

AMERICAN ACADEMY OF CLINICAL TOXICOLOGY  
HERBS & DIETARY SUPPLEMENTS SPECIAL INTEREST GROUP  
Abstracting Service

March 1, 2009

1. Vassilev ZP, Chu AF, Ruck B, Adams EH, Marcus SM. Evaluation of adverse drug reactions reported to a poison control center between 2000 and 2007. *Am J Health Syst Pharm.* 2009;66(5):481-7. PMID: 19233996  
PURPOSE: The likelihood of hospitalization caused by adverse drug reactions (ADRs) from commonly implicated therapeutic groups is discussed. METHODS: A retrospective analysis of the computerized records of exposure cases involving pharmaceutical substances reported to the New Jersey Poison Information and Education System (NJPIES) was conducted from 2000 through 2007. The cases in the National Poisoning Data System that were categorized as an ADR were included in the study set. Only reports involving a single drug were selected for inclusion in the analyses. Characteristics of the ADRs, such as the sex and age of the patient, the therapeutic group involved, and the medical outcome of the exposure, were examined. Reports of ADRs with the most frequently implicated therapeutic groups were analyzed based on whether the patients were managed onsite, referred to a health care facility, or managed at a health care facility. The Adverse Drug Reaction Hospitalization (ADRH) index was calculated for all therapeutic groups, but the focus of the analyses was on the groups that were implicated in 5% or more of all ADRs. RESULTS: A total of 454,520 cases of human poisoning exposure were reported to NJPIES from 2000 through 2007. Of these cases, 162,105 were exposures implicating a single drug, of which 5,461 (3.4%) were classified as an ADR. Of the 5,461 cases, 385 patients were admitted into a health care facility. Antidepressants had the highest ADRH index (20.4%) among the therapeutic groups implicated, and antimicrobials had the lowest (2.2%). CONCLUSION: The analyses revealed a substantial variation in the likelihood of hospitalization associated with ADRs within different therapeutic groups. Among the groups that were most frequently implicated in ADRs, antidepressants showed the highest probability for an ADR-related hospitalization, followed by dietary supplements, herbals, and homeopathics and then by sedatives, hypnotics, and antipsychotics.
2. Schilling LM, Dellavalle RP. Dealing with unanticipated mortality in a large randomized clinical trial of topical tretinoin. *Arch Dermatol.* 2009;145(1):76. PMID: 19153348
3. Hidaka T, Fujii K, Funahashi I, Fukutomi N, Hosoe K. Safety assessment of coenzyme Q10 (CoQ10). *Biofactors.* 2008;32(1-4):199-208. PMID: 19096117  
Coenzyme Q10 (CoQ10) is a naturally occurring component present in living cells. Its physiological function is to act as an essential cofactor for ATP production, and to perform important antioxidant activities in the body. In most countries, CoQ10 has been widely used as a dietary supplement for more than 20 years. Recently, the use of CoQ10 as a dietary supplement has grown with a corresponding increase in daily dosage. The present review describes the safety profile of CoQ10 on the basis of animal and human data. The published reports concerning safety studies indicate that CoQ10 has low toxicity and does not induce serious adverse effects in humans. The acceptable daily intake (ADI) is 12mg/kg/day, calculated from the no-observed-adverse-effect level (NOAEL) of 1200 mg/kg/day derived from a 52-week chronic toxicity study in rats, i.e., 720 mg/day for a person weighing 60 kg. Risk assessment for CoQ10 based on various clinical trial data indicates that the observed safety level (OSL) for CoQ10 is 1200 mg/day/person. Evidence from pharmacokinetic studies suggest that exogenous CoQ10 does not influence the biosynthesis of endogenous CoQ9/CoQ10 nor does it accumulate into plasma or tissues after cessation of supplementation. Overall, these data from preclinical and clinical studies indicate that CoQ10 is highly safe for use as a dietary supplement. Additionally, analysis of CoQ10 bioavailability or its pharmacokinetics provides the pertinent safety evaluation for CoQ10.
4. Carey JC, Martinez L, Balken E, Leen-Mitchell M, Robertson J. Determination of human teratogenicity by the astute clinician method: review of illustrative agents and a proposal of guidelines. *Birth Defects Res A Clin Mol Teratol.* 2009;85(1):63-8. PMID: 19107954  
BACKGROUND: The determination that an exposure is a human teratogen is a complex process

involving the application of the principles of teratology, epidemiology, biology, and clinical medicine. Shepard suggested that the "rare exposure/rare defect" or "case report method", the astute clinician model, was one approach for establishing teratogenicity. The purpose of this article is to review selected exposures with the goal of identifying principles that lead to a working proposal for the application of this approach. **METHODS:** We selected three known exposures--penicillamine, fluconazole and mycophenolate mofetil--for detailed review. These agents were chosen because their evidence for causation arises mostly from clinical observations in the context of biologic plausibility. **RESULTS:** All three agents were originally detected based on astute observations by clinicians reporting on individual cases of a distinctive pattern of malformation or, in the case of penicillamine distinctive phenotype, after the rare exposure. All three have varying degrees of biologic evidence that support the hypothesis that each represents a human teratogen. All three meet Shepard's criteria for "proof." **CONCLUSIONS:** The basic premise of this approach depends on the rarity of both the exposure and the outcome. We propose guidelines for utilization of this approach in the determination of human teratogenicity.

5. Liu Q, Garner P, Wang Y, Huang B, Smith H. Drugs and herbs given to prevent hepatotoxicity of tuberculosis therapy: systematic review of ingredients and evaluation studies. *BMC Public Health*. 2008;8(365). PMID: 18939987  
**BACKGROUND:** Drugs to protect the liver are frequently prescribed in some countries as part of treatment for tuberculosis. The biological rationale is not clear, they are expensive and may do harm. We conducted a systematic review to a) describe the ingredients of "liver protection drugs"; and b) compare the evidence base for the policy against international standards. **METHODS:** We searched international medical databases (MEDLINE, EMBASE, LILACS, CINAHL, Cochrane Central Register of Controlled Trials, and the specialised register of the Cochrane Infectious Diseases Group) and Chinese language databases (CNKI, VIP and WanFang) to April 2007. Our inclusion criteria were research papers that reported evaluating any liver protection drug or drugs for preventing liver damage in people taking anti-tuberculosis treatment. Two authors independently categorised and extracted data, and appraised the stated methods of evaluating their effectiveness. **RESULTS:** Eighty five research articles met our inclusion criteria, carried out in China (77), India (2), Russia (4), Ukraine (2). These articles evaluated 30 distinct types of liver protection compounds categorised as herbal preparations, manufactured herbal products, combinations of vitamins and other non-herbal substances and manufactured pharmaceutical preparations. Critical appraisal of these articles showed that all were small, poorly conducted studies, measuring intermediate outcomes. Four trials that were described as randomised controlled trials were small, had short follow up, and did not meet international standards. **CONCLUSION:** There is no reliable evidence to support prescription of drugs or herbs to prevent liver damage in people on tuberculosis treatment.
6. Nah SY, Bhatia KS, Lyles J, Ellinwood EH, Lee TH. Effects of ginseng saponin on acute cocaine-induced alterations in evoked dopamine release and uptake in rat brain nucleus accumbens. *Brain Res*. 2009;1248(184-90). PMID: 19026615  
In traditional medicine, Panax ginseng has been used to treat various behavioral effects of psychostimulants (e.g., cocaine) and other drugs of abuse and to ameliorate withdrawal symptoms. The neurochemical bases for this efficacy, however, remain to be elucidated. We previously used the real-time fast-scan cyclic voltammetry in rat nucleus accumbens slices to demonstrate that cocaine not only enhances DA release evoked by single-pulse electrical stimulation and inhibits DA uptake during application but also further increases the release upon washout (termed a "rebound" release enhancement). In the present study, we determined whether co-application and washout of ginseng total saponin (GTS), the active ingredient of Panax ginseng, with cocaine attenuate cocaine-induced enhancement of evoked DA release, DA uptake inhibition and/or withdrawal-associated rebound enhancement. Cocaine rapidly potentiated the DA release within the first 10 min of application, and acute cocaine withdrawal caused a rebound increase. Co-application of GTS with cocaine inhibited the release enhancement and subsequently prevented the rebound increase during acute withdrawal. The effect of GTS was concentration-dependent. In contrast, GTS had no significant effects on the cocaine-mediated DA uptake inhibition. These results suggest that the attenuation of the cocaine-induced enhancement of impulse-dependent DA release, rather than uptake inhibition, might be one of the pharmacological bases for attenuation of behavioral effects of cocaine and amelioration of acute withdrawal symptoms by ginseng.

7. Shilova IV, Zhavoronok TV, Souslov NI, Novozheeva TP, Mustafin RN, Losseva AM. Hepatoprotective properties of fractions from meadowsweet extract during experimental toxic hepatitis. *Bull Exp Biol Med.* 2008;146(1):49-51. PMID: 19145348  
Fractions of the extract from meadowsweet aerial parts in 70% ethanol exhibited hepatoprotective properties during CCl<sub>4</sub>-induced toxic hepatitis. This extract produced a normalizing effect on activity of enzymes, markers of cytolysis, lipid peroxidation, and antioxidant defense system in liver cells. Fractionation of the extract was accompanied by dissociation of the effect. These changes reflect specific action of a complex of bioactive substances. The ethyl acetate and chloroform fractions from this extract were most potent. The effectiveness of these fractions by several parameters surpassed that of Carsil.
8. Ghiotto N, Sances G, Galli F, Tassorelli C, Guaschino E, Sandrini G, Nappi G. Medication overuse headache and applicability of the ICHD-II diagnostic criteria: 1-year follow-up study (CARE I protocol). *Cephalalgia.* 2009;29(2):233-43. PMID: 19025549  
Medication overuse headache (MOH) is a growing problem worldwide and a challenge for clinicians and investigators. This study aims to contribute to the ongoing debate surrounding the classification of MOH. Applying the revised diagnostic criteria for MOH contained in the updated International Classification of Headache Disorders (ICHD-II), we enrolled 140 probable MOH (p-MOH) patients. They were submitted to an in-patient detoxification protocol and re-examined 2, 6 and 12 months later to confirm, or otherwise, the diagnosis of MOH and to observe the evolution of their headache. MOH diagnosis was confirmed 2 months after detoxification in 71% of patients, who reverted to an episodic headache pattern and stopped their drug overuse. The overall clinical situation at 2 months closely reflected the 1-year trend. The 2-month period after drug withdrawal should be retained as a diagnostic criterion in the ICHD-II because it is useful not only as a diagnostic parameter, but also as predictor of a good outcome of 1-year drug withdrawal. In addition, the present findings point to the need for a more objective criterion to quantify headache frequency after drug withdrawal.
9. Hagen K, Albrechtsen C, Vilming ST, Salvesen R, Gronning M, Helde G, Gravdahl G, Zwart JA, Stovner LJ. Management of medication overuse headache: 1-year randomized multicentre open-label trial. *Cephalalgia.* 2009;29(2):221-32. PMID: 18823363  
It is a general belief that patients with medication overuse headache (MOH) need withdrawal of acute headache medication before they respond to prophylactic medication. In this 1-year open-labelled, multicentre study intention-to-treat analyses were performed on 56 patients with MOH. These were randomly assigned to receive prophylactic treatment from the start without detoxification, undergo a standard out-patient detoxification programme without prophylactic treatment from the start, or no specific treatment (5-month follow-up). The primary outcome measure, change in headache days per month, did not differ significantly between groups. However, the prophylaxis group had the greatest decrease in headache days compared with baseline, and also a significantly more pronounced reduction in total headache index (headache days/month x headache intensity x headache hours) at months 3 (P = 0.003) and 12 (P = 0.017) compared with the withdrawal group. At month 12, 53% of patients in the prophylaxis group had > or = 50% reduction in monthly headache days compared with 25% in the withdrawal group (P = 0.081). Early introduction of preventive treatment without a previous detoxification programme reduced total headache suffering more effectively compared with abrupt withdrawal. (ClinicalTrials.gov number, NCT00159588).
10. Wu YJ, Luo SF, Yang SH, Chen JY, Yu KH, See LC. Vascular response of Raynaud's phenomenon to nifedipine or herbal medication (duhuo-tisheng tang with danggui-sini tang): a preliminary study. *Chang Gung Med J.* 2008;31(5):492-502. PMID: 19097597  
BACKGROUND: Raynaud's phenomenon (RP) is a common manifestation in connective tissue diseases. Calcium channel antagonists are most effective and frequently used for treating RP. This study compared the efficacy, digital vascular response, and tolerability between nifedipine and a combination of 2 Chinese herbal medications (duhuo-tisheng tang and danggui-sini tang) for treating RP. METHODS: This open-label non-randomized clinical trial included 47 connective tissue disease patients with RP. The herbal group and the nifedipine group included 26 and 21 patients, respectively. The duration of therapy was 4 weeks. Baseline and posttreatment laser Doppler blood flow imaging of both hands were performed at room temperature and after cold challenge. Nailfold capillary microscopy was performed at the baseline and after 4 weeks of therapy. Serum levels of soluble intercellular adhesion molecule-1

(sICAM-1), prostaglandin E2 (PGE2), nitrite (NO2), and nitrate (NO3), and plasma levels of endothelin-1 (ET-1) were also measured. Self-reported symptoms, using a visual analog scale (VAS) and a physician global assessment (PGA), were recorded at the baseline and after treatment. RESULTS: After 4 weeks of treatment, VAS scores improved ( $p = 0.0035$ ) and the physician's global assessment of RP severity decreased in the nifedipine group ( $p = 0.0078$ ) but not in the herbal group. Episodes of RP attacks decreased in the nifedipine group after treatment ( $p = 0.008$ ). The nifedipine group had increased laser Doppler flow ( $116.3 \pm 70.7$  AU) compared to the baseline ( $72.4 \pm 49.0$  AU,  $p = 0.0008$ ). Laser Doppler images improved at various time points after cold challenge in the nifedipine group after therapy. Laser Doppler flow in the herbal group did not significantly change with therapy. Capillary microscopy demonstrated no significant difference in enlargements, avascularity, or hemorrhagic spots between groups. Serum NO2 concentrations were higher in the nifedipine group than in the herbal group. Levels of sICAM-1, PGE2, NO3, and ET-1 after therapy were similar to those at the baseline in both groups. CONCLUSIONS: The digital vascular response in RP improved with nifedipine but was unchanged with a combination of the Chinese medicines Duhuo-Tisheng Tang and Danggui-Sini Tang.

11. Wei ZX. Experiences in treating diabetic peripheral neuropathy with traditional Chinese medicine. *Chin J Integr Med.* 2008;14(4):248-50. PMID: 19082794
12. Schep L, Temple W, Beasley M. The adverse effects of hydrogen cyanamide on human health: an evaluation of inquiries to the New Zealand National Poisons Centre. *Clin Toxicol (Phila).* 2009;47(1):58-60. PMID: 18951270  
 INTRODUCTION: Hydrogen cyanamide is used in New Zealand to induce bud break in kiwifruit vines. The aim of this investigation was to evaluate the calls received by the New Zealand National Poisons Centre (NZNPC) attributed to acute hydrogen cyanamide exposure, and to ascertain the clinical effects of such exposures. METHODS: Call data from the NZNPC telephone collection databases regarding human hydrogen cyanamide exposures were analyzed retrospectively for the years 1990-2006. RESULTS: There were 68 human exposures, 69% were male and 22% female; 88% were adults and there were no suicide attempts. Common exposure routes were inhalation (56%) and skin contact (28%). The workplace accounted for 45% of calls. The predominant toxic effects were nausea and vomiting (29%), headache (22%), contact dermatitis (19%), and erythema (18%). DISCUSSION: Reported symptoms and signs were consistent with the expected effects of hydrogen cyanamide exposure. Other reports of similar exposures describe higher degrees of illnesses among workers using hydrogen cyanamide, which might have been because of lack of training, inadequate access to personal protective equipment, and the absence of engineering controls. CONCLUSIONS: Based on the calls received by the NZNPC, acute exposure to hydrogen cyanamide in the workplace or acute exposure to those living within the vicinity of its use may not pose a significant immediate threat to human health.
13. Brent J. Poisoned patients are different--sometimes fat is a good thing. *Crit Care Med.* 2009;37(3):1157-8. PMID: 19237947
14. Montoya ID, Vocci F. Novel medications to treat addictive disorders. *Curr Psychiatry Rep.* 2008;10(5):392-8. PMID: 18803912  
 Recent discoveries about the effects of drugs of abuse on the brain and the mechanisms of their addictions; new chemical compounds, including immunotherapies; and new actions of available medications are offering many opportunities for the discovery and development of novel medications to treat addictive disorders. Furthermore, advancements in the understanding of the genetic and epigenetic basis of drug addiction and the pharmacogenetics of the safety and/or efficacy of the medications are providing opportunities for more individualized pharmacotherapy approaches. Although multiple medications have been investigated for treating addictions, only a handful have shown acceptable safety and efficacy and are approved by the US Food and Drug Administration. This article reviews the current medications that are medically safe and have shown promising results for treating opioid, cocaine, methamphetamine, and cannabis addictions.
15. Wang JF, Wei DQ, Chou KC. Drug candidates from traditional chinese medicines. *Curr Top Med Chem.* 2008;8(18):1656-65. PMID: 19075772  
 Good progress has been made to modernize traditional Chinese medicines by obtaining active

components from natural herbs. In this review, some recent works on procuring active components and modernizing traditional Chinese medicines will be covered. In addition, some recent works on drug design using modern drug design tools have been described. With some well defined targets, the traditional Chinese medicine databases have been screened so as to identify those compounds for which the potential as a drug candidate was not known before. Among these studies, two have been selected as examples to be discussed in details. First, new anti-HIV candidates have been detected, namely leucovorin and agaritine derivatives. Subsequently, GTS-21 is proved to be a good candidate for Alzheimer's disease. All these findings may provide useful information for finding effective drug candidates with lower cost.

16. Hsieh MJ, Yen ZS, Chen SC, Fang CC. Acute cholinergic syndrome following ingestion of contaminated herbal extract. *Emerg Med J.* 2008;25(11):781-2. PMID: 18955628  
Herbal preparations are becoming more and more popular and increasingly used in the USA. Herbs are from natural plants and therefore often considered to be harmless compared with western medicines. Nevertheless, as the use of herbal remedies has risen, so has the incidence of acute and chronic herbal intoxication. The case history is presented of a 68-year-old man who presented with an acute cholinergic syndrome soon after ingesting a herbal preparation containing *Flemingia macrophylla* and ginseng. His red blood cell acetylcholinesterase activity dropped to 50% of the normal reference range. He was treated successfully with atropine and supportive care. It was thought that contamination with pesticides, such as organophosphate residue, was the probable cause. This case highlights the need to be more aware of the possibility of acute pesticide intoxication in herbal users, even when only small amounts are consumed.
17. Dodd S, Dean O, Copolov DL, Malhi GS, Berk M. N-acetylcysteine for antioxidant therapy: pharmacology and clinical utility. *Expert Opin Biol Ther.* 2008;8(12):1955-62. PMID: 18990082  
BACKGROUND: Glutathione is an endogenous antioxidant and has a ubiquitous role in many of the body's defences. Treatment with N-acetylcysteine (NAC) has been shown to increase levels of glutathione. NAC has been proposed as a treatment for several illnesses. OBJECTIVES: The efficacy and tolerability of NAC was examined across a range of conditions to evaluate the evidence supporting the use of NAC for each indication. METHODS: A literature search was conducted using PubMed. Information was also collected from other online sources including the websites of the Therapeutic Goods Administration of Australia and the FDA. RESULTS: Reports ranged from case studies to clinical trials. There is strong evidence to support the use of NAC for the treatment of paracetamol overdose and emerging evidence suggesting it has utility in psychiatric disorders, particularly schizophrenia and bipolar disorder. NAC is safe and well tolerated when administered orally but has documented risks with intravenous administration.
18. Jones RL. Utility of dexrazoxane for the reduction of anthracycline-induced cardiotoxicity. *Expert Rev Cardiovasc Ther.* 2008;6(10):1311-7. PMID: 19018683  
Dexrazoxane is a derivative of the powerful metal-chelating agent ethyl enediamine tetra acetic acid. Its cardioprotective effect is thought to be due to its ability to chelate iron and reduce the number of metal ions complexed with anthracycline and, consequently, decrease the formation of superoxide radicals. Preclinical studies have confirmed that dexrazoxane has significant activity as a cardioprotective agent against anthracycline-induced cardiotoxicity. Dexrazoxane is well-tolerated, with myelosuppression being the dose-limiting toxicity in Phase I trials. The cardioprotective utility of dexrazoxane has been further illustrated in a number of randomized trials. In addition no significant difference in survival has been observed between the dexrazoxane and control arms of these trials but, in one, a significantly lower response rate was observed in the dexrazoxane compared to placebo arm. Further trials are required to evaluate the efficacy of dexrazoxane in hematological malignancies as well as the adjuvant treatment of breast cancer. Its use in the paediatric setting and in the management of elderly patients with cardiac comorbidity also requires investigation. Recently, interest has focused on the use of dexrazoxane as an antidote for anthracycline extravasation. In addition the general cytoprotective activity of this drug requires further assessment, as well as selectivity in this context.
19. Rhodes A, Bethell J, Jaakkimainen RL, Thurlow J, Spence J, Links PS, Streiner DL. The impact of rural residence on medically serious medicinal self-poisonings. *Gen Hosp Psychiatry.* 2008;30(6):552-60. PMID: 19061682

**OBJECTIVE:** Suicide rates are often high in rural areas. Despite the strong association between deliberate self-harm (DSH) and suicide, few have studied rural residence and DSH. Self-poisonings dominate DSH hospital presentations. We investigate a previously reported association between rural residence and medical severity (defined as a subsequent medical/surgical inpatient stay) among emergency department presentations for medicinal self-poisoning (SP) to determine whether differences in agents taken, mental health service use or hospital-level resources explain the relationship. **METHOD:** A cohort of n=16,294 12-64-year olds presenting with SP to hospital emergency departments in Ontario, Canada, in 2001/2002 was linked to their service records over time. **RESULTS:** The rural-medical severity association was best explained by differences in hospital resources; presenting to hospitals providing inpatient psychiatric services appeared to reduce medical/surgical inpatient stays in favor of psychiatric ones. Among those with a recent psychiatric admission, more intensive ambulatory psychiatric contact may be protective of a psychiatric inpatient stay subsequent to the SP presentation. Compared to nonrural residents, deliberate intent was identified less often in rural residents, particularly males. **CONCLUSIONS:** The rural-medical severity association was best explained by disparities in the delivery systems serving rural and nonrural residents, important to rural suicide prevention efforts.

20. Kahkonen E, Nordstrom K. Toward a nontoxic poison: current trends in (European Union) biocides regulation. *Integr Environ Assess Manag*. 2008;4(4):471-7. PMID: 18605757  
The number of products containing biocides is increasing at the same time as the number of available biocides is decreasing. Biocides are biologically active chemicals with a vast area of applications where demands for maintaining product quality by use of biocides presents a major challenge for developers striving to meet emerging environmental concerns and fulfilling criteria for eco-labeled consumer products. Tightening regulations have, however, led to stagnation in the current development of new biocide chemistries, and the "nontoxic poison" has yet to be formulated. Accordingly, the present article presents a critical overview of European Union regulation of biocides and their usage and of some of the future challenges for meeting demands for environmentally safe products and processes in which biocides are used. The Biocidal Product Directive, which is presently implemented, is one focus in the present article. Regulations of environmental, health, and safety (EHS) risk classifications and their role in the future development of biocide-containing products are also discussed. Studying the biocide dilemma may provide tools for the chemical industry as whole for proactive anticipation of the effect of emerging regulatory demands on product development.
21. Halevy S, Grossman N. Multiple drug allergy in patients with cutaneous adverse drug reactions diagnosed by in vitro drug-induced interferon-gamma release. *Isr Med Assoc J*. 2008;10(12):865-8. PMID: 19160944  
**BACKGROUND:** Multiple drug allergy syndrome is a rarely reported clinical condition characterized by an adverse reaction to more than one different class of pharmacologically and structurally unrelated drugs. The pathogenesis may involve immediate-type or delayed-type hypersensitivity. **OBJECTIVES:** To further characterize patients with MDA in terms of the type of CADR, drug intake and clinical drug suspicion. **METHODS:** The study group comprised 12 patients (6 males, 6 females) with CADRs showing in vitro drug-induced IFN $\gamma$  release for multiple drugs, suggesting the presence of MDA. The diagnostic role of in vitro IFN $\gamma$  release in identifying the culprit drugs was evaluated in terms of clinical data and the results of in vivo tests (withdrawal and/or challenge tests) with the offending drugs. **RESULTS:** Clinical relevance was attributed to in vitro drug-induced IFN $\gamma$  release towards multiple drugs in this series of 12 patients with a variety of CADRs, implying MDA. The results of in vivo tests for the offending drugs confirmed the diagnosis. The main causative agents responsible were antibiotics and non-steroidal anti-inflammatory drugs. **CONCLUSIONS:** The study further supports the role of a T cell-mediated mechanism in the pathogenesis of MDA. The in vitro drug-induced IFN $\gamma$  release test may serve as a laboratory tool to identify the culprit drugs associated with this allergy.
22. Hayes BD, Klein-Schwartz W, Gonzales LF. Causes of Therapeutic Errors in Older Adults: Evaluation of National Poison Center Data. *J Am Geriatr Soc*. 2009. PMID: 19220563  
**OBJECTIVES:** To evaluate the reasons for unintentional therapeutic errors in older adults, the types of medications most frequently involved, and the medical outcomes related to these adverse drug events. **DESIGN:** Retrospective analysis of American Association of Poison Control

Center's National Poison Data System (NPDS). SETTING: NPDS collects data from all U.S. poison centers. Data from 2002 to 2006 were examined. PARTICIPANTS: Cases involving adults aged 65 and older with a potentially toxic exposure due to unintentional therapeutic errors. MEASUREMENTS: Hazard factor analysis was conducted to identify medications that pose risk in this population. RESULTS: There were 140,786 older adults with reported therapeutic errors, of which 49,320 cases were followed to a known medical outcome. A major effect or death occurred in 596 cases (1.2% of cases with known medical outcome). The most common reasons for therapeutic errors were inadvertently took or given medication twice, wrong medication taken or given, and other incorrect dose. The reasons associated with the highest rate of major effect or death were drug interaction, health professional or iatrogenic error, and more than one product containing same ingredient. Certain medication classes such as analgesics, anticoagulants, anticonvulsants, asthma therapies, psychotherapeutics, and some cardiovascular agents were associated with high hazard factors. CONCLUSION: Poison center data can be used to evaluate therapeutic errors in older adults to identify reasons associated with frequently reported errors, as well as reasons and medications involved with errors that result in serious outcomes. Knowing the reasons why they occur can aid in developing strategies for decreasing unintentional errors in older adults.

23. Alexiades-Armenakas M. Retrograde transport and transcytosis of botulinum toxin serotypes to the brain: analysis of potential neurotoxicity. *J Drugs Dermatol.* 2008;7(10):1006-7. PMID: 19112770
24. Yang HY, Wang JD, Lo TC, Chen PC. Increased mortality risk for cancers of the kidney and other urinary organs among Chinese herbalists. *J Epidemiol.* 2009;19(1):17-23. PMID: 19164871  
BACKGROUND: A national survey in Taiwan has shown that Chinese herbal therapy increases the risk of chronic kidney disease. However, it is unknown whether herbal therapy will increase the risk of urological cancers. The purpose of this study was to determine whether Chinese herbalists are at higher risk for urological cancers. METHODS: We studied all Chinese herbalists in Taiwan that were registered in the Chinese Herbalist Labor Union between 1985 and 2000. We retrospectively followed their survival status and causes of death using the National Mortality Registry Database from 1985 to 2004. Standardized mortality ratios (SMRs) for urological cancers in herbalists were calculated and compared with those of the general population of Taiwan. RESULTS: A total of 6548 Chinese herbalists were enrolled and 88,289 person-years were accrued during the observation period. After adjustment for age and sex, the SMR for urological cancers was significantly higher for Chinese herbalists than for the general population (SMR = 3.10; 95% CI: 1.41-5.87). When further stratified by location, the SMR for kidney cancer and other urinary organ cancers (SMR = 3.81; 95% CI: 1.39-8.28) except bladder cancer (SMR = 2.26; 95% CI: 0.47-6.59) were significantly higher for the Chinese herbalists. The SMR for chronic and unspecified nephritis, renal failure, and renal sclerosis were also significantly higher for herbalists (SMR = 2.40; 95% CI: 1.40-3.84). CONCLUSIONS: Chinese herbalists have a significantly higher risk for urological cancers. This increased risk among herbalists highlights the urgent need for safety assessments of Chinese herbs.
25. Calello D, Alpern ER, McDaniel-Yakscoe M, Garrett B, Shaw K, Osterhoudt K. Observation Unit Experience for Pediatric Poison Exposures. *J Med Toxicol.* 2009;5(1):15-19. PMID: 19191210  
Background: Short-Stay Emergency Department Observation Units (OU) are an alternative to hospitalization, but data on OU care of pediatric poisoning exposures is limited. We report the experience of a pediatric OU with this population. Methods: We retrospectively reviewed the charts of children with poison exposure admitted to a pediatric OU during a 30-month period. Data was collected pertaining to demographics, type of exposure, clinical presentation, and rate of hospitalization, and was compared to nonpoisoned OU patients. Results: Of the 91 pediatric patients with poison exposure, 86 complete charts were available for review (94.5%). Of these patients, 49.5% were female, and 82.4% were <6 years of age (range 1.5 months to 16.6 years). There were a total of 98 toxicants implicated, the most common of which were psychoactive drugs (25%) and cardiovascular agents (19%). At OU admission, 33 of 88 patients (38%) had altered mental status or abnormal vital signs. Only 2 of the 53 remaining patients developed abnormal vital signs within the OU. Two patients were hospitalized unexpectedly with respiratory distress due to hydrocarbon and charcoal aspiration pneumonitis, respectively; the unexpected hospitalization rate was 2.2%. Three more planned hospitalizations for endoscopy or psychiatric

evaluation led to a total hospitalization rate of 5.4%. This hospitalization rate is significantly lower (RR=0.26, 95% CI=0.11-0.62) than the hospitalization rate from the OU for nonpoisoned patients (20.3%) during that time. Mean OU length of stay for nonadmitted poisoned patients was 14.35 hours. There were no adverse events noted as a result of OU placement. Conclusion: Select poisoned pediatric patients appear suitable for OU management and had less frequent unexpected hospitalization from the OU than other diagnoses.

26. Griffiths AP, Beddall A, Pegler S. Fatal haemopericardium and gastrointestinal haemorrhage due to possible interaction of cranberry juice with warfarin. *J R Soc Health*. 2008;128(6):324-6. PMID: 19058474  
We report a case of fatal internal haemorrhage in an elderly man who consumed only cranberry juice for two weeks while maintaining his usual dosage of warfarin. We propose that naturally occurring compounds such as flavonoids, which are present in fruit juices, may increase the potency of warfarin by competing for the enzymes that normally inactivate warfarin. While traditionally regarded as foodstuffs, consumption of fruit juices should be considered when patients develop adverse drug reactions.
27. Centers for Disease C, Prevention. Multistate outbreak of Salmonella infections associated with peanut butter and peanut butter-containing products--United States, 2008-2009. *MMWR Morb Mortal Wkly Rep*. 2009;58(4):85-90. PMID: 19194370  
On November 25, 2008, an epidemiologic assessment began of a growing cluster of Salmonella serotype Typhimurium isolates that shared the same pulsed-field gel electrophoresis (PFGE) pattern in PulseNet. As of January 28, 2009, 529 persons from 43 states and one person from Canada had been reported infected with the outbreak strain. This report is an interim summary of results from ongoing epidemiologic studies and recall and control activities by CDC, the Food and Drug Administration (FDA), and state and local public health agencies. Confirmed, reported onset of illness dates have ranged from September 1, 2008, to January 16, 2009. A total of 116 patients were reported hospitalized, and the infection might have contributed to eight deaths. Sequential case-control studies have indicated significant associations between illness and consumption of any peanut butter (matched odds ratio [mOR] = 2.53), and specific brands of prepackaged peanut butter crackers (mOR = 12.25), but no association with national brand jarred peanut butter sold in grocery stores. Epidemiologic and laboratory findings indicate that peanut butter and peanut paste produced at one plant are the source of the outbreak. These products also are ingredients in many foods produced and distributed by other companies. This outbreak highlights the complexities of "ingredient-driven" outbreaks and the importance of rapid outbreak detection and investigation. Consumers are advised to discard and not eat products that have been recalled.
28. Tiranti V, Viscomi C, Hildebrandt T, Di Meo I, Mineri R, Tiveron C, Levitt MD, Prella A, Fagiolari G, et al. Loss of ETHE1, a mitochondrial dioxygenase, causes fatal sulfide toxicity in ethylmalonic encephalopathy. *Nat Med*. 2009;15(2):200-5. PMID: 19136963  
Ethylmalonic encephalopathy is an autosomal recessive, invariably fatal disorder characterized by early-onset encephalopathy, microangiopathy, chronic diarrhea, defective cytochrome c oxidase (COX) in muscle and brain, high concentrations of C4 and C5 acylcarnitines in blood and high excretion of ethylmalonic acid in urine. ETHE1, a gene encoding a beta-lactamase-like, iron-coordinating metalloprotein, is mutated in ethylmalonic encephalopathy. In bacteria, ETHE1-like sequences are in the same operon of, or fused with, orthologs of TST, the gene encoding rhodanese, a sulfurtransferase. In eukaryotes, both ETHE1 and rhodanese are located within the mitochondrial matrix. We created a Ethe1(-/-) mouse that showed the cardinal features of ethylmalonic encephalopathy. We found that thiosulfate was excreted in massive amounts in urine of both Ethe1(-/-) mice and humans with ethylmalonic encephalopathy. High thiosulfate and sulfide concentrations were present in Ethe1(-/-) mouse tissues. Sulfide is a powerful inhibitor of COX and short-chain fatty acid oxidation, with vasoactive and vasotoxic effects that explain the microangiopathy in ethylmalonic encephalopathy patients. Sulfide is detoxified by a mitochondrial pathway that includes a sulfur dioxygenase. Sulfur dioxygenase activity was absent in Ethe1(-/-) mice, whereas it was markedly increased by ETHE1 overexpression in HeLa cells and Escherichia coli. Therefore, ETHE1 is a mitochondrial sulfur dioxygenase involved in catabolism of sulfide that accumulates to toxic levels in ethylmalonic encephalopathy.
29. Hughes B. Industry concern over EU hepatotoxicity guidance. *Nat Rev Drug Discov*.

30. Korkmaz A, Kunak ZI, Paredes SD, Yaren H, Tan DX, Reiter RJ. The use of melatonin to combat mustard toxicity. REVIEW. *Neuro Endocrinol Lett.* 2008;29(5):614-9. PMID: 18987575  
Among the most readily available chemical warfare agents, sulfur mustard (SM) has been the most widely used chemical weapon. The toxicity of SM as an incapacitating agent is of much greater importance than its ability to cause lethality. Oxidative stress is the first and key event in the pathogenesis of SM toxicity. The involvement of inducible nitric oxide (iNOS) in SM toxicity, however, also leads to elevated nitrosative stress; thus, the damage caused by SM is nitro-oxidative stress because of peroxynitrite (ONOO-) production. Once ONOO- is formed, it activates nuclear factor-kappaB (NF-kappaB) and activator protein-1 (AP-1) leading to pro-inflammatory gene expression thereby promoting inflammation; additionally, ONOO- directly exerts harmful effects by damaging all biomolecules including lipids, proteins and DNA within cells. DNA damage is sensed by an important DNA repair enzyme, poly (ADP-ribose) polymerase (PARP); this enzyme repairs molecular damage by using nicotinamide adenine dinucleotide (NAD+) as a substrate. Over-activation of PARP, due to severe DNA damage, consumes vast amounts of the respiratory coenzyme NAD+ leading to a cellular energy crisis. This pathophysiologic mechanism eventually results in cellular dysfunction, apoptosis or necrosis. Therefore, classic antioxidants may have limited beneficial effects on SM toxicity. Melatonin is a multifunctional indolamine which counteracts virtually all pathophysiologic steps and displays significant beneficial effects against ONOO--induced cellular toxicity. Melatonin has the capability of scavenging both oxygen and nitrogen-based reactants including ONOO- and blocking transcriptional factors which induce pro-inflammatory cytokines. The delayed toxicity of SM, however, currently has no mechanistic explanation. We propose that epigenetic aberrations may be responsible for delayed detrimental effects of mustard poisoning. Therefore, as a putative epigenetic modulator, melatonin may also be beneficial to subjects with delayed toxicity of SM.
31. Schaumburg HH, Gellido C, Smith SW, Nelson LS, Hoffman RS. Elemental mercury neurotoxicity from self-injection. *Neurology.* 2009;72(4):377-8. PMID: 19171837
32. Lazrshvili IL, Shukakidze AA, Chkhartishvili NN, Bikashvili TZ. Morphological changes and manganese content in the brains of rat pups subjected to subchronic poisoning with manganese chloride. *Neurosci Behav Physiol.* 2009;39(1):7-12. PMID: 19089633  
Morphological changes in neurons and the distributions of nerve and glial cells were studied, the glial index was calculated, and manganese (Mn) contents were determined in the caudate nucleus, the nucleus accumbens, the dorsal and ventral septal nuclei, and the frontoparietal areas of the cerebral cortex in the 40-day-old offspring of rats given different doses (10 and 20 mg/kg) of manganese chloride (MnCl<sub>2</sub>.4H<sub>2</sub>O) 15-20 days before pregnancy, during pregnancy, and for one month after parturition with the first portion of food. Mn poisoning increased Mn contents in the brains of rat pups, damaged a small proportion of neurons, and produced marked gliosis. These changes are believed to underlie previously described impairments to learning processes and emotional state in rat pups.
33. Lipkin AC, Lenssen P. Hypervitaminosis A in pediatric hematopoietic stem cell patients requiring renal replacement therapy. *Nutr Clin Pract.* 2008;23(6):621-9. PMID: 19033221  
BACKGROUND: Chronic renal failure patients have been known to develop vitamin A toxicity, but a descriptive study of hypervitaminosis A in patients with acute renal failure (ARF) has not yet been published. The authors observed hypervitaminosis A in pediatric hematopoietic stem cell transplant (HSCT) patients. METHODS: All HSCT patients admitted between January 2001 and May 2006 who experienced ARF, received renal replacement therapy (RRT), and had a vitamin A level drawn were included in this retrospective, descriptive study. Molar ratios of vitamin A and retinol-binding protein (RBP) were calculated to more accurately assess vitamin A status. Nineteen patients met the criteria for this study. RESULTS: At initial testing (generally between days 6 and 10 after initiation of RRT), 17 of the 19 patients had abnormally elevated vitamin A levels for their age. Molar ratios of vitamin A to RBP were elevated in 6 patients at initial testing. Prescribed vitamin A intake information (parenteral and enteral) was available for most patients; all but 3 had an average daily intake greater than 2000 IU/kg over the 30 days prior to RRT initiation. Many patients had symptoms possibly related to vitamin A toxicity, although interpretation of hair, skin, and liver abnormalities are difficult to ascertain in HSCT

patients. Seven patients had other findings that may have been associated with vitamin A toxicity. CONCLUSION: Children undergoing HSCT who receive nutrition support (predominantly parenteral nutrition), experience ARF, and require RRT are at risk for hypervitaminosis A and toxicity.

34. Buhimschi CS, Weiner CP. Medications in pregnancy and lactation: Part 2. Drugs with minimal or unknown human teratogenic effect. *Obstet Gynecol.* 2009;113(2 Pt 1):417-32. PMID: 19155916  
This is the second of a two-part series on the use of medication during pregnancy and lactation. Pregnancy risk factors together with an increased incidence of chronic diseases and the rise in mean maternal age predict an increase in medication use during gestation. However, as highlighted in the first installment of this series, relatively few medications have specifically been tested for safety and efficacy during pregnancy, and, therefore, responses to those inquiries can be uninformed and inaccurate. Whereas the first installment provided new insight into the nature of medications with known human teratogenic effects, this part concentrates on drugs with minimal or no known human teratogenic effect. It is important that clinicians become familiar with all of the aspects of the drugs they prescribe, in addition to the controversies surrounding them, through consultation with maternal-fetal medicine specialists and through references and Web sites providing up-to-date information in an effort to promote safer prescribing practices.
35. Karr C. Reducing childhood lead exposure: translating new understanding into clinic-based practice. *Pediatr Ann.* 2008;37(11):748-56. PMID: 19024842
36. Creel AM, Crawford D, Prabhakaran P. Anaphylaxis and superior vena cava thrombus in a pediatric patient with acute lymphoblastic leukemia. *Pediatr Emerg Care.* 2008;24(11):771-3. PMID: 19018221  
Pediatric patients with malignancies are at significant risk for complications from their underlying condition and medical therapy. Emergency medicine physicians must be quick to suspect life-threatening events, which can present insidiously. We describe a case of anaphylaxis and superior vena cava syndrome in an 18-year-old female patient after polyethylene glycol-conjugated asparaginase chemotherapy for acute lymphoblastic leukemia. Pertinent literature surrounding risk factors, diagnosis, and treatment is also reviewed.
37. Peng C, Xie X, Wang L, Guo L, Hu T. Pharmacodynamic action and mechanism of volatile oil from *Rhizoma Ligustici Chuanxiong Hort.* on treating headache. *Phytomedicine.* 2009;16(1):25-34. PMID: 19121572  
The volatile oil from *Rhizoma Ligustici Chuanxiong Hort.* (CXVO) is likely to be the mainly active ingredient of *Chuanxiong* in curing headache. In this study, oral administration of CXVO (45.0, 90.0, and 135.0 microl/kg) to mice significantly elevated the pain threshold in the hot-plate test and reduced the number of abdominal writhing caused by acetic acid. CXVO (90.0 and 135.0 microl/kg) not only reduced locomotor activity, but also prolonged the sleeping time induced by sodium pentobarbital (35 mg/kg), and the number of mice with sleeping time over 1 min by sodium pentobarbital (25 mg/kg) was markedly enlarged by CXVO (45.0, 90.0, 135.0 microl/kg) administration. The three doses of CXVO significantly increased the pain threshold of rabbits with headache due to hot radiation and the level of plasma ET of rats with headache due to nitroglycerin injection. Besides, for the nitroglycerin-induced headache rats, the c-fos gene expression in the brain stem and hypothalamus was remarkably inhibited and the level of plasma CGRP was reduced significantly after CXVO administration at both doses 90.0 and 135.0 microg/kg. The latter dosage could also raise the level of plasma 5-HT markedly. The study suggests that CXVO acts probably as the active ingredient of *Rhizoma Ligustici Chuanxiong Hort.* (CX) on treating headache and has potential to be an agent for treating headache.
38. Chey H, Buchanan S. Toxins in everyday life. *Prim Care.* 2008;35(4):707-27. PMID: 18928826  
This article reviews the sources of exposure and health effects of common toxicants encountered by patients in primary care practice. The recognition and management of exposure to indoor and outdoor pollutants, heavy metals, pesticides, electromagnetic fields, and endocrine-disrupting chemicals are listed. A sample environmental history form is included.
39. Fischer A, Nakai Y, Eubanks LM, Clancy CM, Tepp WH, Pellett S, Dickerson TJ, Johnson EA, Janda KD, et al. Bimodal modulation of the botulinum neurotoxin protein-conducting channel.

*Proc Natl Acad Sci U S A.* 2009;106(5):1330-5. PMID: 19164566

Clostridium botulinum neurotoxin (BoNT) is the causative agent of botulism, a neuroparalytic disease. We describe here a semisynthetic strategy to identify inhibitors based on toosendanin, a traditional Chinese medicine reported to protect from BoNT intoxication. Using a single molecule assay of BoNT serotypes A and E light chain (LC) translocation through the heavy chain (HC) channel in neurons, we discovered that toosendanin and its tetrahydrofuran analog selectively arrest the LC translocation step of intoxication with subnanomolar potency, and increase the unoccluded HC channel propensity to open with micromolar efficacy. The inhibitory profile on LC translocation is accurately recapitulated in 2 different BoNT intoxication assays, namely the mouse protection and the primary rat spinal cord cell assays. Toosendanin has an unprecedented dual mode of action on the protein-conducting channel acting as a cargo-dependent inhibitor of translocation and as cargo-free channel activator. These results imply that the bimodal modulation by toosendanin depends on the dynamic interactions between channel and cargo, highlighting their tight interplay during the progression of LC transit across endosomes.

40. Payne RA, Oliver JJ, Bain M, Elders A, Bateman DN. Patterns and predictors of re-admission to hospital with self-poisoning in Scotland. *Public Health.* 2009;123(2):134-7. PMID: 19185887  
OBJECTIVES: To identify factors influencing hospital re-admission with self-poisoning.  
STUDY DESIGN: Retrospective cohort follow-up study using national linked hospital discharge data. METHODS: All Scottish adult hospital episodes with self-poisoning admissions were captured using NHS Scotland Information Services Division data, and first-time 'index' admissions between 1996 and 2002 were identified. Re-admission rate was defined as the proportion of index admissions who went on to have one or more further self-poisoning admissions within 2 years. The effects of various potential risk factors for re-admission were examined using logistic regression. RESULTS: In total, 50,891 index admissions were identified; of these, 8278 patients were re-admitted. The 1-year re-admission rate was 12.2%. Older patients (>65 years) were least likely to be re-admitted [odds ratio (OR) 0.40, P<0.01, compared with patients aged 15-24 years]. No differences were found between males and females. Previous psychiatric hospital admission was associated with an increased re-admission rate (OR 2.85, P<0.01), with a diagnosis of personality disorder associated with the highest rate of re-admission (OR 4.59, P<0.01). Other factors predicting re-admission were: increased deprivation (quintile 3: OR 1.16, P<0.01; quintile 5: OR 1.15, P<0.01, compared with quintile 1); taking medicines for chronic disease, drug dependency (OR 1.6 and 1.19, P < or = 0.02) or antidepressants (OR 1.11, P=0.01) (compared with paracetamol); and co-ingestion of three or more agents (OR 1.37, P<0.01). CONCLUSION: Younger age, higher deprivation, ingestion of certain drug groups or multiple drug types, and prior psychiatric hospital admission are all risk factors for re-admission with self-poisoning. Personality disorder carried the greatest risk of re-admission. These findings may provide a basis to develop policies to reduce re-admission rates in the future.
41. O'Toole TE, Conklin DJ, Bhatnagar A. Environmental risk factors for heart disease. *Rev Environ Health.* 2008;23(3):167-202. PMID: 19119685  
In this review, we discuss current evidence linking environmental pollutants to cardiovascular disease (CVD). Extensive evidence indicates that environmental factors contribute to CVD risk, incidence, and severity. Migrant studies show that changes in the environment could substantially alter CVD risk in a genetically stable population. Additionally, CVD risk is affected by changes in nutritional and lifestyle choices. Recent studies in the field of environmental cardiology suggest that environmental toxins also influence CVD. Exposure to tobacco smoke is paradigmatic of such environmental risk and is strongly and positively associated with increased cardiovascular morbidity and mortality. In animal models of exposure, tobacco smoke induces endothelial dysfunction and prothrombotic responses and exacerbates atherogenesis and myocardial ischemic injury. Similar mechanism may be engaged by other pollutants or food constituents. Several large population-based studies indicate that exposure to fine or ultrafine particulate air pollution increases CVD morbidity and mortality, and the plausibility of this association is supported by data from animal studies. Exposure to other chemicals such as polyaromatic hydrocarbons, aldehydes, and metals has also been reported to elevate CVD risk by affecting atherogenesis, thrombosis, or blood pressure regulation. Maternal exposure to drugs, toxins, and infection has been linked with cardiac birth defects and premature CVD in later life. Collectively, the data support the notion that chronic environmental stress is an important determinant of CVD risk. Further work is required to assess the magnitude of this risk fully and

to delineate specific mechanisms by which environmental toxins affect CVD.

42. Rollin L, Carre N, Garnier R, Greater Paris lead poisoning monitoring s. Follow-up of children suffering from lead poisoning or at risk of lead poisoning in Greater Paris, 1992--2002. *Rev Epidemiol Sante Publique*. 2008;56(6):391-7. PMID: 19013038  
BACKGROUND: It is essential for children suffering from or at risk of lead poisoning to have regular follow-up, and specifically for their blood lead (Pb) levels to be monitored. The present study assessed the occurrence of late follow-up testing of blood lead levels in children in Greater Paris, and factors related to such delays. METHODS: Since 1992, the SSSIILF has been systematically recording data on lead levels in blood tests conducted for screening and follow-up in Greater Paris. For Pb greater or equal to 45 microg/dL (Group 4), a further blood lead test has to be done within three weeks. For levels of 25 microg/dL < or = Pb < 45 microg/dL (Group 3) and 10 microg/dL < or = Pb < 25 microg/dL (Group 2), a second test must be done within 6 months. For Pb less than 10 microg/dL combined with one or more risk factors (Group 1: children at risk of poisoning), a second test is required within 6 to 12 months. Children aged 1 to 6 years who were screened between 1992 and 2002 were selected. The occurrence of late follow-up testing was estimated, and the independent effect of each variable associated with a delay was measured using a logistic regression model. RESULTS: Delays in re-testing were reported for 66.9% of Group 4 children (n=356), 45.3% of Group 3 children (n=921), 74.1% of Group 2 children (n=5,466), and 88.7% of Group 1 children (n=15,612). In the three groups with Pb greater or equal to 10 microg/dL, there was better follow-up (i.e. less delay to re-testing) for children screened most recently, those whose initial blood lead test results were elevated, those who lived in sub-standard housing built before 1949, and those who lived in suburban districts of Paris. The delay was longer for children aged 4 to 6 compared to younger children. When the size of the group was large enough, these differences were significant. In Group 1, similar results were observed except for a home address in a suburban district. Furthermore, follow-up was better for children of Sub-Saharan African parents, children whose initial prescription had been issued by a "PMI" mother/child healthcare centre and children from large families. CONCLUSION: Despite substantial delays in carrying out follow-up blood lead level testing, these delays were shorter for the populations with the greatest exposure.
43. Arora A, Neema M, Stankiewicz J, Guss ZD, Guss JG, Prockop L, Bakshi R. Neuroimaging of toxic and metabolic disorders. *Semin Neurol*. 2008;28(4):495-510. PMID: 18843577  
Imaging of the brain, magnetic resonance imaging (MRI) in particular, is a key adjunctive tool in the diagnosis and management of toxic-metabolic disorders such as alcoholism, mitochondrial encephalopathies, disorders of iron or copper metabolism, exposure to carbon monoxide, radiotherapy, immunosuppressive agents, toluene, and recreational drugs. In this article, we review the neuroimaging findings of common toxic and metabolic disorders focusing on the role of conventional MRI. We also consider advanced imaging methods, such as magnetic resonance spectroscopy, diffusion MRI, and positron emission tomography. We hope this article will prove useful to trainees and practitioners in the clinical and imaging fields of the neurosciences.
44. Indraccolo U, Palombino K, Greco P. Anaphylactic-like reaction to lugol solution during colposcopy. *South Med J*. 2009;102(1):96-7. PMID: 19077773  
There are a lack of reports about the adverse effects of Lugol iodine solution staining of the genital epithelia, known as a Schiller test, during colposcopy. We report that during the Schiller test, a patient complained of an anaphylactic-like reaction to the Lugol solution with vaginal and generalized pruritus, vaginal edema, hypotension, tachycardia, and breathing difficulties. Vaginal iodine was completely washed out with saline solution, resulting in improvement and a disappearance of the symptoms without the use of any drugs. The safety of Lugol staining during colposcopy needs to be assessed.
45. Kiran Kumar B, Prabhakara Rao Y, Noble T, Weddington K, McDowell VP, Rajanna S, Bettaiya R. Lead-induced alteration of apoptotic proteins in different regions of adult rat brain. *Toxicol Lett*. 2009;184(1):56-60. PMID: 19026729  
In our earlier investigations, we have demonstrated the alteration of antioxidant enzymes in adult rat brain exposed to lead. This study was carried out to investigate the effect of lead on inducing apoptosis by choosing poly (ADP-ribose) polymerase (PARP), bcl-2 and caspase-3 expression as marker proteins in the cerebellum, the hippocampus, the brain stem and the frontal cortex. Adult

male rats were treated with lead acetate (500ppm) through drinking water for a period of 8 weeks and parallel controls were maintained on sodium acetate. Both control and exposed rats were sacrificed at intervals of 4 and 8 weeks, brains were isolated and different regions namely the cerebellum, the hippocampus, the frontal cortex and the brain stem were separated and processed to investigate PARP, bcl-2 and caspase-3 expression using western blotting. The results suggest that lead induces region-specific response of expression in apoptotic proteins of rat brain showing more effect in hippocampus and cerebellum and less effect in frontal cortex and brain stem and it is tissue specific. However, results appear to conclude that PARP induced expression in hippocampus and cerebellum was more followed by mitochondrial and cytosolic damage.

46. Liu Q, Wang Q, Yang X, Shen X, Zhang B. Differential cytotoxic effects of denitroaristolochic acid II and aristolochic acids on renal epithelial cells. *Toxicol Lett.* 2009;184(1):5-12. PMID: 19026731

Aristolochic acids (AAs), naturally occurring nephrotoxins and rodent carcinogens, are commonly found in medicinal plants such as *Radix aristolochiae*. The toxicity of AAs is believed to be associated with the formation of promutagenic AA-DNA adducts, and it has also been suggested that the nitro group in AAs might be important in the process. In order to investigate the role of the nitro group in AA-mediated cytotoxicity, the effects of denitroaristolochic acid II (dN-AAII), aristolochic acid II (AAII) and aristolochic acid I (AAI) on renal tubular epithelial Madin-Darby canine kidney (MDCK) cells were examined and compared. The cytotoxicity of AAI, AAII and dN-AAII was found to be time- and concentration-dependent. As determined by MTT assay, AAI was found to be most toxic in MDCK cells upon exposure for 24, 48 and 72h, followed by AAII, and dN-AAII showed the least cytotoxicity. The effect of AAI and AAII on the integrity of cell membrane was found to be similar and appeared to be more prominent than that of dN-AAII. Based on the results obtained from the flow cytometric analysis, significant apoptosis in MDCK cells was observed with AAI and AAII at as low as 25micromol/L following exposure for 24h, whereas significant apoptosis was induced by dN-AAII at a much higher concentration, 300micromol/L, suggesting that both AAI and AAII were significantly more cytotoxic than dN-AAII. In addition, the levels of reactive oxygen species (ROS) were increased following treatment with AAI, AAII and dN-AAII at concentrations of 5, 25 and 25micromol/L, respectively, for 4h. The results suggest that the nitro group plays an important role in AA-mediated cytotoxicity in MDCK cells and increased intracellular ROS levels may be associated, at least in part, with the cell injury observed in MDCK cells.