color. What clinical complications may be associated with the presence of PPD in henna tattoos?

Answer: The authors of the cited reference indicate that PPD "is responsible for most of the complications reported after henna tattoos: localized or generalized contact dermatitis, hypertrophic or keloid scars, and temporary or permanent hyper- or hypopigmentation. More rarely, type I hypersensitivity reactions (urticaria, angioedema, or anaphylaxis) with potentially lethal outcomes have been reported." (Kluger N et al. Tatouages temporaires au henne: des effects indesirables parfois graves. 2008 Presse Med 37:1138-1142).

Commentary: Physicians should be aware of the health hazards unique to henna, as the author reports its use is increasing in popularity. RS.

Question 291: The reference cited below notes "Scombroid poisoning occurs after the ingestion of fresh, canned or smoked fish with high histamine levels due to improper processing or storage." What are the effects of high levels of histamine in fish meat with regard to appearance, taste and smell of the fish?

Answer: The cited reference states " Scombroid poisoning is frequently misdiagnosed. Because histamine does not alter the organoleptic quality, the fish may seem normal. However, elevate histamine levels can occur in fish owing to improper refrigeration before processing or to storage of the fish at room temperature after cooking. Therefore, the appearance, taste and smell of the fish are poor guides as to the presence of histamine." (Stratta P and Badino G. Five things to know about Scombroid poisoning. 2012 CMAJ 184(6): 674).

Commentary: Symptoms of scombroid poisoning are secondary to histamine release and may include urticaria, flushing, dizziness, and sweating. Symptoms typically develop within 90 minutes of eating the implicated fish. RS.

Question 292: According to the reference cited below, "Mercury, particularly methylmercury, is known to be neurotoxic to humans. Vulnerability of the central nervous system to these substances is increased during early development, especially during the prenatal period." What is currently considered to be the major source for human exposure to mercury?

Answer: The cited reference notes "Diet is currently considered the major source contributing to mercury exposure levels, especially consumption of marine species. Predatory fish such as swordfish, shark, and tuna have the highest concentrations of methylmercury. Moreover, methylmercury bioaccessibility in these fishes, for example, swordfish, may reach 94%. Several studies have confirmed a relation between mercury blood levels in humans and fish consumption. (Llop S et al. Prenatal exposure to mercury and infant neurodevelopment in a multicenter cohort in Spain: Study of potential modifiers. 2012 Am J Epidem 175(5): 451-465).

Commentary: Epidemiologic studies have been conducted on fish-eating populations in order to identify an association of chronic mercury exposure and cognitive development. Two of the most famous of these studies occurred in the Seychelles and Faroe Islands and they produced conflicting evidence regarding if a significant association exists (Steuerwald U et al. Maternal seafood diet, methylmercury exposure, and neonatal neurologic function. 2000 The Journal of pediatrics. 136 (5):599-605. Davidson PW et al. Neurodevelopmental effects of maternal nutritional status and exposure to methylmercury from eating fish during pregnancy. 2008 Neurotoxicology. 29(5):767-775). RS.

Question 293: What is "progressive massive fibrosis" (PMF)?

Answer: The cited reference reports "Coal workers' pneumoconiosis, also known as "black lung disease," is an occupational lung disease caused by overexposure to respirable coal mine dust. Inhaled dust leads to inflammation and fibrosis in the lungs, and coal workers' pneumoconiosis can be a debilitating disease. The Federal Coal Mine Health and Safety Act of 1969 (Coal Act), amended in 1977, established dust limits for U.S. coal mines and created the National Institute for Occupational Safety and Health (NIOSH)–administered Coal Workers' Health Surveillance Program with the goal of reducing the incidence of coal workers' pneumoconiosis and eliminating its most severe form, progressive massive fibrosis (PMF), which can be lethal. The prevalence of PMF fell sharply after implementation of the Coal Act and reached historic lows in the 1990s, with 31 unique cases identified by the Coal Workers' Health Surveillance Program during 1990–1999. Since then, a resurgence of the disease has occurred, notably in central Appalachia. This report describes a cluster of 60 cases of PMF identified in current and former coal miners at a single eastern Kentucky radiology practice during January 2015–August 2016. This cluster was not discovered through the national surveillance program. This ongoing outbreak highlights an urgent need for effective dust control in coal mines to prevent coal workers' pneumoconiosis, and for improved surveillance to promptly identify the early stages of the disease and stop its progression to PMF." (Blackley DJ et al. Resurgence of Progressive Massive Fibrosis in Coal Miners — Eastern Kentucky, 2016. Dec 16, 2016 MMWR 65(49):1385-1389).

Commentary: The cited reference emphasizes that "effective dust control, enhanced educational outreach, and improved surveillance are needed to protect the respiratory health of U.S. coal miners." RS.

Question 294: What is the mechanism for QT prolongation in cases of quetiapine overdose?

According to the cited reference "QT-prolongation may occur with any pharmaceutical substances inhibiting potassium efflux in cardiac myocytes, including quetiapine. Sodium channel blocker toxicity, often described as 'membrane stabilizing effects', can be seen on the ECG as a widening of the QRS complex. Among the substances with these effects are local anesthetics, tricyclic antidepressants, quinine, propranolol and verapamil. QRS widening is uncommon in quetiapine poisoning, but has been reported in some cases. Quetiapine is a tricyclic compound, and it is structurally related to some agents with membrane stabilizing effects. Still the mechanism for QRS widening in the case of quetiapine intoxication remains

unexplained." (Lannemyr L and Knudsen K. Severe overdose of quetiapine treated successfully with extracorporeal life support. 2012 Clin Tox 50(4): 258-261).

Commentary: Seroquel has affinity for several other receptors and in addition to QT prolongation, toxicity may also produce anticholinergic symptoms, extrapyramidal symptoms, and hypotension. RS.

Question 295: A recent report (see citation below) described "ocular flutter" as a rare manifestation of the serotonin syndrome. What is ocular flutter?

Answer: "Nystagmus refers to eye movement abnormalities that are characterized by an abnormal slow phase followed by either a slow phase or a fast phase. Saccadic intrusions, on the other hand, are abnormal eye movements that have a pathologic fast saccade followed by a fast corrective saccade, with or without an intersaccadic interval. Ocular flutter, by contrast, is clinically characterized by intermittent bursts of conjugate, horizontal saccades without an intersaccadic interval." (Kruger JM et al. Ocular flutter as the presenting sign of adenocarcinoma 2014 Digital J Ophthalmology and Sim SS and Sun JT. Ocular flutter in the serotonin syndrome. 2016 NEJM 375e38).

Commentary: Additional clinical findings that may occur with serotonin syndrome include altered mental status, autonomic instability, and neuromuscular changes. Critically ill patients may present with hyperthermia that may require neuromuscular blockade to effectively eliminate muscular activity and successfully cool (Boyer EW and Shannon M. The Serotonin Syndrome. 2005 NEJM. 352:1112-1120.) RS.

Question 296: What is the most common cause of acquired nephrogenic diabetes insipidus? What is the current management for this problem?

Answer: According to the cited reference, "The most common cause of acquired nephrogenic diabetes insipidus is long-term lithium treatment. The management of lithium-induced nephrogenic diabetes insipidus is challenging, even when the drug is discontinued and therapy is changed to thiazide diuretics, amiloride, and reduced sodium intake. Amiloride inhibits lithium entry into renal collecting-duct cells through the epithelial sodium channel. Thiazide diuretics and a low-sodium diet result in hypovolemia-induced activation of the renin–angiotensin–aldosterone which stimulates proximal tubule sodium and water resorption resulting in less volume delivery to the distal nephron." (Gordon CE et al. Acetazolamide in lithium-induced nephrogenic diabetes insipidus. 2016 NEJM 375:2008-2009 and Sands JM and Bichet DG. Nephrogenic diabetes insipidus. Ann Intern Med 2006;144:186-94).

Commentary: Lithium is widely used for the treatment of bipolar disorders. Chronic lithium use may also cause endocrinology dysfunction including hypothyroidism. RS.

Question 297: What are so-called "red tides"? What toxins have been associated with "red tides" and what human health effects have reportedly resulted from inhalational exposure to "red tides"?

Answer: "Red tides" are the manifestation of so-called oceanic "harmful algal blooms" and are caused by dinoflagellates that produce brevetoxins which are potent neurological toxins. The cited reference notes "Exposure to seafood contaminated by brevetoxins is associated with neurotoxic shellfish poisoning in humans and the inhalation of aerosols containing these toxins has been reported to cause various degrees of respiratory irritation as well as asthma." (Fleming LE et al. Exposure and effect assessment of aerosolized red tide toxins and asthma. 2009 Env Health Perspectives 117:1095-1100).

Commentary: Harmful algal blooms are of increasing concern in environmental health and toxicology. Florida "red tides" are of particular concern as they "cause the death of millions of fish in the Gulf of Mexico, as well as morbidity and mortality among marine animals and sea birds." RS.

Question 298: What characteristics differentiate rodenticide superwarfarins from warfarin?

Answer: (1)Greater affinity for vitamin K¬12-3-epoxide reductase; (2) the ability to disrupt the vitamin K1-epoxide cycle at more than one point; (3) hepatic accumulation; and (4) unusually long biological half-lives due to high lipid solubility and enterohepatic circulation have been credited for the greater potency and duration of action of the long-acting anticoagulant rodenticides. Watt, B. E., A. T. Proudfoot, et al. (2005). Anticoagulant rodenticides. Toxicol Rev 24(4): 259-69.

Commentary: Superwarfarins are widely used as rodenticides. A primary clinical difference between superwarfarins and warfarins is bleeding may be delayed up to weeks or months with superwarfarins. RS.

Question 299: PRES or posterior reversible encephalopathy syndrome is characterized by confusion, headache, altered mental status, seizures, and visual disturbances in conjunction with MRI findings consistent with vasogenic edema especially involving the occipito-parietal areas of the brain. The use of which drugs has been implicated in the development of PRES?

Answer: PRES has been associated with the use of immunosuppressant agents and certain chemotherapeutic drugs as well as a variety of medical conditions including sepsis, autoimmune disease, renal disease, eclampsia, and hypertensive encephalopathy. The cited article posits that PRES may also be related to the use of nitrite containing inhalants. (Casetta I, et al. An acutely confused young woman. 2011 The Lancet, 378(9789):456).

Commentary: The pathophysiology of PRES is not fully understood however the cited article identifies the "ultimate underlying process seems to be an increase in capillary hydrostatic pressure or endothelial dysfunction with a breakdown of the blood-brain barrier." RS.

Question 300: How is isopropyl alcohol poisoning typically diagnosed?

Answer: According to the cited reference, "Poisoning can be diagnosed using the measurement of isopropanol serum concentrations, though these may not be readily available. Diagnosis is therefore more typically made on the basis of the patient's history and clinical presentation. An osmol gap, ketonemia, and/or ketonuria without metabolic acidosis, along with a fruity or sweet odor on the breath and CNS depression support the diagnosis." (Slaughter RJ et al. Isopropanol poisoning. 2014 Clin Tox 52(5): 470-478).

Commentary: Isopropyl alcohol is found in many household products including rubbing alcohol, cleaners, disinfectants, cosmetics, and solvents. The treatment for isopropyl alcohol toxicity is primarily supportive.